Piero Manfredi
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Preface

This book is about the rather new discipline of "behavioral epidemiology" of infectious diseases (BE). And "behavioral epidemiology" was indeed the title we originally planned to give this book when its first ideas were grown. Unfortunately, we have discovered soon after that the description "behavioral epidemiology" is quite common in other areas of applied epidemiology, though unrelated to infectious diseases, and it already appeared as the title of at least two published books. This is why we eventually preferred to choose the present title which, though perhaps less evocative, should anyhow clearly explain what is currently meant by "behavioral epidemiology" of infectious diseases.

BE is a new branch of the epidemiology of infectious diseases focusing on the complex interplay between human behavior and its determinants (e.g. acquisition of information, risk perception, perceived benefits and costs of different actions) and the transmission and control of infectious diseases.

In the last 25 years, mathematical models of infectious diseases have become highly sophisticated tools for assisting public health decisions and policies, which are used in an increasing number of countries worldwide. A major example is provided by the huge advancements in the modeling and prediction in relation to the pandemic threats, from the avian flu scare, to the SARS outbreaks, to the H1N1 influenza pandemic that scared the world in 2009.

Despite these advancements, there is an increasing awareness that in this sophisticated modeling there is a neglected "layer" of complexity, which is critical to understand the mechanisms underlying infection transmission and control. This missing layer is human behavior.

For example, we finally know something about social contact patterns. But what we know mostly deals with social behavior in "normal life" days, therefore in absence of illness, of serious life-threatening conditions, and so on. How might people socially respond in the presence of a big, real, pandemic threat, and how these individual responses might impact on transmission and control, we simply do not know. But there are other areas, beyond pandemic threats, where human

behavior is becoming a critical determinant of infectious diseases dynamics, first of all the area of immunization choices.

Filling these knowledge gaps, by including the "missing layer," is the main task of behavioral epidemiology. BE integrates traditional mathematical modeling of infectious diseases with tools from a variety of behavioral sciences, ranging from economics and sociology to psychology, in order to model and predict the impact of information about infections and vaccines on human behavior, its epidemiological consequences, and their ultimate feedback on behavior.

Behavioral epidemiology is certainly one of the major news of the research landscape in epidemiological modeling. As argued in the historical overview BE incubated prior to 2000, thanks to the many studies motivated by the onset of HIV/AIDS, and entered thereafter in its epidemic phase, as documented by the many dozens of papers published on the subject, by the increasing rate of growth of publications, by the widening spectrum of scientific journals publishing papers on the subject, which has expanded to leading public health and medical journals, and, last but not least, by the increasing number of national and international grants that are funded on the subject.

In this first phase, most behavioral epidemiology studies have been largely theoretical. This is not surprising. Given the novelty of the discipline, appropriate data are most often lacking, and what can at most be done is inferring the presence of behavioral responses from infection trajectories. In these circumstances "behavioral" mathematical, or computational, models, integrating behavioral elements into epidemiological models, become a unique tool for investigating and quantifying these complex feedbacks.

Obviously, the true challenge for the future therefore lies in the design of appropriate data collection plans that might make possible to robustly estimate, and possibly predict, behavioral parameters, thereby allowing behavioral–epidemiological models to overtake their current role, still sometimes seen as that of elegant theoretical tools, to become useful policy supporting tools.

In this important phase for behavioral epidemiology of infectious diseases, this is also the first book devoted to the subject: this was surprising for us, and we indeed felt that time has come to ripen the above research work in order to collect a carefully selected number of contributions by some of the scientists who mostly contributed to the building up of this new discipline.

This book is opened by a historical overview aiming to motivate the historical and cultural background underpinning the BE revolution, which is identified in the changed relationship between man and disease in modern industrialized countries on the one hand, and, on the other hand, to access the heart of the book by reviewing the current epidemic phase of BE studies and by introducing some of its baseline models.

The core of this book is divided into three parts.

The first part includes two contributions on field work about the two main foci of interest of this volume, i.e., behavioral responses to the threat of a pandemic event

and attitudes towards routine immunization. The first contribution by Rizzo et al. aims to assess beliefs and behavior change in relation to the 2009 H1N1 pandemic, based on the main field study conducted on the topic, via two surveys carried out in 4 European countries, one at the beginning and the other one after the first wave of the 2009 pandemic. The second contribution, by Theeten et al., investigates, based on questionnaire data from the Flanders, the determinants of vaccine uptake for a number of infant and adolescent immunizations, focusing on central issues, e.g., the parents' willingness to accept multiple concomitant injections for their children.

The second part of the volume deals with the modeling, from various viewpoints and by using a variety of mathematical tools, of behavior change in response to an epidemic outbreak of a serious threatening infection. Motivated by the fact that behavior changes is possibly one of the only options available in the early stages of an emerging epidemic of a serious disease, Del Valle et al. investigate both simple models, where people change their behavior to decrease their probability of infection, and complex agent-based models including isolation scenarios such as school closures and fear-based home isolation, suggesting that behavior changes can be effective in containing the disease spread.

On the same theme Poletti et al. use a model coupling the classic simple susceptible-infective-removed (SIR) transmission model with an imitation dynamics process to account for the diffusion of different behaviors as a response to the epidemic threat. They suggest that perception of risk and diffusion of behavior are the most critical factors capable to determine remarkable alterations in the epidemic course, and they also try to identify from data the extent of behavior change during the 2009 H1N1 pandemic in Italy.

The spread of information and awareness about the disease and the way awareness affects the disease spread through behavior change, e.g., through protective measures people can adopt, are the core of the contribution by Funk and Jansen. They in particular focus on the word-of-mouth information exchanged through person-to-person in a double-network model, where one network describes the spread of awareness, and the other the spread of infection.

Perra and Vespignani also focus on the diffusion of awareness about the infection. They investigate single and multi-population SIR models where contacts either between susceptible and infected people or between uninformed and informed susceptible individual yield newly "informed susceptible" people who then migrate towards a lower risk group. They show that when awareness is lost, complex epidemic behavior, including multiple epidemic peaks, can result from the interplay of information and transmission.

Still on the dynamic interplay between information and infection, Kiss revisits a pairwise model for the concurrent spread of an epidemic of a sexually transmitted infection (STI) and the related information about it to discuss the relation between information generating and transmission mechanisms and their implications for modeling complexity. The results of the pairwise model are compared with those of simpler variants, and a general discussion about alternative modeling strategies, is carried out.

Lió et al. provide a general discussion of the determinants of the heterogeneity in the perception and assessment of risk as a critical shaping factor of behavioral

responses in relation to infectious diseases, ranging from the types of information to the mental heuristics used by agents to assess the risk. They also expand their discussion to fairly advanced issues, such as the challenges faced by mathematical modeling when risk perception is modulated by other relevant process acting at different micro- and macroscopic scales. Fenichel and Wang investigate the characteristics of adaptive human behavior in relation to an epidemic outbreak described by a SIR model with a variable contact rate depending on the actions taken by individuals according to an evaluation of benefits and costs of such actions provided by micro-economic first principles, i.e., utility maximization. They find that assumptions about information processing, first of all the form of the utility function of individuals, may have a substantial influence on the course of the epidemic.

The third part of the volume deals with models of vaccinating behavior under a variety of situations. On the same lines of reasoning as those of the contribution by Fenichel and Wang, there are the two papers by Gersovitz and Chen, which link the second and third parts of the volume. Both papers focus on the economic approach to infectious diseases, i.e., utility maximization, to determine optimal either protective (e.g., decreasing at-risk contacts, or vaccinating) or therapeutic actions in the context of recurrent infections of the susceptible-infective-susceptible (SIS) type.

In particular, Chen develops a discrete-time framework to illustrate the equilibrium implications of risk-reduction actions (including vaccination) that forward-looking, utility-maximizing agents can take to lower the probability of acquiring an infection. He illustrates the various concepts of equilibria which appear as a consequence of combining economic and mathematical epidemiology approaches and shows several counter-intuitive consequences of the interplay of individual actions and public policies. Gersovitz uses a continuous-time framework to discuss the issue of "externalities," i.e., the discrepancy between costs and benefits at the level of the individuals who make choices about the infection (e.g., about prevention and therapy) and at the level of the society as a whole. Such discrepancy provides the rationale for public policies (e.g., subsidies for prevention and therapies) aimed to offset the externality, i.e., to align private and social choices. He also suggests that the absence of such interventions might have perverse effects on welfare.

Two contributions (Vardavas and Marcum, and Breban, respectively) focus on the issue of voluntary vaccination choices against sequences of seasonal influenza epidemics, where individuals must decide every year whether or not to get immunized, by using the inductive reasoning games approach. This is a flexible adaptive approach allowing to update influenza vaccination decisions for a new epidemic year based on the past experience with vaccination (i.e., whether effective or not) and infection (mild or not) and expectations about future influenza epidemics.

In particular, on the one hand, Vardavas and Marcum show that individual immunization choices can cause severe influenza epidemics and illustrate the actions that might be undertaken to prevent them. These include commitment-based incentives or the release, by the mass media, of appropriate epidemiological information that individuals can use to evaluate the importance of vaccination.

On the other hand, Breban includes age structure both in social contact patterns and vaccination decisions. He shows that age structure affects the game dynamics for not only epidemiological but also behavioral reasons. In particular, unlike the unstructured case, the inclusion of age structure makes it possible to eliminate influenza through voluntary vaccination and induces much more complex dynamical patterns.

Finally, the last set of contributions of the third part focuses on the issue of vaccinating behavior in relation to immunization for vaccine-preventable infections.

Bhattacharyya and Bauch aim to give a broader perspective of the issue of behavior in relation to vaccination programs, by departing from the classical free-rider problem, to suggest that various types of dynamic behavior can emerge from the interplay between vaccinating strategies and information about disease, which range from policy resistance, i.e., free-riding, to policy reinforcement, outcome inelasticity, and outcome variability, and suggest the potential implications for vaccination policies.

Shim et al. use a game-theoretic dynamic model of measles' transmission with two groups, one composed by "vaccine skeptics" and the other by "vaccine believers," characterized by widely different perceptions about the risks of vaccine side effects and disease, to examine the impact of perceived risks of measles' vaccination on vaccine uptake as a possible cause of decline in herd immunity. They conclude that the most important factor for decline in herd immunity and consequent measles' resurgence is the size of the proportion of vaccine skeptics.

d'Onofrio et al. review and extend their work on the implications of vaccinating behavior for the dynamics of common vaccine-preventable infections. They consider both prevalence-based models with vaccine uptake given by a phenomenological function of the information about prevalence of infection, or of vaccine side effects, and models where perceptions about benefits and costs of vaccination spread through to an imitation process. They discuss the relationships between the two frameworks and highlight the importance of appropriately taking into account delayed information, as well as oscillations in the contact rate.

In a more mathematical vein Buonomo et al. focus on the global stability properties of the endemic states of prevalence-based SIR models with phenomenological behavioral responses either in vaccine uptake or in contact rates, by using the modern geometric approach to stability. This approach, proposed by Li and Muldowney, extends the classical Poincaré–Bendixson theory to dynamical systems of arbitrary—but finite—dimensions. They apply the methodology to prove in particular the global stability of the endemic state of a model of vaccination of adult susceptible subjects.

The book is ended by the concluding overview by Edmunds et al. Their title "Capturing human behaviour: is it possible to bridge the gap between data and models?" suggests which are the major future challenges for behavioral epidemiology of infectious diseases. Whether we will, in the future, be able to predict behavior in relation to infections, thereby making behavioral models useful policy tools, is

hard to answer right now. But now that we have the models, the first step towards predictability would surely be to create the appropriate bridge between models and data.

We finally thank Springer Verlag for having allowed this book to exist and, in particular, the Springer officer Vaishali Damle for her cooperating attitude—and remarkable patience—during all phases of development of this volume.

Pisa, Italy — Piero Manfredi
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Contents

Behavioral Epidemiology of Infectious Diseases: An Overview

Chris Bauch, Alberto d'Onofrio, and Piero Manfredi

Abstract The focus of the growing discipline of behavioral epidemiology (BE) of infectious diseases is on individual behavior as a key determinant of infection trajectories. This overview departs from the central, but static, role of human behavior in traditional mathematical models of infection to motivate the importance of including behavior into epidemiological models. Our aim is threefold. First, we attempt to motivate the historical and cultural background underpinning the BE revolution, focusing on the issue of rational opposition to vaccines as a natural endpoint of the changed relation between man and disease in modern industrialized countries. Second, we review those contributions, from both mathematical epidemiology and economics, that forerun the current "epidemic" of studies on BE. Last, we offer a more detailed overview of the current epidemic phase of BE studies and, still motivated by the issue of immunization choices, introduce some baseline ideas and models.

1 Introduction

The severe acute respiratory syndrome coronavirus (SARS-CoV) outbreaks of the early 2003 yielded worldwide panic. The characteristics of the SARS virus, mainly transmitted through close contact from person to person [20], brought to everyone's

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mind, more than HIV/AIDS, the spectrum of a "modern plague," at risk of being triggered by historically unprecedented population mobility. The SARS chapter closed leaving only 8,500 cases worldwide (though 800 deaths), but having given a sharp demonstration of how effective might be the diffusion of fear in the globalized world, with the dramatic decline in traveling, tourism, and investments to the Far East [65].

The SARS outbreaks are only one dramatic example of an endless list. In October 2009, in the middle of the H1N1 crisis, the Italian Public Health System started advertising a national immunization campaign against the pandemic flu, targeting 21 million individuals with two doses. A few months later, when the Italian epidemic ended, vaccine coverage was a mere 4.2 % [87], the worse result in H1N1 immunization in Europe.

In 1998 the prestigious medical journal The Lancet reported an apparently highly circumstantial evidence by Wakefield and coworkers on the striking hypothesis that measles–mumps–rubella (MMR) vaccination might be causally linked with autism. Although the Wakefield's paper was strongly criticized by other scientists and retracted in 2010 by *The Lancet* [102], and although its data could not be replicated by other research groups, in subsequent years UK measles immunization fell from 92 % to less than 80 % in 2003, yielding a protracted marked decline in herd immunity, ultimately responsible for measles resurgence [60, 78].

What possibly happened with H1N1 immunization in Italy was that individuals perceived that H1N1 was a mild disease and therefore were not motivated to accept the risk of vaccine adverse events (VAE) from a vaccine which they also perceived as being of insufficiently proven safety. We note that it was not important that the perception was not informed from the best science: what mattered was that this misperception spread faster than other, more correct perceptions, and it was ostensibly confirmed by the subsequent course of the epidemic, which was mild only in comparison to what had been feared based on the early, confused events in Mexico. So eventually only a small proportion were immunized. What happened with MMR uptake in the UK was that news reports of the Wakefield study suddenly raised the perceived risk of VAE, thereby making the perceived utility of vaccination strongly negative. Especially in the context of very low measles circulation at the time, many parents therefore decided not to immunize their children. We note that the perception of measles rarity was "myopic"—rarity was the consequence of herd immunity generated by 20 years of successful immunization—but this is not relevant. What matters is that the rumor spread fast, possibly aggravated by apparently coming from the "best science."

There are also examples where human behavioral responses played a critical role in controlling infections. There is little doubt that in the HIV/AIDS catastrophe in Sub-Saharan Africa (SSA), sexual behavior change has been the key in the Ugandan success story [1, 77], which is currently the major instance of success in the control of HIV in SSA, and is becoming an effective strategy as well in other SSA settings such as Zimbabwe where a major HIV epidemic is still ongoing [51, 52].

All these examples document how important human behavior might be for infection spread and for determining the success of public health interventions.

2 Human Behavior and Epidemiological Modeling

The current mathematical theory of infectious disease transmission was built on a few cornerstone ideas and models developed during the so-called Golden Age of theoretical ecology [61, 88, 92]. The most important among such milestones is the homogeneous mixing SIR (susceptible-infective-recovered) model in its two variations, for epidemic outbreaks as seasonal influenza and for endemic infections as measles in large communities in absence of any immunization [3]. In this class of models, behavior is absent: individuals contact (and infect) each other at random, as particles of a perfect gas (the so-called law of mass action [28]) and therefore behavioral influences are ruled out by definition.

In the last 25 years however, thanks to pioneering works aiming to better integrate models with data [3, 53, 54], mathematical models of infectious diseases have crossed their traditional biomathematical boundaries to become central supporting tools for public health decisions, such as determining the duration of travel restrictions or of school closure during a pandemic event, or the fraction of newborn to be immunized for a vaccine-preventable infection, as measles. Some of these models are highly sophisticated both from the computational and data requirements' viewpoints [5,39,73]. In these models, the importance of human behavior is implicit in the acknowledged role of social or sexual contact patterns as the key determinant of the transmission of both close-contact infections, as influenza or measles, and sexually transmitted infections (STIs), such as HIV/AIDS. In recent years there have been great advances in the understanding of contact patterns [59, 75, 108], which made available rich information about, for example, the average number of persons of different ages an individual encounters in a typical day. This information is allowing great improvements in model parameterization and validation. However, the point of behavioral epidemiology lies exactly here: though sophisticated, current models treat these contact patterns statically, as a universal constant, exactly as in the simple SIR model. This means that behavior is totally unaffected by the state of the disease, for example, individuals continue to contact each other however low or high might be the perceived risk of contracting the infection. As these static contact patterns refer to normal situations, the ensuing models are unlikely to apply under stressed conditions as those observed during a dangerous epidemic or a period of panic raised by a pandemic threat [38]. Similarly, models used to evaluate the impact of immunization programs treat vaccine uptake as a constant [3], totally unaffected by individuals' risk perceptions about the disease and the vaccine, and despite the fact that it is the degree of acceptance of the public that will ultimately determine the success of the program unless mandatory policies can be strictly enforced. Clearly, phenomena such as vaccine scares cannot be captured by treating vaccine coverage as a fixed, exogenously determined input parameter.

As suggested by the above examples, this postulated static human behavior is therefore an unrealistic abstraction. Individuals are neither static nor passive: they can change their social behavior spontaneously in response to a pandemic threat, can adaptively vaccinate in response to a sequence of seasonal influenza

epidemics, or can decide not to vaccinate their children after a comparison between the perceived costs and benefits of a vaccination program, thereby threatening its success. In modern times, these decision dynamics are facilitated by the power of modern communication technologies, which allow real-time, selective access to broadly available information to the extent that certain reliable influenza data can now be mined from individuals' search activities on the web during influenza seasons [49].

The challenging task of modeling, explaining and possibly predicting these phenomena is the ultimate purpose of the emerging field of behavioral epidemiology of infectious diseases. As the above examples clearly show, the major novelty that distinguishes BE from, for instance, traditional biomathematical approaches or economic approaches in epidemiology (e.g., cost–benefit analyses of public programs) is the focus on modeling behavioral changes in response to infection dynamics [44] as a key determinant of infection trajectories, and therefore on the complex interplay between agents' decisions, on one hand, and the transmission and control of infections, on the other hand [38, 44].

3 Behavioral Epidemiology: Why Now?

Later on in this overview, BE is described as currently being in its "epidemic" phase. A question is then, why right now? We argue that a rich "humus" was supplied by the current scientific, cultural, and socio-demographical context of industrialized countries which has dramatically changed the relationship between humans and disease. In this context, individuals frantically demand "predictability" during a pandemic event [38] or "rationally" refuse a vaccine—the invention that has protected so much human life in the last hundred years. In short, technology has turned us from victims of nature *per se* to victims of our own actions locked in a feedback loop with natural forces. This is why it is now that studying BE is important, and we expand on this in the following paragraphs. Until 1750 the millenary fight between man

Fig. 1 (continued) (*upper left panel*) Thucydides, who described with many details the plague outbreak that frightened Athens during 430–429 BC and resulted in significant socioeconomic reactions. The etiological agent is still unknown; (*upper right*) Giovanni Boccaccio, whose Decameron (written between 1351 and 1353) supplied a dramatic description of the devastating impact of the Black Death passed through Florence in 1350. The book is the story of ten young people (seven women and three men) who flee from the devastated Florence and self-quarantine (an early example of social distancing) into a villa in the countryside, where they pass time telling stories. (*bottom left*) Daniel Defoe, who was five years old when the bubonic plague struck London in 1665, which he subsequently described in his Journal of the Plague Year. (*bottom right*) collection of dead bodies during the outbreak of bubonic plague in Milan, described in Manzoni's "The Betrothed." In Chap. 22 he underlies the possibly devastating role played the great procession authorized by the Cardinal of Milan, Federico Borromeo, ironically undertaken to invoke God's favor

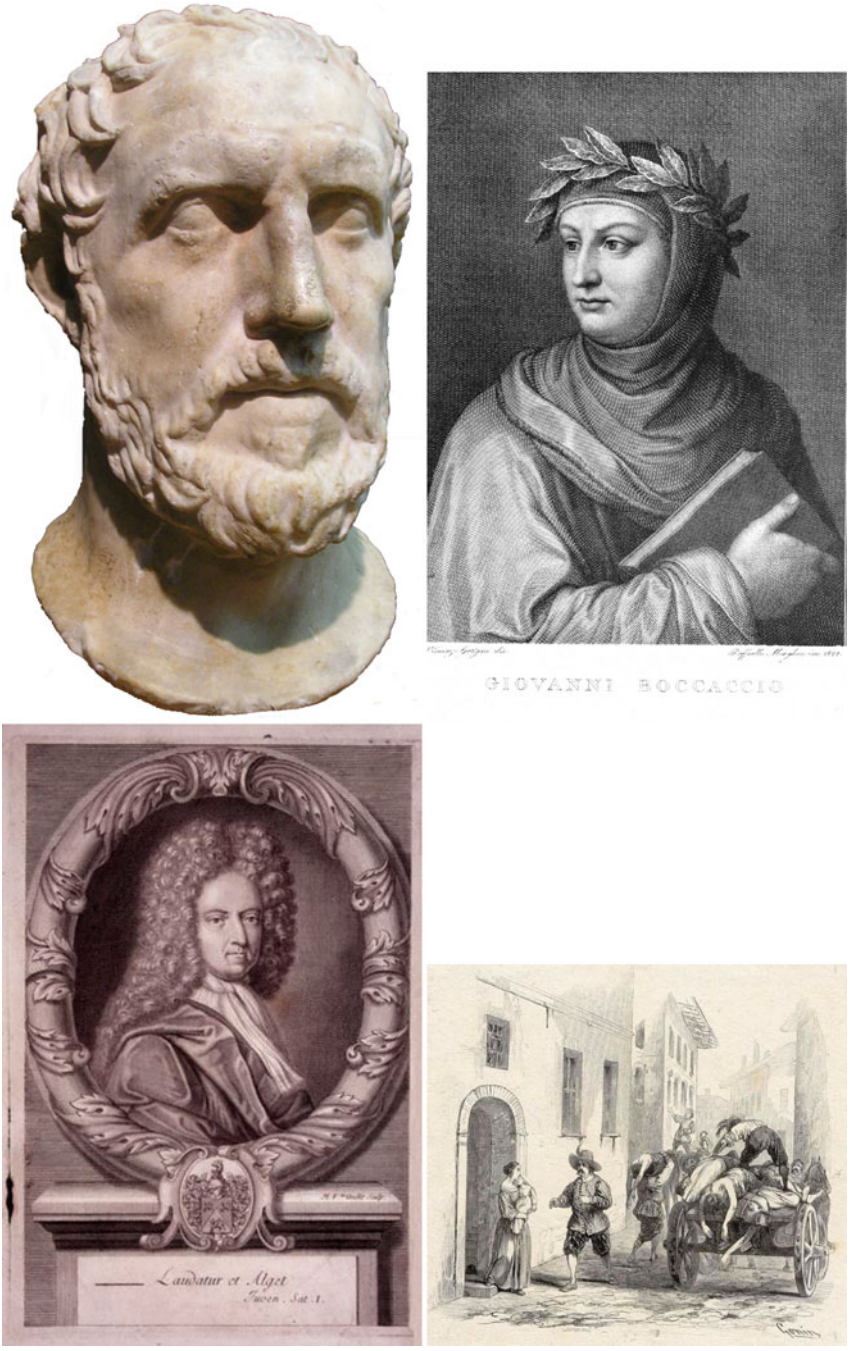

Fig. 1 (continued)

and disease—the third horseman of the Apocalypse—is the story of a long-lasting unperturbed ecological equilibrium. During this fight human behavioral responses to infectious disease threats always took place, as is documented by the great writers, from the Athens' "plague" described by Thucydides, to the Black Death whose visit to Florence was immortalized by Giovanni Boccaccio in the "Decameron," to the seventeenth-century plague described by Daniel Defoe and Samuel Pepys, and two centuries later on by Alessandro Manzoni (Fig. 1). However, most these responses are reported by historians as taking place at the community level (e.g., enforcing quarantine of sick individuals and also of goods [97], or closing the city gates,[1] and mass migrations—especially by rich people—toward the country[2]), so that individual actions, though reported, were usually perceived as minor and passive. Most of all these actions, collective or individual, were lacking any scientific basis.[3] Most importantly, these actions were unable to mitigate plague epidemics or to perturb the ecological equilibrium between man and disease: infectious diseases continued to impose a major and intractable health burden on populations worldwide for several millenniums.

During the last two centuries, however, thanks to the sanitation revolution (such as potable water) and to medical discoveries (such as vaccines), humanity has attained amazing achievements in the control of infectious diseases and reduction in associated mortality. These achievements have perturbed the equilibrium between humans and disease, yielding that epochal change in the casual composition of mortality from infectious (and nutritional) diseases to chronic degenerative ones known as the "epidemiological transition" [76, 96, 103]. The epidemiological transition has been a major determinant of the huge progress in survival and health in industrialized countries, where life expectancy increased from 25 to 30 years in preindustrial societies to more than 80 years in the current period

[1] In Rome, during the seventeenth-century plague special additional walls were built around the city [97].

[2] As S. Pepys wrote during the London Plague: "I find all the town almost going out of town, the coaches and wagons being all full of people going into the country," as reported by [97]. The same paper also reports that the parish of Covent Garden, London, wrote "all the gentry and better sort of tradesmen being gone."

[3] For example, based on historical documents, Manzoni describes in his masterpiece novel *The Betrothed* the behavioral changes of the citizens of Milan, during the plague in 1629, mainly due to their fear of the "*poisoners*": imaginary villains that were thought to voluntarily spread the disease through mysterious ointments causing the disease. In particular, Manzoni describes as the epidemic peak following a procession against the plague is not attributed to the crowding during the procession nor to "*the infinite multiplication of random contacts*" (note the surprising accuracy of Manzoni's language in describing the contagion process, despite this phrase has been written in 1827). The most of people attributed, indeed, the peak to the poisoners, who would have had an easier task, in the crowd of the procession, in diffusing their evil ointments in order to accomplish their "*impious plan*."

[69, 103], which in turn triggered fertility decline, the escape from Malthusian traps, and eventually, in a virtuous circle, sustained economic development [14, 45]. Further advances with vaccines, such as vaccines that protect against oncogenic viruses such as HBV and HPV, are making a reality out of previously utopian conceptions of life in a future world free from infectious diseases [22].

This amazing success against infectious diseases and their associated mortality in the industrialized world, and the ensuing huge increase in the value of human life in current low-mortality/low-fertility societies, is however changing the relation between man and infection. What was the rule in the ancient demographic regime—losing 50 % of children before age 15 as a consequence of infections and malnutrition [69]—has been completely reversed in today's small, highly educated postindustrial families.

There are several evidences of this changed attitude, and surely the main one is represented by the increasing frequency of episodes of oppositions to vaccines [47, 70, 78], the single invention that possibly more than other has contributed to the changed relation between man and infection.

The history of immunization in the western world has always been characterized, already since the introduction of smallpox vaccine, by phases of declining uptake. However, most of this historical opposition to vaccination is thought to be due to conscientious, religious, or philosophical reasons [90][4] In contrast, current societies are gradually facing the more complex challenge of rational opposition to vaccines [8, 9, 31, 33].[5] Consider the example of an infection that is preventable by childhood immunization, as measles, for which we assume there are only two options, i.e., vaccinating or not vaccinating at birth. By rational opposition we mean, under voluntary vaccination, the parents' choice not to vaccinate children after a comparison between the perceived benefit and cost of vaccination.

The cost of vaccination can be conceived of as the perceived risk of suffering some vaccine-associated adverse event (VAE). In the simplest case this can be taken as a constant (e.g., as in [8]), though individuals' perceptions about a given vaccine are possibly affected by perceptions about other vaccines as well. On the other hand the perceived benefit of vaccination can be estimated by the perceived risk of suffering death (or serious morbidity) from the disease, which can in turn be estimated as the product of some measure of the current perceived risk of acquiring infection, i.e., the force of infection, and the conditional probability of death, as a consequence of infection. European data suggest that, due to improved nutrition and sanitation, the probability of death following infection from measles and other childhood infections fell off at least two orders of magnitude from

[4] We shortly mention that there are also a number of *a priori* opposers to vaccinations, who irrationally believe that vaccines are a sort of Manzoni's "*ointments*." Quite interestingly, this observation is in line with the fact that some anti-vaccination arguments remained unchanged since the Jenner's times [107].

[5] Although out of the aims of this work, we remark here that the partisans of most extreme anti-vaccination positions are very able in spreading their ideas through the World Wide Web [107], so that WWW 2.0 might represent not only an opportunity but also a challenge for vaccination decisions [12]. This topic, in particular, is worthwhile to be studied in the future.

1860 to 1950 [34, 35], i.e., prior to when most immunization began. As for the risk of infection, the simple endemic SIR model with immunization at birth [3] suggests that for highly transmissible infection as measles, with a basic reproduction number about 15, a vaccine uptake of approximately 90 %, as was typical in many European countries during the last two decades, would create strong herd immunity by decreasing both the endemic prevalence and the risk of infection by about 30 times compared to the case of no vaccination. This straightforwardly yields the perception that the infection is no longer circulating. These numbers suggest that sanitation progress and mass immunization, two major factors underlying the changed relation between humans and their diseases, are now acting as "killers" of the perceived rewards of immunization [33]. In simple words it is the vaccine's success in controlling infections that promotes "rational" opposition, leading to declining vaccine coverage and potentially to infection reemergence.

The modeling of vaccination choices and rational opposition is currently a major topic of investigation in BE [8–10, 13, 29–33, 72, 85, 86]. Details about how vaccination choices can be incorporated into transmission models to capture the emergent population-level implications of vaccinating behavior will be presented in Sect. 5 of this overview.

4 Incubation of BE: Mathematical Forerunners, HIV/AIDS, and the Free-Rider Problem

The first mathematical epidemiology papers incorporating behavioral concepts date back to the end of the 1970s and were mainly motivated by mathematical questions, i.e., investigating extensions of the basic SIR model including nonlinear forces of infection. The first among such efforts [19] investigated the effects of a prevalence-dependent [44] contact rate, i.e., a contact rate reacting to the (perceived) prevalence of infective individuals, on the epidemic SIR model. To our knowledge, this is the first study including the concept of social distancing in epidemic modeling. Extensions of these ideas to endemic infections were developed shortly thereafter [67, 68].

However, the first great impulse to the development of behavioral epidemiology as a discipline was provided by the HIV/AIDS threat, beginning in the 1980s. The combination of a long incubation period, with difficult and costly treatment, and the lack of a vaccine have made instilling preventive behavior through the dissemination of information on risky behavior with respect to sexual or intravenous drug use the main control strategy, especially in poor resource settings.

In a situation almost completely lacking reliable data on individuals' responses to the spread of epidemics, mathematical modeling has rapidly become the main tool for understanding the effects of behavior change on HIV trajectories. The first contribution is [91], where the effects of switching from high to low risk behavior on the epidemic threshold parameter were investigated by a two-group model with preferred mixing, subsequently extended in [66], and estimated in [99].

In [15] data on HIV/AIDS in San Francisco are used to provide a model-based estimate of the decline in at-risk behavior required to eliminate, even in presence of a vaccine, the infection. The first warning on the possibility that a protective vaccine increases epidemic severity by raising at-risk behavior is also put forth. Several papers have used simple models to investigate the static and dynamic effects of various forms of behavioral responses including prevalence-dependent recruitment into the at-risk population and reducing contact rates after screening or treatment [50, 56, 105, 106]. The effects of prevalence-dependent sexual mixing patterns were investigated in [58]. A first attempt to integrate optimal choices of sexual partners into HIV transmission models is [64]. These are pioneering works of an endless list.

In parallel to the explosion of studies on behavior change in relation to HIV/AIDS, the first studies on vaccinating behavior appeared. In a seminal epidemiological paper, Fine and Clarkson [40] compare the different perspectives of the individual and the public good toward immunization and supply the first formulation of the result that under voluntary vaccination, rational individuals' decisions would most often yield a lower vaccine uptake than is optimal for the community as a whole. This result remained essentially unnoticed to epidemiological modelers until recent times and was independently rediscovered later by economists as well, but in relation to the debate between free market and compulsory immunization formulated as a free-rider problem. Immunization against a communicable infection by a vaccine that protects against infection has a twofold protective effect: a direct one for those who are immunized and an indirect one for those who are not, due to the reduced circulation of the virus in the community which reduces the risk of acquiring infection for those non-immunized. Free-riding arises when some individuals take advantage of this indirect protection (herd immunity) created by those who choose to be vaccinated, to avoid immunization and its related costs. In [18] the conditions under which free-riding can be overcome without compulsory vaccination, through taxes or subsidies, are investigated, while [41] departs from the problem investigated in [18] and shows that in a special case of SI infections the market and the government optimal solutions may be identical. Geoffard and Philipson [48] use an SIR model for a childhood infection with vaccine uptake dependent upon infection prevalence as a measure of perceived risk of infection, as empirically supported by analyses in [80], to offer the first proof of the supposed impossibility of eliminating infection under voluntary vaccination. The simple argument is that a successful immunization program will strongly reduce infection prevalence and therefore also reduce the perceived risk of disease, thereby killing the vaccine demand. These works formed the "humus" for the current outbreak of BE studies, discussed in the next section.

5 The "Epidemic Phase" of Behavioral Epidemiology

Behavioral epidemiology is arguably in an "epidemic phase," with many dozens of publications in the area in the past decade [2, 4, 6–11, 13, 16, 17, 21, 23–27, 29–33, 36, 37, 42–44, 46, 62, 63, 72, 79, 81–86, 89, 93–95, 101, 104, 109]. This attention

has come primarily from biomathematicians and theoretical biologists, for whom an interest in behavioral epidemiology comes naturally due to their long-standing involvement in both mathematical epidemiology [53] and evolutionary game theory [71]. It is also possible that the MMR vaccine scare of the late 1990s and the oral polio vaccine (OPV) scare early in the twenty-first century contributed to this surge of interest [57].

Some of this development has been described in recent review papers [13,44,63]. Here, we provide a broad overview of the behavioral epidemiology literature in the past ten years, starting with a discussion of the broad range of approaches that have been adopted.

5.1 Model Taxonomy

Funk et al. suggest that the literature can be classified in terms of (1) source of information used by decision-makers, (2) type of information used by decision-makers, and (3) effect of behavioral change [44]. For example, decision-makers may either base their decisions on global sources of information available to everyone (television, World Wide Web) [7, 8, 11, 21, 24, 27, 31, 32, 37, 46, 62, 86, 101, 104], or they may base their decisions on local sources available only to a subset of the population (such as information passed through word of mouth between acquaintances) [4, 36, 37, 43, 79, 89, 93, 109]. Likewise, decision-makers may base their decisions on perfect knowledge of disease prevalence [4, 7, 9, 11, 21, 27, 31, 32, 46, 79, 86, 93, 104, 109], and/or they may base their decisions on sources completely independent from prevalence or base only loosely on prevalence, such as peer opinions or faulty media representations [8, 24, 36, 37, 43, 62, 89, 101]. Finally, the effect of behavioral change may be to change individual disease states [7–9, 11, 21, 24, 31, 32, 36, 46, 79, 86, 89, 104], model parameters [4, 27, 37, 43, 62, 101] or contact structure [37, 84, 93, 109].

One could also distinguish the literature by the intervention concerned. For instance, the majority of papers are specifically concerned with vaccinating behavior, although some papers are concerned with social distancing [43, 84, 93, 109] or antiviral drugs [100]. Some models are intended for specific diseases, such as influenza [17, 46, 94, 104], smallpox [6, 11, 27], or human papillomavirus [7], while many models are intended to be more general [8, 9, 16, 21, 36, 43, 72, 86, 93].

Earlier models in behavioral epidemiology tended to be either mechanistic with respect to transmission and phenomenological with respect to behavior [19] or mechanistic with respect to behavior and phenomenological with respect to transmission [40], whereas more recent models represent both behavior and transmission mechanistically. If mechanistic with respect to both, they have sometimes been termed “behavior-prevalence” or “behavior-incidence” models, because the full mechanistic model is formed by coupling two independent mechanistic submodels, one for behavior and one for transmission [13, 63].

Mechanistic transmission models are often deterministic compartmental models, although there is also a distinct subset of the literature concerned with contact networks [26, 42, 43, 79, 93, 109]. Likewise, mechanistic behavioral models may be based on theory about behavior or perception stemming from psychology [4, 8, 16, 24, 26, 27, 29, 42, 43, 79, 93], and/or some of these approaches may be specifically game theoretical, assuming that individuals act to rationally optimize their own payoffs [9, 11, 72, 83, 84, 86, 94]. In the next two sections, we describe two examples of behavior-incidence models, the first of which represents a game theoretical approach to behavioral epidemiology.

5.2 A Game Theoretical Example

Game theoretical approaches specify a game that entails strategic interactions between individuals, and identify the Nash equilibrium of the game. When each player is playing their Nash equilibrium strategy, no player can obtain a higher payoff by switching to another strategy. Therefore, a population at the Nash equilibrium is expected to remain there. We note that one can furthermore define a convergently stable Nash equilibrium, meaning that a population whose initial conditions place it away from the Nash equilibrium will eventually converge to the Nash equilibrium and stay there [9]. Many behavioral epidemiological approaches are akin to game theory, in that they describe scenarios where strategic interactions exist and they specify payoffs [40, 43, 79, 93], but strictly speaking they are not game theoretical unless they specify a game and identify its Nash equilibria (or its evolutionarily stable states [71] or similar such solutions).

5.2.1 Model Description

An example of an approach to behavioral epidemiology that combines a game theoretical model of human behavior with a mechanistic disease transmission model is the simple vaccination game for pediatric infectious diseases, appearing in [9]. This game captures many of the basic features of mechanistic approaches to behavioral epidemiology modeling. We explain the game and its Nash equilibrium intuitively as follows. The game is a population game where individuals play against the outcome of the average behavior of the population. Individuals can either vaccinate or not vaccinate. The payoff to vaccinate is $-r_v$, where r_v is the vaccine cost, i.e., the perceived probability of complications due to vaccine (the payoff is negative because maximizing payoff is the same as minimizing adverse health impacts). The parameter r_v could equally well be interpreted as being the financial costs plus monetized health costs due to complications. This payoff function implies that the vaccine is perfectly efficacious, because the individual only pays the one-time cost r_v upon vaccinating and never any infection cost. The payoff

not to vaccinate is $-r_i\pi(p)$, where $\pi(p)$ is the perceived lifetime probability that a nonvaccinator becomes infected if the vaccine coverage in the population is p and r_i is the perceived probability of significant morbidity if a nonvaccinator ends up getting infected. We suppose that $\pi(p)$ is strictly decreasing in p and that $\pi(p_{crit}) = 0$ for some $p_{crit} < 1$, due to herd immunity. We allow individuals to adopt a mixed strategy to vaccinate with probability P, where $0 \leq P \leq 1$. At a steady-state equilibrium in a population where everyone is playing P, we note that $p = P$.

5.2.2 Finding the Nash Equilibrium

Suppose first that $r_v \geq r_i\pi(0)$, such that the cost to vaccinate exceeds the cost not to vaccinate, even if no one else is vaccinating and hence the infectious disease is rampant. Then $P^* = 0$ is the Nash equilibrium: suppose that everyone is playing $P^* = 0$; then, a small group considering switching to a strategy $Q > P^*$ would, as a result of their actions, increase the vaccine coverage slightly; this would decrease the probability that nonvaccinators are infected since $\pi(p) < \pi(0)$ for all $p > 0$, and meanwhile, the payoff to vaccinate would remain unchanged; thus, by starting to vaccinate with a higher probability, the small group would only worsen their payoff by changing strategies; as a result, there is no incentive for anyone to start vaccinating and so $P^* = 0$ is the Nash equilibrium when $r_v \geq r_i\pi(0)$.

Now suppose that $r_v < r_i\pi(0)$. In this case, the Nash equilibrium occurs at P^* such that the payoff to vaccinate equals the payoff not to vaccinate, i.e., $-r_v = -r_i\pi(p^*)$ (where $P^* = p^*$). The reason for this lies in the fact that $\pi(p)$ must be strictly decreasing in p. Suppose in a population where everyone is playing P^* a small group of individuals considers playing $Q > P^*$. This would increase the overall vaccine coverage in the population slightly, meaning that the probability that a nonvaccinator is infected would be lower, meaning that the payoff not to vaccinate now exceeds the payoff to vaccinate. As a result, the small group would only receive a lower payoff if they switched to $Q > P^*$ and, if they are rational, would probably decide against that option. Similarly, at P^*, there is no incentive for anyone to start vaccinating with probability $Q < P^*$. Hence, we expect that a population existing at P^* would stay at P^*, where P^* satisfies $-r_v = -r_i\pi(P^*)$.

It is also possible to show that P^* is unique and locally convergently stable and that $p^* < p_{crit}$, such that the Nash equilibrium coverage is always below the threshold coverage at which the infection would be completely eliminated from the population. Because self-interested behavior thereby precludes eradication of a vaccine-preventable infection, this can be interpreted as a form of "free-riding," or equivalently, policy resistance [98]. Free-riding is a common prediction of behavioral epidemiological models, although exceptions occur (e.g., see [79, 94]). Much work in behavioral epidemiology is concerned with the extent of free-riding behavior and conditions for its emergence.

5.2.3 Introducing a Mechanistic Disease Transmission Model

By introducing a compartmental model such as the susceptible-infectious-recovered (SIR) model with births and deaths, it becomes possible to specify a function form for $\pi(p)$ and thus make quantitative predictions of the Nash equilibrium coverage. The SIR model equations are

$$\frac{dS}{dt} = \mu(1-p) - \beta SI - \mu S, \tag{1}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I, \tag{2}$$

$$\frac{dR}{dt} = \mu p + \gamma I - \mu R, \tag{3}$$

where S is the proportion of the population that is susceptible, I is the proportion infectious, R is the proportion recovered, μ is the mean birth and death rate, β is the mean transmission rate, $1/\gamma$ is the mean infectious period, and p is the vaccine coverage (assuming, for simplicity, that individuals are never infected before being vaccinated) [53]. From the equilibrium solutions of these equations we can determine $\pi(p)$ and thus p^* from $-r_v = -r_i\pi(p^*)$. For the pediatric infectious disease vaccination game using (1)–(3), the Nash equilibrium coverage p^* when $r_v < r_i\pi(0)$ is:

$$p^* = 1 - \frac{1}{R_0(1 - r_v/r_i)}, \tag{4}$$

suggesting that Nash equilibrium vaccine coverage in a population attempting to optimize their own health-related payoff is higher when the basic reproduction number R_0 is higher, when r_v is lower or when r_i is higher.

5.3 An Example Based on Imitation Processes

A contrasting, non-game theoretical approach appears in [8, 10]. In order to achieve the dynamic description required to capture temporally extended phenomena such as vaccine scares, the SIR equations with birth and death are modified by replacing a constant vaccine coverage p by a potentially time-varying vaccine coverage x, where x is determined by a differential equation capturing how individuals learn their strategic behaviors from others:

$$\frac{dS}{dt} = \mu(1-x) - \beta SI - \mu S, \tag{5}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I, \tag{6}$$

$$\frac{dR}{dt} = \mu x + \gamma I - \mu R, \tag{7}$$

$$\frac{dx}{dt} = kx(1-x)\left[-r_v + r_i m I\right]. \tag{8}$$

In these equations, all parameters and variables are as in Sect. 5.3, except x is the proportion of the population favoring vaccination at time t, m is the sensitivity of individuals to prevalence I (where higher values of m mean that individuals perceive the disease as more harmful), and k quantities are the combined rate at which individuals sample others and probability of switching strategies if they find that others are receiving a higher payoff for playing the other strategy. The probability of switching strategies is proportional to the difference in the vaccinator payoff, $-r_v$, and the nonvaccinator payoff, $-r_i m I$. Individuals do not know their lifetime probability of being infected, but rather adopt a "rule of thumb" that the cost of not vaccinating is proportional to the current disease incidence I, hence the nonvaccinator payoff $-r_i m I$. Since $R = 1 - S - I$, we note that equation (7) can be dropped.

The analysis of [8] is not really game theoretical because the Nash equilibria were not identified and the focus was on dynamics away from equilibrium. This type of approach has been described as a game dynamic approach, since it describes how populations may evolve over time toward, or away from, Nash equilibria [55]. However, the model equations (5)–(8) nonetheless describe a situation where strategic interactions exist due to the feedbacks between vaccinating behavior and disease prevalence. And, in principle, connections exist and can be made between the equilibria of the model equations and Nash equilibria of the underlying game. For example, Lyapunov stable or asymptotically stable equilibria of the model equations can also be Nash equilibria under certain conditions [55].

Equations (5)–(8) exhibit a broad range of behavior, including a disease-free equilibrium where no one vaccinates ($I = x = 0$), a disease-free equilibrium where everyone vaccinates ($I = 0, x = 1$), an endemic equilibrium where a fixed proportion of the population vaccinates ($I > 0$, $x > 0$), an endemic equilibrium where no one vaccinates ($I > 0, x = 0$), and a stable limit cycle where x and I oscillate indefinitely (see Fig. 2) [74]. However, as before, because of free-riding behavior, vaccine coverage x never reaches the level p_{crit} that enables elimination of the infection. Variants of this model have been shown to provide parsimonious explanations of vaccine coverage and case notification data from vaccine scares in England and Wales, and in the deterministic regime the model also appears to have predictive power [10].

5.4 A Prevalence-Based Modeling Example

A contrasting approach appears in [31]. In order to achieve the dynamic description required to capture temporally extended phenomena such as changing levels of vaccine coverage over time, many approaches augment a compartmental model

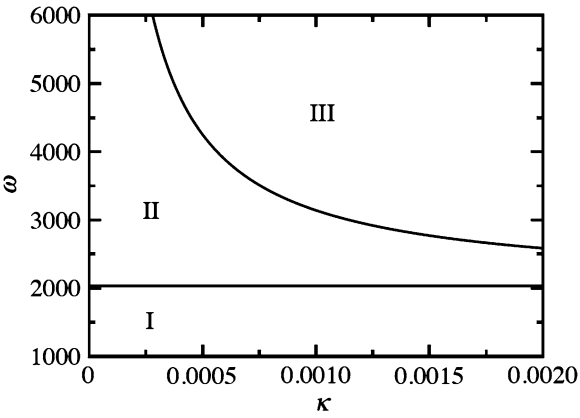

Fig. 2 The κ-ω parameter plane illustrating dynamics of model described by (5)–(8). $\kappa \equiv kr_v$ and $\omega \equiv mr_i/r_v$. I: stable endemic, pure nonvaccinator equilibrium. II: stable endemic, partially vaccinating equilibrium. III: stable limit cycle. Other parameters are $\mathscr{R}_0 = 10$, $1/\gamma = 10$ days, $1/\mu = 50$ years. Figure reproduced from [8]

by replacing a constant vaccine coverage by an information dependent, potentially time-varying vaccine coverage that captures how individuals make vaccinating decisions according to information about incidence or prevalence of infection:

$$\frac{dS}{dt} = \mu(1 - p(M)) - \mu S - \beta(t)SI, \tag{9}$$

$$\frac{dI}{dt} = \beta(t)SI - (\mu + \gamma)I, \tag{10}$$

$$\frac{dR}{dt} = \gamma I - \mu R, \tag{11}$$

$$\frac{dU}{dt} = \mu p(M) - \mu U. \tag{12}$$

Here, S, I, R, p, $\beta(t)$ and μ are as in Sect. 5.3 except β is potentially time-varying. U is the proportion of vaccinated individuals and M is an information variable governing the signal available to individuals as a function of prevalence or incidence of infection. Since $R = 1 - S - I - U$, we note that equation (7) can be dropped.

Rather than taking p from game theoretical considerations, in this approach, $p = p(M)$ where M depends directly on current or past states of the disease in the population. When depending on current states, the authors explore three possibilities for M:

- $M = \alpha\beta SI$: information governing vaccinating behavior depends on the current incidence, where α is a reporting rate.
- $M = kI$: information governing vaccinating behavior depends on the current prevalence, where k is a parameter subsuming aspects such as pathogenicity [8].
- $M = \alpha\beta I/(\mu + \alpha\beta I)$: information governing vaccinating behavior is a saturating function of current incidence [86].

In comparison, M can also depend on past states, such as according to

- $M(t) = \int_{-\infty}^{t} g(S(\tau), I(\tau))K(t-\tau)d\tau$,

where K governs memory decay. The parameter p can in turn depend upon M according to a constant term p_0 plus a saturating Michaelis–Menten function $p_1(M)$, for example:

$$p(M) = p_0 + p_1(M) = p_0 + \frac{CM}{DM+1}. \tag{13}$$

Strictly speaking, the analysis of [31] is not game theoretical because Nash equilibria are not identified. However, this type of approach might potentially be described as a game dynamic approach, since it may describe how populations may evolve over time toward, or away from, Nash equilibria [55]. The model equations (5)–(8) nonetheless describe a situation where strategic interactions exist due to the feedbacks between vaccinating behavior and disease prevalence. And, in principle, connections exist and can be made between the equilibria of the model equations and Nash equilibria of the underlying game. For example, Lyapunov stable or asymptotically stable equilibria of the model equations can also be Nash equilibria under certain conditions [55].

Equations (5)–(8) exhibit a broad range of behavior, including fixed points and stable limit cycles where vaccine uptake and disease prevalence oscillate over time in a "boom-bust" cycle, even when memory decays exponentially. Hence, as a result of information-dependent vaccination, the globally asymptotically stable endemic equilibrium of the basic SIR equations is often destabilized. Moreover, as in Sect. 5.3, for p_0 sufficiently small, vaccine coverage p can never be sustained at the level p_{crit} that enables elimination of the infection because of "free-riding behavior" or equivalently "rational exemption." Under some assumptions, it is also possible to derive an expression for the classic interepidemic interval in the presence of information-dependent vaccination [31].

6 Concluding Comments

The growth in the behavioral epidemiology literature has been significant, but what will be required for this "epidemic" to become an "endemic?" In order that this approach becomes an established part of applied mathematics and theoretical biology, we suggest that one potential future course for these models involves greater realism in how behavior is captured in the models, greater realism in transmission processes, and closer integration of models and data [7, 10, 38, 46, 82, 94]. Other answers to this question will appear in the following pages, and these directions by no means exhaust how the field can be further developed. Incorporating greater realism in transmission processes should come easily to the mathematical epidemiologists; however, incorporating greater realism into models of vaccinating behavior will require closer collaboration with psychologists, sociologists, epidemiologists, and economists.

References

1. Allen, T., Heald, S.: J. Int. Dev. **16**, 1141 (2004)
2. Althouse, B.M., Bergstrom, T.C., Bergstrom, C.T.: Proc. Natl. Acad. Sci. USA **107**, 1696 (2009)
3. Anderson, R.M., May, R.M.: Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford (1991)
4. Bagnoli, F., Lio, P., Sguanci, L.: Phys. Rev. E **76**, 061904 (2007)
5. Bajardi, P., Poletto C., Ramasco, J.J., Tizzoni, M., Colizza, V., Vespignani, A.: PLOS ONE **6**, e16591 (2011)
6. Barrett, S.: Public Choice **130**, 179 (2007)
7. Basu, S., Chapman, G., Galvani, A.: Proc. Natl. Acad. Sci. USA **105**, 19018 (2008)
8. Bauch, C.T.: Proc. R. Soc. Lond. B **272**, 1669 (2005)
9. Bauch, C.T., Earn, D.J.D.: Proc. Natl. Acad. Sci. USA 101, 13391 (2004)
10. Bauch, C.T., Bhattacharyya, S.: PLoS Comput. Biol. **8**, e1002452 (2012)
11. Bauch, C.T., Galvani, A.P., Earn, D.J.D.: Proc. Natl. Acad. Sci. USA **100**, 10564 (2003)
12. Betsch, C., Brewer, N.T., Brocard, P., Davies, P., Gaissmaier, W., Haase, N., Leask, J., Renkewitz, F., Renner, B., Reyna, V.F., Rossmann, C., Sachse, K., Schachinger, A., Siegrist, M., Stryk, M.: Vaccine **30**, 3727 (2012)
13. Bhattacharyya, S., Bauch, C.T.: Hum. Vaccin. Immunother. **8**, 842 (2012)
14. Bloom, D., Cannings, D.: World Econ. **5**, 57 (2004)
15. Blower, S.M., McLean, A.R.: Science **265**, 1451 (1994)
16. Brauer, F.: BMC Public Health **11**(Suppl 1), S3 (2011)
17. Breban, R., Vardavas, R., Blower, S.: Phys. Rev. Lett. E **76**, 031127 (2007)
18. Brito, D., Sheshinski, E., Intriligator, M.: J. Pub. Econ. **45**, 69 (1991)
19. Capasso, V., Serio, G.: Math. Biosci. **42**, 43 (1978)
20. CDC: SARS. http://www.cdc.gov/sars
21. Chen, F.: J. Math. Biol. **53**, 253 (2006)
22. Chen, R.T., Orenstein, W.A.: Epidemiol. Rev. **18**, 99 (1996)
23. Chen, F., Cottrell, A.: J. Biol. Dyn. **3**, 357 (2009)
24. Coelho, F.C., Codeco, C.T.: PLoS Comput. Biol. **5**, e1000425 (2009)
25. Cojocaru, M.G., Bauch, C.T., Johnston, M.D.: Bull. Math. Biol. **69**, 1453 (2007)
26. Cornforth, D.M., Reluga, T.C., Shim, E., Bauch, C.T., Galvani, A.P., Meyers, L.A. PLoS Comput. Biol. **7**, e1001062 (2010)
27. Del Valle, S., Hethcote, H., Hyman, J.M., Castillo-Chavez, C.: Math. Biosci. **195**, 228 (2005)
28. Diekmann, O., Heesterbeek, J.A.P.: Mathematical Epidemiology of Infectious Diseases. Springer, Berlin (2000)
29. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **256**, 473 (2009)
30. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **264**, 237 (2010)
31. d'Onofrio, A., Manfredi, P., Salinelli, E.: Theor. Pop. Biol. **71**, 301 (2007)
32. d'Onofrio, A., Manfredi, P., Salinelli, E.: Math. Med. Biol. **25**, 337 (2008)
33. d'Onofrio, A., Manfredi, P., Poletti, P.: J. Theor. Biol. **273**, 63 (2011)
34. Duncan, C.J., Duncan, S.R., Scott, S.: Theor. Pop. Biol. **52**, 155 (1996)
35. Duncan, C.J., Duncan, S.R., Scott, S.: Epidemiol. Infect. **117**, 493 (1996)
36. Eames, K.T.D.: J. R. Soc. Interface **6**, 811 (2009)
37. Epstein, J.M., Parker, J., Cummings, D., Hammond, R.A.: PLoS ONE **3**, e3955 (2008)
38. Ferguson, N.: Nature **446**, 733 (2007)
39. Ferguson, N.M., Cummings, D.A.T., Cauchemez, S., Fraser, C., Riley, S., et al.: Nature **437**, 209 (2005)
40. Fine, P., Clarkson, J.: Am. J. Epidemiol. **124**, 1012 (1986)
41. Francis, P.J.: J. Public Econ. **63**, 383 (1997)
42. Fu, F., Rosenbloom, D.I., Wang, L., Nowak, M.A.: Proc. R. Soc. Lond. B **278**, 42 (2011)
43. Funk, S., Gilad, C., Watkins, C., Jansen, V.A.A.: Proc. Natl. Acad. Sci. USA **106**, 6872 (2009)

44. Funk, S., Salathe, M., Jansen, V.A.A.: J. R. Soc. Interface **7**, 1247 (2010)
45. Galor, O., Weil, D.N.: Am. Econ. Rev. **89**, 150 (1999)
46. Galvani, A., Reluga, T., Chapman, G.: Proc. Natl. Acad. Sci. USA **104**, 5692 (2007)
47. Gangarosa, E.J., Galazka, A.M., Wolfe, C.R., Phillips, L.M., Gangarosa, R.E., et al.: Lancet **351**, 356 (1998)
48. Geoffard, P.-Y., Philipson, T.: Am. Econ. Rev. **87**, 222 (1997)
49. Ginsberg, J., Mohebbi, M.H., Patel, R.S., Brammer, L., Smolinski, M.S., et al.: Nature **457**, 1012 (2009)
50. Hadeler, K.P., Castillo-Chavez, C.: Math. Biosci. **128**, 41 (1995)
51. Hallett, T.B., Gregson, S., Mugurungi, O., Gonese, E., Garnett, G.P.: Epidemics **1**, 108 (2009)
52. Halperin, D.T., Mugurungi, O., Hallett, T.B., Muchini, B., Campbell, B., Magure, T., Benedikt, C., Gregson S.: PLoS Med. **8**, 061904 (2012)
53. Hethcote, H.: SIAM Rev. **42**, 599 (2000)
54. Hethcote, H.W., Yorke, J.A.: Gonorrhea. Transmission Dynamics and Control. Springer, Berlin (1984)
55. Hofbauer, J., Sigmund, K.: Evolutionary Games and Population Dynamics. Cambridge University Press, Cambridge (1998)
56. Hsieh, Y.H.: IMA J. Math. Appl. Med. Biol. **13**, 151 (1996)
57. Hughes, V.: Nature Med. **12**, 1228 (2006)
58. Hyman, J.M., Li, J.: SIAM J. Appl. Math. **57**, 1082 (1997)
59. Iozzi, F., Trusiano, F., Chinazzi, M., Billari, F.C., Zagheni, E., et al.: PLoS Comput. Biol. **6**, e1001021 (2010)
60. Jansen, V.A.A., Stollenwerk, N., Jensen H.J., Ramsay, M.E., Edmunds, W.J., Rhodes, C.J.: Science **301**, 804 (2003)
61. Kermack, W.O., McKendrick, A.G.: Proc. R. Soc. Lond. A **115**, 700 (1927)
62. Kiss, I.Z., Cassell, J., Recker, M., Simon, P.L.: Math. Biosci. **225**, 1–10 (2009)
63. Klein, E., Laxminarayan, R., Smith, D.L., Gilligan, C.A.: Env. Dev. Econ. **12**, 707 (2007)
64. Kremer, M.: Q. J. Econ. **111**, 549 (1996)
65. Kuo, H.-I., Chen, C.-C., Tseng, W.-C., Ju, L.-F., Huang, B.-W.: Tour. Mgmt. **29**, 917 (2008)
66. Li, J.: Math. Comput. Model. **16**, 103 (1992)
67. Liu, W.M., Levin S.A., Iwasa Y.Y.: J. Math. Biol. **23**, 187 (1986)
68. Liu, W.M., Hethcote, H.W., Levin S.A.: J. Math. Biol. **25**, 359 (1987)
69. LiviBacci, M.: A Concise History of World Population. Blackwell, Oxford (2005)
70. Luman, E.T., Fiore, A.E., Strine, T.W., Barker, L.E.: J. Am. Med. Assoc. **291**, 2351 (2004)
71. Maynard-Smith, J.: Evolution and the Theory of Games. Cambridge University Press, Cambridge (1982)
72. Manfredi, P., Della Posta, P., d'Onofrio, A., Salinelli, E., Centrone, F., Meo, C., Poletti, P.: Vaccine **28**, 98 (2009)
73. Merler, S., Ajelli, M., Pugliese, A., Ferguson, N.M.: PLoS Comput. Biol. **7**, e1002205 (2011)
74. Montopoli, L., Bhattacharyya, S., Bauch, C.T.: Can. Appl. Math. Q. **17**, 317 (2009)
75. Mossong, J., Hens, N., Jit, M., Beutels, P., Auranen, K., et al.: PLoS Med. **5**, e74 (2008)
76. Omran, A.R.: Milbank Mem. Fund. Q. **49**, 509 (1971)
77. Parkhurst, J.O.: Lancet **360**, 9326 (2002)
78. Pearce, A., Law, C., Elliman, D., Cole, T.J., Bedford, H.: Br. Med. J. **336**, 754–757 (2008)
79. Perisic, A., Bauch, C.T.: PLoS Comput. Biol. **5**, e1000280 (2009)
80. Philipson, T.: J. Hum. Res. **31**, 611 (1996)
81. Poletti, P., Caprile, B., Ajelli, M., Pugliese, A., Merler, S.: J. Theor. Biol. **260**, 31 (2009)
82. Poletti, P., Ajelli, M., Merler, S.: PLoS ONE **6**, e16460 (2011)
83. Reluga, T.: J. Biol. Dynamics **3**, 515 (2009)
84. Reluga, T.: PLoS Comput. Biol. **6**, e1000793 (2010)
85. Reluga, T., Galvani, A.P.: Math. Biosci. **230**, 67 (2011)
86. Reluga, T., Bauch, C.T., Galvani, A.: Math. Biosci. **204**, 185 (2006)
87. Rizzo, C., Rota, M.C., Bella, A., Giannitelli, S., De Santis, S., et al.: Euro Surveill. **15**, 49 (2010)

88. Ross, R.: Proc. Royal Soc. London **92**, 204 (1916)
89. Salathe, M., Bonhoeffer, S.: J. Roy. Soc. Interface **5**, 1505 (2008)
90. Salmon, D.A., Teret, S.P., MacIntyre, C.R., Salisbury, D., Burgess, M.A., et al.: Lancet **367**, 436 (2006)
91. Scalia-Tomba, G.: Math. Biosci. **107**, 547 (1991)
92. Scudo, F.M., Ziegler, J.R.: The golden age of theoretical ecology: 1923–1940. Lecture Notes Biomathematics, vol. 22. Springer, Berlin (1978)
93. Shaw, L.B., Schwartz, I.B.: Phys. Rev. E **77**, 066101 (2008)
94. Shim, E., Chapman, G.B., Townsend, J.P., Galvani, A.P.: J. Roy. Soc. Interface **9**, 2234 (2012)
95. Smith, D.L., Levin, S.A., Laxminarayan, R.: Proc. Natl. Acad. Sci. USA **102**, 3153 (2005)
96. Solomon, J., Murray, C.J.L.: Popul. Dev. Rev. **28**, 205 (2002)
97. Staiano, J.: ESSAI: **6** (2008). http://dc.cod.edu/essai/vol6/iss1/46(lastvisit24/10/2012).
98. Sterman, J.: Am. J. Public Health **96**, 505 (2006)
99. Stigum, H., Magnus P., Bakketeig L.S.: Am. J. Epidemiol. **145**, 644 (1997)
100. Sun, P., Yang, L., de Vericourt, F.: Oper. Res. **57**, 1320 (2009)
101. Tanaka, M.M., Kumm, J., Feldman, M.W.: Theor. Popul. Biol. **62**, 111 (2002)
102. The Editors Of The Lancet "Retraction—Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children". Lancet **375**, 445 (2010) DOI: 10.1016/S0140-6736(10)60175-4
103. United Nations: Changing Levels and Trends in Mortality: the role of patterns of death by cause. UN (2012)
104. Vardavas, R., Breban, R., Blower, S.: PLoS Comput. Biol. **3**, e85 (2007)
105. Velasco-Hernandez, J.X., Hsieh, Y.: J. Math. Biol. **32**, 233 (1994)
106. Velasco-Hernandez, J.X., Brauer, F., Castillo-Chavez, C.: IMA J. Math. Appl. Med. Biol. **13**, 175 (1996)
107. Wolfe, R.M., Sharp, L.K.: Br. Med. J. **325**, 430 (2002)
108. Zagheni, E., Billari, F.C., Manfredi, P., Melegaro, A., Mossong, J., et al.: Am. J. Epidemiol. **168**, 1082 (2008)
109. Zanette, D., Risau-Gusman, S.: J. Biol. Phys. **34**, 135 (2008)

Part I
Field Data on Behaviour

Survey on the Likely Behavioural Changes of the General Public in Four European Countries During the 2009/2010 Pandemic

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Abstract In order to assess the likely impact of public health interventions, it is important to predict the acceptance of control measures, as well as the behavioural changes that may occur among the general public in response to epidemics, in particular lethal ones. The emergence of 2009 pandemic allowed us to assess the general public's behaviour during the pandemic, via two surveys: one at the beginning and one after the first wave of the 2009 pandemic, in four European countries.Results showed some differences between participating countries in previous behaviours relating to seasonal flu and in beliefs and knowledge about 2009 pandemic influenza. No substantial differences were detected among the four countries in the first survey

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with respect to the intended behaviours in anticipation of the spread of the pandemic virus. However, results from the second survey showed differences within and among the four participating countries. The two surveys were useful in showing differences between behavioural intentions and actual actions related to the 2009 pandemic influenza. To our knowledge this is the first study investigating the actual behaviour of the population in four EU countries and provides crucial descriptions of pandemic impact on social-network dynamics parameters which can be included in mathematical models.

1 Background

Novel influenza viruses with pandemic potential have emerged every few decades, and the fear of rapid global transmission of a deadly pathogen, as experienced during the influenza pandemic in 1918, has shaped research and public health policies in this area. Moreover, in the last two decades, the emergence of health threats, such as the highly virulent avian A/H5N1 virus in 1997 [28], the SARS [3] in 2003 and the A/H1N1 pandemic influenza virus in 2009 [4], has made pandemic preparedness a crucial issue for public health worldwide especially with regard to population behaviour and population compliance with public health measures. Spontaneous behaviour change by the population, which alters transmission risk in a pandemic, may affect the impact of organized control measures. In fact, during outbreaks, one of the major problems has always been to communicate with the population in order to influence behaviours and reduce the spread of disease [2].

For centuries, the response strategy adopted by health authorities dealing with outbreaks was mainly based on restrictive non-pharmaceutical measures (quarantine, isolation, compulsory hospitalization) and, in case of non-adherence to response measures recommended, sanctions for non-compliant individuals (Balinska et al. 2009). The increasing recognition that human behaviour (compliance with recommended response measures) critically influences infectious disease transmission has led to a greater effort to communicate with the public and enlist their help in reducing disease transmission.

In March 2009 a new influenza virus emerged in Mexico [29] and rapidly spread around the world in the first influenza pandemic of the twenty-first century [6]. As the number of 2009 pandemic influenza cases increased and spread and as extensive media coverage and government advertising campaigns began to appear, the behaviour of the population changed [1]. Higher perceived risk of infection and higher perceived severity of infection were associated with greater use of recommended behaviours in the UK [24]. Other studies have examined the behavioural changes and initial response to the 2009 pandemic in China [30], Hong Kong [5], India [16] and Europe [12] and internationally [15].The FluModCont project, a collaborative project funded by the Seventh Framework Programme (FP7), started in 2008 and ended in May 2011 (www.flumodcont.org). Main objective of the project was to arrive at an accurate and data-based modelling of the expected

course of an influenza pandemic and of the impact of public health measures on its scale and severity. Aims of the project include the study of the social acceptability of public health measures during a pandemic and of the behavioural changes that are to be expected in such circumstances. Within the FluModCont project we investigated how populations would react to respond to and comply with interventions foreseen in national pandemic preparedness plans, which aim to produce accurate and data-based modelling of the potential course of an influenza pandemic and of the impact of public health measures on its scale and severity.

A cross-sectional survey had been planned among adults in four EU countries: Finland, Italy, Romania and the UK. As the 2009 pandemic influenza virus began to spread in EU countries during the development of the common questionnaire for the survey, we decided to conduct two surveys at different times in order to assess behaviour during the pandemic. In particular, the objectives of the surveys were to investigate behavioural responses and social acceptance of mitigation measures, and to assess the reliability and validity of behavioural intentions regarding public health interventions, declared at the beginning of the 2009 influenza pandemic, through comparison with real behavioural responses to the 2009 pandemic, at the end of the pandemic wave in 2010 in order to obtain behavioural relevant parameters to be included in modelling the expected course of an influenza pandemic.

2 Materials and Methods

2.1 Sampling Procedures

In Italy, Romania and the UK, a two-stage stratified sampling with unequal probabilities of sampling was used: (1) a stratified sample of household telephone lines was selected through random digit dialling (RDD); (2) the adult (18 years or over) with the most recent birthday (to the date of the interview) was selected from each sampled household according to predefined quota (Table 1). A detailed study protocol was prepared and distributed to the four participating countries.

Table 1 Sample description of the two FluModCont surveys conducted

	Number of respondents successfully interviewed		Proportion of re-contacted individuals in the 2nd survey (%)	Response rate (%)	
Country	1st survey	2nd survey		1st survey	2nd survey
Finland	681	683	73	42	–
Italy	1,025	1,025	32	12	–
Romania	1,025	1,025	43	37	–
UK	1,025	1,000	24	15	–

In order to mitigate the fact that certain social groups are more likely to be at home (i.e. older people and women) and so may be over-represented in the eventual sample, the interviewers were instructed, in case the household member with the most recent birthday was not at home, to skip to the next household instead of replacing him/her with another household member. Moreover, in order to reduce this possible bias, the interviews were conducted between 6.00 PM and 8.00 PM, when people are more likely to be at home. The sample size for these three countries was fixed at 1,025 individuals in order to estimate a compliance of 80 % for the main behaviour measures with a precision of ±3 %, while assuming a confidence level equal to 95 % and in order to improve standard variance estimators in health surveys, based on previous studies, a design effect equal to 1.5 [13].

In Finland, a simple random sampling of adults from the population register with a link to telephone numbers was used. The sample size, under the same assumptions made for the other three countries with the exception of design effect, was fixed at 683 individuals. For the second survey we planned to re-contact the sample of the 1st survey and depending on the response rate in each participating country to 'top up' the sample using an identical sampling procedure as used in the initial sample until we reached n=1025 for Italy, Romania and UK (two stage stratified sampling), and n=683 for Finland.

2.2 Data Collection

The surveys were conducted in comparable period of time in the four countries (Fig. 1) and were conducted by market research companies in each country.

The interviews for the first survey were conducted using a four-stage questionnaire to collect information on (1) health status and behaviour during seasonal influenza, (2) beliefs and level of knowledge about the new A/H1N1 influenza, (3) behavioural intentions (i.e. social distancing measures, pre-pandemic vaccination and attitude to use antivirals) according to different scenarios of disease severity (worst and mild) and (4) socio-demographic characteristics. Beliefs, knowledge and behavioural responses were measured on 4-point Likert scales.

For the second survey a second specific questionnaire based on the first one was developed including questions on actual behavioural responses to the A/H1N1 pandemic (experience of taking pandemic vaccine and antiviral medications, following public health advice, isolation at home).

Before the surveys, the questionnaires, originally developed in English, were translated into the languages of the population to be surveyed and then back-translated by a different native speaker to verify consistency. The questionnaires were pretested for qualitative purposes on a small number of participants (from 10 to 15) in all the four countries involved in the studies.

All individuals recruited in the first survey were re-contacted and requested to answer to the second; in case of refusal, new household telephone lines were randomly selected using the RDD methodology above described (Table 2).

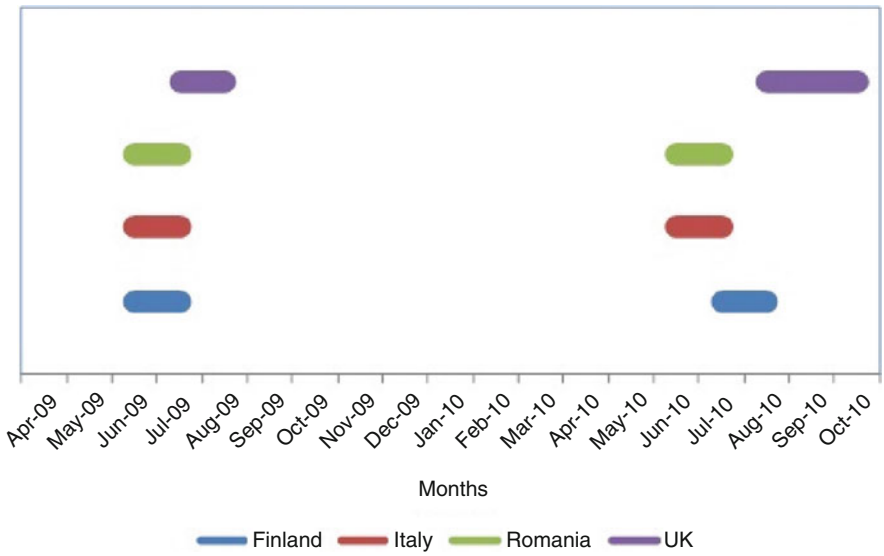

Fig. 1 Timing of the behavioural surveys

The study protocol and the standard questionnaires have been revised in order to be applicable and conform to ethical standards in all countries for both surveys.

2.3 Data Analysis

Data were checked for validity of values, ranges and consistency, cleaned and made anonymous at the research centre of each participating country. The databases were then sent to the coordinating research centre in Italy for analysis.

For both surveys in Italy, Romania and the UK, the individual probability to be sampled, based on the number of adult household members and the number of working telephone lines available in the household, has been considered for data weighting. Moreover, data were also weighted to reflect the socio-demographic structure of the national adult populations. No weights were applied to data collected in Finland.

Variables measured on 4-point Likert scales were re-coded into two categories for the analysis (e.g. "very likely" and "fairly likely" were grouped together in a unique category, as well as "not very likely" and "not at all likely"). Values coded as "don't know" were considered as "negative" outcomes (e.g. "no", "unlikely", "not willing") and included in the analysis, while missing values and values coded as "not applicable" were excluded from the analysis.

Univariate analysis was performed using percentages and 95 % confidence interval (CI). Differences between percentages estimated in 2009 and those estimated

in the whole sample in 2010 were evaluated using logistic regression models while controlling for sex, age, education, occupation, level of information about "swine flu", and household composition (when appropriate) as potential confounders.

For Italy, Romania and the UK, the analysis was conducted accounting for survey design and data weighting in order to improve standard variance estimators [13]. The post-survey estimate of the average design effect among the main outcome measures for these three countries was 1.53, 1.51, and 1.81, respectively, thus supporting the assumption made for sample size calculation.

The analysis was conducted using Stata 11.2 software (Stata Corporation, College Station, TX).

3 Results

3.1 Demographic Characteristics

Table 1 shows the sample sizes and response rates for the two surveys. The response rates, calculated as the percentage of valid interviews out of the valid interviews plus refusals and missed appointments during the first survey, varied across countries, as did the percentage of the successfully re-contacted individuals in the second survey.

The socio-demographic characteristics of respondents (shown in Table 2) were similar among the four countries in both surveys, except for religion (about 50 % of respondents in the UK described themselves as religious compared with more than 80 % in the other countries) and household composition (almost 30 % of respondents in Finland were single compared with about 10 % or less in the other three countries). Most of the respondents in all countries in both surveys had a secondary level of education and about half said that they were working at the time of interview and living in a household with no children.

3.2 Past Behaviour and Beliefs

During the 2009 survey, respondents from Italy and Romania reported having sought medical advice last time they had flu more frequently than respondents from the UK and Finland, mainly through home visit by or visit to a doctor.

About one-third of respondents in Italy, Romania and the UK and about two-thirds in Finland had the seasonal flu vaccine in the past. Those who had never had the seasonal flu vaccine reported their low likelihood of catching flu and their good health status as the main reasons for this.

In case of need, most of the respondents to the 2009 survey from all the four countries said they would seek health advice about swine flu from their local GP/nurse and other local and national health authorities. However, about half of

Table 2 Socio-demographic characteristics

	Italy		Romania		UK		Finland	
	2009	2010	2009	2010	2009	2010	2009	2010
	$n = 1,025$	$n = 1,025$	$n = 1,025$	$n = 1,025$	$n = 1,025$	$n = 1,000$	$n = 681$	$n = 683$
	%		%		%		%	
Sex								
Male	48.0	48.8	49.2	49.7	47.7	49.8	45.7	45.4[a]
Female	52.0	51.2	50.8	50.3	52.3	50.2	54.3	54.6[a]
Age group								
18–34 years	23.7	30.1	35.7	33.3	35.2	34.5	19.5	19.5[a]
35–54 years	40.3	34.5	36.1	35.1	35.2	36.4	31.7	31.4[a]
55–74 years	27.7	27.1	25.2	28.9	24.9	29.1	48.5	47.6[a]
75 years	8.3	8.3	3.0	2.7	4.7		0.3	1.6[a]
Education								
Primary or lower	11.8	13.8	3.4	2.5	13.8	16.3	23.5	23.3
Secondary	73.1	71.6	64.3	61.5	53.2	48.3	38.0	40.5
University or higher	15.1	14.6	32.3	36.0	33.0	35.4	38.5	36.1
Religion								
Christian	91.0	89.4	94.0	91.3	48.7	50.1	82.4	85.1[a]
Other	0.7	0.2	5.2	7.5	18.8	18.4	2.1	2.2[a]
None	8.3	10.4	0.8	1.2	32.5	31.5	15.5	12.7[a]
Occupational status								
Working	57.5	59.1	48.6	44.6	63.3	67.7	53.2	50.5
Not working	34.9	34.0	41.5	46.1	32.1	28.0	43.2	47.4
Student	7.6	6.9	9.9	9.3	4.6	4.3	3.6	2.1
Household composition								
Single	5.6	4.0	3.8	3.8	10.0	11.2	26.7	25.2
Only adults	65.9	69.6	58.2	59.2	58.3	53.9	50.8	53.3
With children	28.5	26.4	38.0	37.0	31.7	34.9	22.5	21.5
Weekly time spent away from home for working/studying								
None	34.1	NA	35.9	NA	33.7	NA	44.0	NA
<35 h	19.6	NA	15.7	NA	33.7	NA	14.3	NA
35–44 h	22.2	NA	26.2	NA	21.2	NA	35.4	NA
≥45 h	24.1	NA	22.2	NA	11.4	NA	6.3	NA
Availability towork/study fromhome for 7–10 days[b]								
Yes	24.6	NA	32.1	NA	29.4	NA	23.7	NA
No	75.2	NA	66.3	NA	70.5	NA	74.1	NA
Don't know	0.2	NA	1.6	NA	0.1	NA	2.1	NA

NA not available

[a]Percentages among the 185 new respondents in Finland (data not available for the 498 old respondents)

[b]Among those who reported to work/study some time in a week away from home

the respondents from the UK and Finland also reported the media and internet as a source of information, thus partly explaining the fact that they were more likely to perceive themselves as well informed about A/H1N1 than respondents from Italy and Romania. Subsequently, during the 2010 survey, respondents from Finland, Romania and the UK were less likely to report that their local GPs and nurse were their main source of information about swine flu, with the media being a more prominent source (proportion reporting the media: 26.9 % vs. 77.0 % in Finland; 7.2 % vs. 55.8 % in Romania; and 16.3 % vs 67.6 % in the UK in 2009 and 2010, respectively) (Table 3). Most respondents in all countries thought that, in case of need, it would be possible to get antiviral medication through a chemist (with or without a GP prescription), hospitals or health authorities.

The proportion of individuals worried about catching swine flu during both surveys is reported in Fig. 2. The level of worry significantly decreased in Italy and Finland, remained stable in Romania and increased in the UK from 2009 to 2010.

3.3 Behavioural Intentions

In all countries, about 70–80 % of respondents, during the 2009 survey, stated they would get vaccinated against swine flu and would take antivirals as precautionary measure, assuming both treatments were free of charge (Table 3). A higher proportion of respondents would be willing to give the same treatments to their children if recommended by health authorities. In 2010, the proportion of respondents reporting to be willing to take the antiviral drugs as a preventive measure significantly decreased to 36.7 % in Italy and 68.8 % in the UK, while remaining stable at about 70 % in Romania and Finland.

Concerning non-pharmaceutical measures, approximately 63 % (range 56–66 %) of respondents to the first survey in each country reported spending some time away from home for working/studying and, among them, approximately 27 % (range 24–32 %) would be able to stay at home for 7–10 days if needed (Table 2). Of these more than 80 % of both singles and respondents living with other persons stated they would be available to stay at home for 7–10 days, if recommended by health authorities; this was true both if they had been in contact with someone who has swine flu or if they had themselves symptoms of swine flu. More than 70 % of respondents living with other people said they would be able to isolate a sick adult from other household members in a separate room, and about half of single respondents reported that they would be able to find someone to take care of them for 7–10 days if they caught swine flu.

During 2009, more than 60 % would take time off from work/school for 7–10 days in case of symptoms, as recommended by health authorities. These proportions significantly increased in Romania and the UK in the 2010 survey to 70 % and 71 %, respectively.

Furthermore, about 80 % stated they would stay away and keep children away from large gatherings if the new influenza outbreak spread, with no significant

Table 3 Comparison between 2009 and 2010 data reported by all respondents

	Italy		Romania		UK		Finland	
	(2009: $n = 1,025$) (2010-all resp.: $n = 1025$) (2010-old resp.=328) (2010-new resp.=697)		(2009: $n = 1,025$) (2010-all resp.: $n = 1,025$) (2010-old resp.=442) (2010-new resp.=583)		(2009: $n = 1,025$) (2010-all resp.: $n = 1,000$) (2010-old resp.=247) (2010-new resp.=753)		(2009: $n = 681$) (2010-all resp.: $n = 683$) (2010-old resp.=498) (2010-new resp.=185)	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
Previous flu and vaccination								
Ever had flu	82.9	79.8–85.5	95.4	93.6–96.7	76.8	73.0–80.2	63.1	59.4–66.8
Took time off of work/school last time with flu[a,b]	77.1	72.6–81.0	28.3	24.2–32.8	56.4	51.2–61.5	63.2	58.6–67.8
Sought medical advice last time with flu[a]	71.1	67.0–74.9	60.8	56.8–64.6	37.9*	32.8–43.2	38.8	34.2–43.5
Ever been offered the seasonal flu vaccine	52.8	48.9–56.5	51.5	47.5–55.4	45.8	41.6–50.0	55.8	52.1–59.5
Did have the seasonal flu vaccine	30.3	27.1–33.7	44.6	40.7–48.5	39.1	35.0–43.3	65.5	60.7–70.3
Belief and level of knowledge								
Heard of A/H1N1	97.1	95.2–98.3	98.2	96.6–99.1	91.9	89.2–94.0	100.0	95.4–100.0
Well informed about swine flu								
- 2009	51.5	47.7–55.2	55.2	51.2–59.1	88.4	85.1–91.0	91.6	89.5–93.7
- 2010 (whole sample)	62.5	58.3–66.5	65.7	61.8–69.4	81.1	77.5–84.1	96.9	95.6–98.2
- 2010 (previously interviewed)	67.8	60.0–74.8	68.3	62.5–73.6	88.1	82.6–92.0	97.2	95.7–98.6
- 2010 (newly interviewed)	60.2	55.1–65.0	63.6	58.2–68.6	79.0	74.8–82.7	96.2	93.4–99.0
Swine flu is transmitted only from someone who clearly shows symptoms								
- 2009	59.2	55.4–62.8	62.3	58.4–66.0	82.5	79.4–85.2	63.9	60.3–67.5
- 2010 (whole sample)[i]	44.0	39.8–48.3	53.1	49.0–57.2	65.7	62.2–69.1	46.9	43.0–50.7
- 2010 (previously interviewed)[i]	41.7	34.1–49.8	58.5	52.5–64.3	69.8	63.2–75.7	46.7	42.2–51.2
- 2010 (newly interviewed)[i]	44.9	39.9–50.1	48.7	43.1–54.3	64.5	60.3–68.5	47.2	39.8–54.6

(continued)

Table 3 (continued)

	Italy		Romania		UK		Finland	
	(2009: $n = 1,025$) (2010-all resp.: $n = 1025$) (2010-old resp.=328) (2010-new resp.=697)		(2009: $n = 1,025$) (2010-all resp.: $n = 1,025$) (2010-old resp.=442) (2010-new resp.=583)		(2009: $n = 1,025$) (2010-all resp.: $n = 1,000$) (2010-old resp.=247) (2010-new resp.=753)		(2009: $n = 681$) (2010-all resp.: $n = 683$) (2010-old resp.=498) (2010-new resp.=185)	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
Swine flu will become a serious problem in my country in the coming years	41.8	38.1–45.6	56.2	52.3–60.1	73.3	69.1–77.1	29.6	26.2–33.0
Catching swine flu while carrying daily life as usual is likely in case of outbreak								
- 2009	17.2	14.6–20.3	23.8	20.6–27.3	47.1**	42.8–51.5	16.5	13.7–19.3
- 2010 (whole sample)[i]	16.6	13.7–20.0	17.3	14.5–20.5	28.6	25.4–32.0	14.0	11.3–16.6
- 2010 (previously interviewed)[i]	21.0	15.3–28.1	18.4	14.3–23.5	29.1	23.0–36.1	12.7	9.7–15.7
- 2010 (newly interviewed)[i]	14.8	11.7–18.7	16.4	12.9–20.7	28.4	24.7–32.4	17.4	11.8–23.0
Catching swine flu is serious to own health								
- 2009	59.7	55.9–63.4	80.8	77.4–83.8	47.0**	42.7–51.4	59.9	56.2–63.6
- 2010 (whole sample)[i]	37.8	33.7–42.1	71.1	67.1–74.8	57.5	53.8–61.3	41.6	37.8–45.4
- 2010 (previously interviewed)[i]	38.1	30.2–46.6	77.4	72.2–81.8	55.6	48.5–62.5	41.9	37.4–46.3
- 2010 (newly interviewed)[i]	37.7	32.9–42.7	66.0	60.2–71.4	58.1	53.7–62.4	41.0	33.8–48.3
Actual behaviour								
Getting vaccinated against swine flu if free of charge	78.8	75.5–81.7	77.1	73.7–80.1	84.7	81.7–87.3	86.0	83.4–88.7
Getting children vaccinated against swine flu if free of charge and recommended by health authorities[d]								
- 2009	**91.6**	86.9–94.6	**81.3**	75.3–86.2	**87.6**	81.4–91.9	90.8	86.2–95.5
- 2010 (whole sample)	NA	NA	**33.0**	26.5–40.3	**60.1**	52.8–67.0	NA	NA

- 2010 (previously interviewed)	NA	NA	42.5	32.5–53.3	66.0	47.7–80.6	NA	NA
- 2010 (newly interviewed)	**39.3**	n.d.	25.6	17.7–35.6	59.2	51.2–66.7	NA	NA
Taking antivirals as a precautionary measure if free of charge								
- 2009	**64.7**	60.9–68.2	69.3	65.6–72.8	**75.2**	71.4–78.6	74.7	71.5–78.0
- 2010 (whole sample)[i]	**36.7**	32.7–41.0	67.4	63.4–71.1	**68.8**	65.0–72.3	73.7	70.3–77.1
- 2010 (previously interviewed)[i]	39.4	31.5–47.9	71.1	65.4–76.1	72.6	65.9–78.5	77.4	73.6–81.2
- 2010 (newly interviewed)[i]	35.7	31.0–40.6	64.4	58.8–69.5	67.7	63.2–71.9	64.0	57.0–71.1
Giving antivirals to children as a precautionary measure if a member of the household is sick[d]	92.2	87.1–95.4	89.0	83.5–92.8	92.1	86.7–95.4	96.1	93.0–99.2
Staying at home for 7–10 days if the new influenza would spread	80.5	77.4–83.3	85.8	83.0–88.2	92.7***	89.9–94.7	96.3***	94.9–97.7
Keeping children away from large gatherings for 1 month if recommended[d]								
- 2009	83.5	76.3–88.8	86.5	80.8–90.7	70.6	62.5–77.6	82.4	76.2–88.5
- 2010 (whole sample)	76.8	n.d.	84.8	78.2–89.8	73.8	68.4–78.5	85.3	79.4–91.2
- 2010 (previously interviewed)	89.0	n.d.	93.0	84.8–96.9	68.4	53.6–80.3	86.1	79.3–93.0
- 2010 (newly interviewed)	70.3	61.5–77.8	78.4	68.1–86.0	74.6	68.7–79.7	83.3	71.8–94.8
If showing mild symptoms,								
Taking time off of work/school[e]								
- 2009	81.5	77.8–84.7	**60.0**	56.0–63.8	69.1	64.3–73.5	**59.1**	54.5–63.7
- 2010 (whole sample)[i]	76.9	72.5–80.8	**70.0**	65.2–74.3	67.5	63.1–71.6	**71.0**	66.4–75.7
- 2010 (previously interviewed)[i]	75.7	67.2–82.5	73.9	67.3–79.7	71.5	63.0–78.8	73.7	68.4–79.1
- 2010 (newly interviewed)[i]	77.4	72.1–82.0	66.7	59.9–72.8	66.5	61.5–71.2	64.5	55.5–73.6
Avoiding to go to crowded areas (> 20 persons)								
-2009	87.4	84.5–89.8	77.0	73.6–80.1	79.4	75.4–82.9	75.8	72.5–79.0
- 2010 (whole sample)	83.7	80.4–86.5	76.7	72.9–80.1	74.8	71.1–78.1	79.8	76.8–82.9

(continued)

Table 3 (continued)

	Italy		Romania		UK		Finland	
	(2009: $n = 1,025$) (2010-all resp.: $n = 1025$) (2010-old resp.=328) (2010-new resp.=697)		(2009: $n = 1,025$) (2010-all resp.: $n = 1,025$) (2010-old resp.=442) (2010-new resp.=583)		(2009: $n = 1,025$) (2010-all resp.: $n = 1,000$) (2010-old resp.=247) (2010-new resp.=753)		(2009: $n = 681$) (2010-all resp.: $n = 683$) (2010-old resp.=498) (2010-new resp.=185)	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
- 2010 (previously interviewed) [i]	86.0	80.5–90.2	83.2	78.3–87.2	78.6	72.3–83.8	81.6	78.1–85.1
- 2010 (newly interviewed)[i]	82.8	78.6–86.3	71.2	65.6–76.2	73.7	69.3–77.7	75.3	68.9–81.6
Avoiding to go to church or religious services[f]								
-2009	**87.1**	84.1–89.5	77.6	4.2–80.6	**82.0**	78.2–85.2	83.2	80.2–86.2
- 2010 (whole sample)	**79.6**	75.9–82.9	74.5	70.6–78.0	**71.9**	67.5–75.8	82.5	79.3–85.6
- 2010 (previously interviewed)[i]	80.2	73.0–85.8	80.1	74.7–84.5	75.6	68.0–81.9	85.1	81.6–88.5
- 2010 (newly interviewed)[i]	79.4	74.9–83.3	69.7	64.0–74.8	70.8	65.6–75.5	75.3	68.4–82.3
Scenario A[g]								
Staying at home for 7–10 days								
- People living together with other persons	82.9	79.6–85.8	83.1	79.9–85.8	56.7	51.8–61.4	78.4	74.7–82.0
- People living alone	87.9	80.4–92.7	77.6	68.0–85.0	NA	NA	59.3	52.1–66.5
Staying at home for 7–10 days if recommended by health authorities								
- People living together with other persons	91.0	88.2–93.2	88.2	85.5–90.4	83.6	79.5–87.1	93.4	91.2–95.6
- People living alone	91.0	83.8–95.2	80.5	71.6–87.2	NA	NA	89.0	84.4–93.6
Isolating a sick adult from other household members in a separate room								
- People living together with other persons	73.8	70.1–77.3	83.5	80.3–86.3	76.8	72.2–80.9	69.7	65.7–73.8

Scenario B[h]								
Staying at home for 7–10 days								
- People living together with other persons	87.7	84.5–90.3	84.8	81.9–87.4	77.2	72.7–81.2	78.8	75.2–82.4
- People living alone	89.3	81.4–94.0	78.5	68.6–85.9	82.2	75.9–87.2	84.0	78.6–89.4
Staying at home for 7–10 days if recommended by health authorities								
- People living together with other persons	88.5	85.5–91.0	84.4	81.2–87.2	82.3	77.9–85.9	86.0	82.9–89.0
- People living alone	92.4	85.1–96.2	84.7	75.9–90.7	87.1	81.4–91.2	91.2	87.0–95.3
Having someone who takes care of you for 7–10 days								
- People living alone	78.3	69.0–85.4	55.8	45.0–66.1	46.2	39.6–53.0	46.7	39.4–54.0

Bold-underscored percentages in the section Actual Behaviour indicate the presence of a statistical significant difference ($P<0.05$) between the percentages estimated in 2009 and those estimated in the whole sample in 2010. These differences were evaluated using logistic regression models while controlling for sex, age, education, occupation, level of information about swine flu and household composition (when appropriate) as potential confounders

NA not available, *n.d.* CI not calculated by STATA

*In the UK, the question on medical advice last time with flu was only posed to people who were working at that time

**In the UK, in 2009, the questions on likelihood of catching swine flu were only posed to people who reported to have not had it (31 at q18 and 24 at q19: data are not consistent)

***In the UK and Finland, the question on availability to stay at home for 7–10 days was posed assuming a scenario where the interviewed individuals have developed swine flu (in Italy and Romania the same question was posed only assuming the general spread of swine flu in the general population)

[a]Among those who reported to have had flu at least once in their lifetime

[b]Among those who reported to work/study last time they had flu

[c]The percentage for Finland may represent an overestimate compared with other countries because it has been calculated only among people who were offered the vaccine

[d]Among those living with children

[e]Among those usually working/studying

[f]Among those usually attending church or religious services

[g]Scenario A people living together with other persons: someone within the household has swine flu; People living alone: have been in contact with someone who has swine flu

[h]Scenario B people living together with other persons: after having taken care of someone with swine flu within the household, now they have symptoms; people living alone: have influenza

[i]Among those who have not had swine flu

[l]Among those who have not had or have not been offered/recommended the vaccine against swine flu

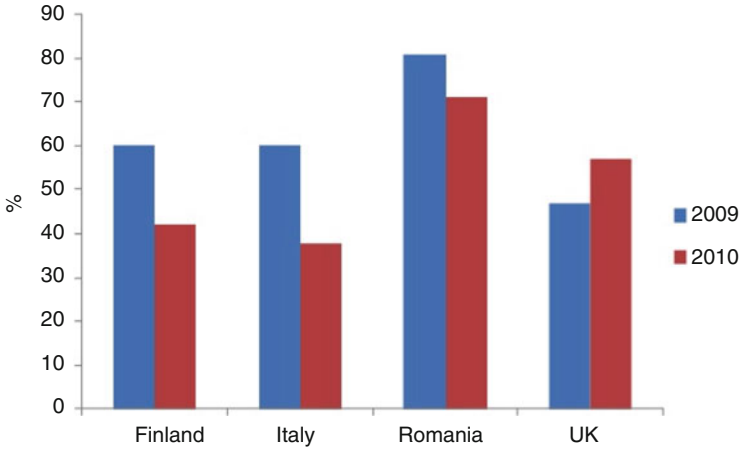

Fig. 2 Comparison of the proportion of individuals worried about catching swine flu by country and survey, 2009–2010

changes in 2010. About 80 %, of those that regularly attend, would avoid going to church or religious services, if showing mild symptoms, in 2009, with a slight reduction for Italy and the UK in 2010.

Few respondents suggested other actions against swine flu in addition to those mentioned in the questionnaire, and among these individuals, washing hands frequently was the most frequently reported behaviour in 2009 and 2010.

3.4 Actual Behaviour

During the 2010 survey, of those individuals who reported having had swine flu, 81 % in Finland, 33 % in Italy, 31 % in Romania and 14 % in the UK reported having been diagnosed through a medical test.

In case of symptoms, more than 70 % of Italian individuals interviewed reported having taken days off from work/school; the proportion decreases to 65 % in Finland and to 23 % in Romania. In Italy, Romania and the UK, 87 %, 62 % and 67 % of individuals, respectively, reported having isolated themselves in a separate room, if not living alone, while symptomatic while in Finland the proportion was lower (34 %).

The proportion of individuals that reported they would be vaccinated against swine flu (intended behaviour) in 2009 was higher than the proportion of those who really had the pandemic vaccine (actual behaviour) in 2010, when offered, in all the four participating countries (Fig. 3),with the lowest difference in Finland and the largest in Italy.

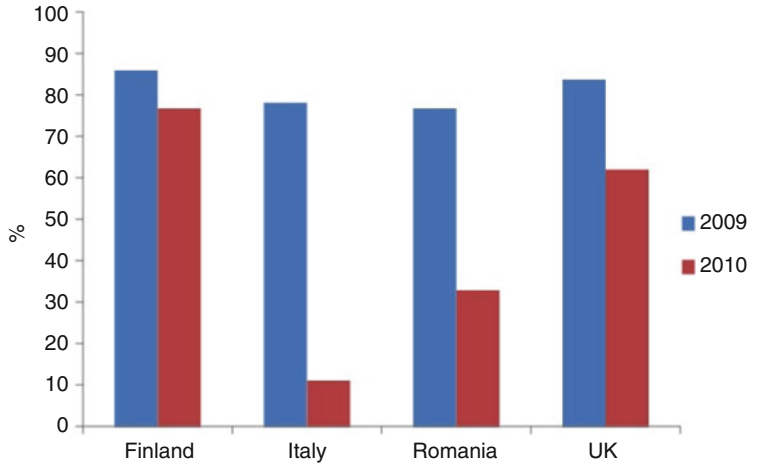

Fig. 3 Comparison of the proportion of individuals getting vaccinated against swine flu if recommended by country and survey, 2009–2010: comparison between intended (2009) and actual behaviour (2010)

The pandemic vaccine was offered to 30 % of respondents in Italy and the UK, to 40 % in Romania and to 50 % in Finland, and of those 14 %, 55 %, 31 % and 60 %, respectively, reported having received it. The reasons accounted for not receiving it, if offered, were mostly related to possible side effects of the vaccine, to the belief that the vaccine was not effective and to the perceived healthy status of the participant. Interestingly, 11 % of individuals in Italy, 5 % in Romania and 3 % in the UK were advised by their GP against getting the pandemic vaccine.

Concerning children, the pandemic vaccine was offered to 16 % in Italy, to 15 % in the UK and to all of them in Finland; 2 %, 19 % and 85 % reported to have vaccinated their children against pandemic influenza, respectively. About 68 % in Italy, 80 % in Romania, 86 % in the UK and 91 % in Finland reported to have given antiviral medications to ill children if offered.

Of respondents, 3.1 % in Italy, 10 % in Romania, 8 % in the UK and 1 % in Finland reported that schools were closed as a result of the swine flu, and in Italy (100 %), Romania (40 %) and the UK (35 %), parents were the main carers of children, while in Finland children took care of themselves (50 %) or were cared by a family member not living in the same household (50 %).

The worry about the possibility of catching swine flu was strongly associated with increased likelihood of performing protecting behaviour with regard to social distancing and vaccination in both 2009 and 2010 surveys except for Italy.

4 Discussion

We conducted a study in four EU countries (Finland, Italy, Romania and the UK) to assess the reliability and validity of behavioural intentions regarding public health interventions through comparison with real behavioural responses to the 2009 A/H1N1 pandemic.

Comparable surveys in a number of different countries have been previously conducted in order to make inter-country comparisons and assess factors that may lead to precautionary actions for SARS, avian influenza [7, 8, 25] and 2009 pandemic [5, 12, 15, 16, 30]. However, few have investigated reliability and validity of behavioural intentions regarding public health interventions, declared at the beginning of the 2009 influenza pandemic, through comparison with real behavioural responses at the end of the pandemic wave in 2010. The lay public's behavioural responses during a disease outbreak play an important role in bringing the outbreak under control and should be considered in the development of mathematical models that have been and are largely used to evaluate and inform infectious disease prevention and control policy. Behavioural changes of the population can significantly affect the epidemic spread both quantitatively (mainly slowing the epidemic spread or determining different final epidemic size) and qualitatively (mainly varying the epidemic dynamics). Including parameters that account for spontaneous behavioural changes in mathematical models could be very useful for giving insight to public health policy makers, for planning public health control strategy (e.g. vaccination, antivirals) and better estimating the burden for health-care settings over time. In one, recently published, study it has been demonstrated that the estimation of key epidemiological parameters (in particular the reproductive number) could be largely modified by human behavioural changes [21].

During the 2009 pandemic, because of the mild nature of most cases [17] and the existing immunity in the elderly [14, 20, 23], the initial fears of a moderately severe pandemic with a 1918-like case fatality rate [10] declined. Public behaviour is likely to be similar in some respects (waning compliance with prevention measures as worry declines), but it is difficult to determine the respective effects on the population of the ongoing heightened perception of personal health and exposure to risk.

In our study, we have been able to assess the beliefs and the behavioural intentions before the actual beginning of the epidemic wave, at least for 3 of the countries involved (the UK had already seen a first summer wave of A/H1N1 pandemic, before the survey was run), and to compare them with actual behaviour during the epidemic and with stated intentions afterwards.

There were some differences among participating countries in 2009 as for previous behaviours related to seasonal flu, and belief and level of knowledge about A/H1N1 influenza; on the other hand, no substantial differences were observed among the four countries with respect to the expected behaviours should swine flu begin to spread.

However, when comparing results of the two surveys, we observed in all countries a significant reduction in those who reported to be willing to vaccinate their children against swine flu if free of charge and recommended by health authorities, but the reduction ranged from extreme in Italy and Romania to modest in the UK and Finland. A significant reduction with respect to the use of antivirals as a precautionary measure was reported only in Italy and the UK.

On the other hand, when considering non-pharmaceutical measures (e.g. staying at home for 7–10 days and keeping children away from large gatherings) there were no significant changes in population behavioural intentions between the two surveys. Exceptions are that in Romania and Finland the proportion of individuals reporting to take time off from work/school in case of mild symptoms increased; instead, individuals from Italy and the UK significantly reduced their willingness to avoid religious services in case of mild symptoms.

In our study worry about the possibility of catching swine flu was strongly associated with increased likelihood to perform protecting behaviour with regard to social distancing and vaccination in both 2009 and 2010 surveys except for Italy. In most of the participating countries except Finland, peoples' anxiety about 2009 pandemic and the preventive pharmacological measures (both antivirals and pandemic vaccine) they took to avoid infection declined from June to July 2009 to June 2010.

Considering the actual behaviour, Italy, Finland and the UK reported a high proportion of individuals that took days off from work/school in case of influenza symptoms, while in Romania the proportion was low compared to other countries. Except for Finland, a high proportion of individuals reported having isolated themselves in a separate room, if not living alone, in case of symptoms.

Most published studies in the literature report possible behavioural intentions and preventive strategies adopted by the population in the early phase of the 2009 pandemic [5, 12, 15, 16, 24, 26, 30]. Studies on behavioural response to the initial phase of the 2009 pandemic influenza have highlighted an initial high level of anxiety about the pandemic [12] and different behavioural responses to the risk of infection [5, 15, 16, 24, 26, 27, 30]. In the USA, data collected on public response to 2009 pandemic influenza from May 2009 to June 2009 suggest that 16–25 % of Americans avoided mass gathering events, like sporting events, malls or public transportation and 20 % reduced contact with people outside [their] household as much as possible [27].

Published studies have shown a behavioural change in the population against the 2009 pandemic [12, 24] and our results support this. Suboptimal adherence to preventive measures as a function of risk perception has been previously described [18, 19] and is also confirmed by our results showing that the reduction in some avoidance behaviours may indicate a decrease in risk perception with consequent decline in population adherence to public health authorities recommendations.

The role of human behaviours on mathematical model estimation of epidemiological parameters (such as the reproductive number) has previously been discussed [9, 11, 21, 22] because of the possible role of behavioural changes on the contact network and in the virus transmissibility [9]. Recent published studies [21, 22] have

started to investigate the role of spontaneous behavioural changes in the population, not accounted for by the large majority of influenza transmission models showing that individual choices can drastically affect the dynamics, the overall number of cases and epidemic spread, mostly by altering timing.

To our knowledge our study is the only one to have investigated the actual behaviour of the population in EU countries and provides crucial descriptions of pandemic impact on social-network dynamics parameters to be included in mathematical models in order to obtain more accurate and realistic scenarios and for giving better insight to public health policy makers.

References

1. Anonymous: J. Indian Med. Assoc. **107**(8), 511 (2009)
2. Balinska, M., Rizzo, C.: PLoS Curr. **1**, RRN1037 (2009)
3. Bell, D.M.: Emerg. Infect. Dis. **10**(11), 1900 (2004)
4. Bell, D.M., Weisfuse, I.B., Hernandez-Avila, M., del Rio, C., Bustamante, X., Rodier, G.: Emerg. Infect. Dis. **15**(12), 1963 (2009)
5. Cowling, B.J., Ng, D.M., Ip, D.K., Liao, Q., Lam, W.W., Wu, J.T., Lau, J.T., Griffiths, S.M., Fielding, R.: J. Infect. Dis. **202**(6), 867 (2010)
6. Dawood, F.S., Jain, S., Finelli, L., Shaw, M.W., Lindstrom, S., Garten, R.J., Gubareva, L.V., Xu, X., Bridges, C.B., Uyeki, T.M.: N. Engl. J. Med. **360**(25), 2605 (2009)
7. de Zwart, O., Veldhuijzen, I.K., Elam, G., Aro, A.R., Abraham, T., Bishop, G.D., Voeten, H.A., Richardus, J.H., Brug, J.: Int. J. Behav. Med. **16**(1), 30 (2009)
8. de Zwart, O., Veldhuijzen, I.K., Richardus, J.H., Brug, J.: BMC Infect. Dis. **10**:114 (2010)
9. Ferguson, N.: Nature **446**, 7137 (2007)
10. Fraser, C., Donnelly, C.A., Cauchemez, S., Hanage, W.P., Van Kerkhove, M.D., Hollingsworth, T.D., Griffin, J., Baggaley, R.F., et al.: Science **32**(5934), 1557 (2009)
11. Funk, S., Salathe, M., Jansen, V.A.: J. R. Soc. Interface **7**(50), 1247 (2010)
12. Goodwin, R., Haque, S., Neto, F., Myers, L.B.: BMC Infect. Dis. **9**, 2009
13. Graubard, B.I., Korn, E.L.: Stat. Methods Med. Res. **5**(3), 263 (1996)
14. Hancock, K., Veguilla, V., Lu, X., Zhong, W., Butler, E.N., Sun, H., Liu, F., Dong, L., DeVos, J.R., Gargiullo, P.M., Brammer, T.L., Cox, N.J., Tumpey, T.M., Katz, J.M.: N. Engl. J. Med. **361**(20), 1945 (2009)
15. Jones, J.H., Salathe, M.: PLoS One **4**, 12 (2009)
16. Kamate, S.K., Agrawal, A., Chaudhary, H., Singh, K., Mishra, P., Asawa, K.: J. Infect. Dev. Countries **4**(1), 7 (2010)
17. Kelly, H.A.: Med. J. Aust. **192**(2), 81 (2010)
18. Lau, J.T., Kim, J.H., Tsui, H., Griffiths, S.: Am. J. Infect. Control **35**(1), 38 (2007)
19. Leppin, A., Aro, A.R.: Int. J. Behav. Med. **16**(1), 7 (2009)
20. Miller, E., Hoschler, K., Hardelid, P., Stanford, E., Andrews, N., Zambon, M.: Lancet **375**(9720), 1100 (2010)
21. Poletti, P., Ajelli, M., Merler, S.: PLoS One **6**, 2 (2011)
22. Poletti, P., Ajelli, M., Merler, S.: Math. Biosci. **238**(2), 80 (2012)
23. Rizzo, C., Rota, M.C., Bella, A., Alfonsi, V., Declich, S., Caporali, M.G., Ranghiasci, A., Lapini, G., Piccirella, S., Salmaso, S., Montomoli, E.: Vaccine **28**(20), 3558 (2010)
24. Rubin, G.J., Amlot, R., Page, L., Wessely, S.: Br. Med. J. **339**:b2651 (2009)
25. Sadique, M.Z., Edmunds, W.J., Smith, R.D., Meerding, W.J., de Zwart, O., Brug, J., Beutels, P.: Emerg. Infect. Dis. **13**(9), 1307 (2007)
26. Setbon, M., Le Pape, M.C., Letroublon, C., Caille-Brillet, A.L., Raude, J.: Prev. Med. **52**(2), 178 (2011)

27. SteelFisher, G.K., Blendon, R.J., Bekheit, M.M., Lubell, K.: N. Engl. J. Med. **362**(22):e65 (2010)
28. Vandegrift, K.J., Sokolow, S.H., Daszak, P., Kilpatrick, A.M.: Ann. N. Y. Acad. Sci. **1195**, 113 (2010)
29. World Health Organization. http://www.who.int/csr/don/2009_04_24/en/index.html seen on 2012/05/18/ (2009)
30. Yuan, J., Zhang, L., Xu, W., Shen, J., Zhang, P., Ma, H.: Epidemiol. Infect. **137**(7), 988 (2009)

Factors Influencing Infant and Adolescent Vaccine Uptake in Flanders, Belgium

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Abstract This chapter focuses on the determinants of a number of immunization programme outcomes in Flanders (Belgium), such as vaccine initiation and uptake, completion of the vaccination schedule and compliance to official validity criteria. These were assessed in both infant and adolescent age groups. Three main groups of potential influencing factors are looked at: (1) individual background variables; (2) family level variables; (3) external factors such as the governmental vaccination programme and other initiatives to promote vaccination. Data on parental willingness to pay for and willingness to accept multiple concomitant injections and their determinants are discussed as well. Exploring relationships between vaccination programme outcomes and influencing factors can give important information to optimize vaccination programme performance.

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1 Introduction

During the previous century, highly effective vaccines have been developed and vaccination programmes have been implemented. Together, these have allowed for primary prevention of infectious diseases that once disabled or killed large numbers of adults and children, such as measles, polio and diphtheria. However, continued and extensive surveillance of diseases, vaccines and vaccination programmes is necessary since any of these diseases can be reintroduced, as has happened in the past. Such reintroduction of diseases can be induced by, among others, vaccine failure or failure to vaccinate for reasons such as programme performance regression or changes in people's attitudes and perceptions towards vaccinations. Accurate information on vaccine uptake, disease susceptibility in the target groups, disease epidemiology and changes in people's attitudes and preferences towards vaccines and vaccination programmes is highly needed to evaluate the performance of recommended vaccination programmes. This information can also be used to guide decisions on adaptation of the existing programmes or on the introduction of new vaccines.

This chapter summarizes findings from studies on infant and adolescent vaccination in Flanders, the northern region of Belgium, representing about 2/3 of the Belgian population. The studies explored various indicators of vaccine uptake (vaccination initiation, vaccination completion), compliance with the recommended validity criteria and attitudes and preferences towards vaccinations. In order to understand the setting of these studies some background information on the organization of the vaccination programme in Belgium seems appropriate.

Belgium is governed both by a national and sub-national (regional) governments. Vaccination policy is a shared responsibility of the national and the regional Ministries of Health. A national schedule of recommended vaccines is provided and regularly updated by the national Superior Health Council (SHC). The regional authorities are responsible for the organization and promotion of the immunization programmes in their respective regions. The way the vaccination programme is organized in each region (supply of vaccines via the public and the private health setting vs via the private health setting only) as well as the price of the vaccine (free of charge, partially or not reimbursed) are jointly decided by the national and the regional governments. With regard to the organization of the vaccination programme, for most vaccines recommended by the SHC, parents can choose to have their child vaccinated in a public or in a private health care setting. In the case of infant vaccinations, the public health setting consists of well-baby clinics. These clinics systematically offer vaccines to all children between 0 and 3 years of age through regular preventive consultations. Most of these vaccines are free of charge, while for some of them an out-of-pocket cost is required. In the case of school-aged children, the public health setting consists of free of charge preventive consultations by school health services. Throughout the school career of a child, the vaccination status is checked at regular points in time and recommended vaccines are offered systematically to children at specific ages. All vaccines offered by these school health services are currently (situation April 2012) free of charge.

The private health care setting for both infant and school-aged children consists of general practitioners and paediatricians, who can order and administer free of charge vaccines as well. Nevertheless, they charge a fee for the consultation.

In practice, many vaccines, once the SHC recommends them, are first available only via the private health care setting during some time, prior to an agreement on financing between the national and the regional governments. This was the case for, e.g., the hepatitis B vaccine, the *Haemophilus influenzae* type b vaccine, pneumococcal vaccines and human papilloma virus (HPV) vaccines. If no final agreement is reached between the national and the regional government on a specific vaccine, this vaccine can still be obtained via the private health setting, but the initiative for vaccination lies entirely with the parents or with the physicians, and there is no systematic offer of these vaccines to the eligible children. Partial reimbursement is in some cases provided by the national government or by private, non-profit sickness funds.

2 Studies

The results described in this section can be divided into two subsections. In the first subsection, indicators of vaccine uptake and its determinants are described. In the second subsection, we look at other indicators relevant for the surveillance and monitoring of the vaccination programme, namely parental attitudes with regard to the administration of concomitant vaccines and willingness to pay to avoid an extra injection. Table 1 gives an overview of the different studies that are summarized below.

2.1 Determinants of Vaccine Uptake

We first describe the indicators of vaccine uptake and its determinants for various vaccines supplied via both the public and the private setting, and subsequently indicators for one specific vaccine (HPV vaccine) during the period it was only supplied via the private health care setting (partly reimbursed). For all vaccines we identified low-uptake risk groups. Identification of low-uptake risk groups allows for targeted strategies that can enhance the uptake of vaccines, overall or in certain risk groups.

2.1.1 Vaccines Offered Both via the Public and the Private Health Care Setting

A first series of studies [1, 4, 7, 8] investigated indicators of vaccine uptake for vaccines offered free of charge to infants and school children both via the public and the private health care setting. Information was obtained through two immunization

Table 1 Overview of selected studies in Flanders, Belgium

Reference	Study population	Main outcome	Factors studied	Design
[4]	1,349 infants (°2003, interviewed 2005)	Coverage per vaccine dose recommended in infancy, full series coverage, validity of the schedule	Socio-demographic background (child/family/parent level), vaccinator types involved, side effects of vaccination, frequency of illness of the child, use of day care	Random cluster sample, interview at home, written documentation of recommended vaccine doses at home, supplemented with vaccination data from medical files, survey regression analysis for association between factors and outcome
[1]	915 infants (°2006, interviewed 2008)			
[8]	1,344 adolescents (°1991, interviewed 2005)	Coverage per recommended vaccine dose for measles-mumps-rubella, hepatitis B, diphtheria-tetanus-polio[1] and meningococcal C[2] vaccines up to 13 years of age, validity of the schedule	Socio-demographic background (child/family/parent level), vaccinator types involved[2], side effects of vaccination, school career of the adolescent	(see above)
[1]	1,319 adolescents (°1994, interviewed 2008)			
[7]	792 children (7–8 years of age) (°1997, interviewed 2005)	Coverage per vaccine dose recommended up to 6 years of age, full series coverage, validity of the schedule	Socio-demographic background (child/family/parent level), degree of urbanization	(see above)

[6]	cfr. [4] and [8]	Willingness to pay to avoid a concomitant injection, number of concomitant injections parents would allow during one visit	cfr. [4] and [8], each outcome variable as a factor in the analysis of the other outcome variable	(see above)
[2]	117,151 girls (12–18 years of age) (°1989–1996, analysed 2010)	HPV vaccination initiation	Age, socio-economic background (family level), place of residence, reimbursement regime, information campaign	Analysis of reimbursement claims[3] Cox regression model for factors predicting HPV vaccination initiation
[3]	127,854 girls (12–18 years of age) (°1989–1996, analysed 2010)	HPV vaccination initiation	Age, socio-economic background (family level), place of residence, cervical cancer screening by mother	Analysis of reimbursement claims[3], generalized linear mixed model for association between mother's cervical cancer screening and daughter's HPV vaccination initiation

Legend: infants were 18–24 months of age, adolescents were 13–14 years of age

[1] Administration of the tetanus-diphtheria-polio booster doses recommended at 6 years of age was not assessed in adolescents in 2005

[2] A once-only meningococcal C conjugate vaccine catch-up campaign in 2002–2004 targeted both cohorts of adolescents

[3] Limited to reimbursement claims made at the National Alliance of Christian Mutualities

coverage surveys performed in 2005 and 2008, both ordered by the Flemish Ministry of Health. Their principal aim was to assess coverage of the following infant and adolescent vaccines: poliomyelitis (polio), diphtheria-tetanus-pertussis (DTP), H. *influenzae* type b (Hib), hepatitis B (HBV), measles-mumps-rubella (MMR) and meningococcal C (MenC) vaccines. The survey comprised samples of 18–24-month-old infants (°2003 and °2006), 7–8-year-old school-aged children (°1997) and 13–14-year-old adolescents (°1991 and °1994) (Table 1). Two-step random cluster samples were selected as recommended by the Expanded Programme on Immunization (EPI) of the World Health Organization. Families were interviewed at home. The obtained vaccination data were updated from medical files of private physicians or public health services (if necessary and if possible), as well as from the child's individual record in Vaccinnet, Flanders' online vaccine ordering and registration system. The main results with regard to vaccine uptake are summarized in Table 2.

Vaccine coverage in Flanders was found to be higher at infant age (where it surpassed 90 % for all assessed vaccines) than at later age (where the coverage of most recommended vaccines was below 90 %). Note that non-availability of vaccination documents at home was also more frequent at later age and can thus have biased the findings. First dose coverage (limited to multi-dose vaccines), an indicator of vaccination initiation, ranged from 96.9 to 99.0 % in infants and from 80.6 to 83.3 % in adolescents in 2005. In 2008, vaccination initiation levels of close to 100 % and between 86.4 and 92.5 % were noted in infants and adolescents, respectively. Full series coverage (vaccination completion) per vaccine in infants ranged from 92.2 to 94.1 % in 2005 and from 95.1 to 96.6 % in 2008. In adolescents, full series were assessed for HBV and MMR vaccines only. Full series coverage for MMR in this age group rose from 74.6 in 2005 to 83.5 % in 2008; for HBV a rise from 75.7 to 89.3 % was noted. Age-appropriate vaccination rate (full series of all recommended vaccines) in infants was stable at 89.5 and 89.6 % in 2005 and 2008, respectively, whereas in adolescents it increased from 58.1 to 72.8 %. Excluding invalid doses (as based on official criteria for minimal age at administration and minimal interval between doses) resulted in a reduction of full series coverage only in infants. Valid series coverage per vaccine in that age group ranged from 85.6 to 90.1 % in 2005 and from 88.4 to 93.4 % in 2008. Several predictors of the vaccination coverage per vaccine and per dose in each surveyed age cohort were studied, using parametric and non-parametric methods (Table 2). The most important predictor of lower vaccination coverage in infants was the main vaccinator, with children vaccinated in the private health care setting having a higher risk of undervaccination than children vaccinated in the public health care setting. In adolescents an atypical school career was a consistent risk factor, but several socio-economic factors were found to be significant as well, with, e.g., children from families with a lower family income or children whose parents or grandparents were born outside the EU having a higher risk of undervaccination. For a lot of factors the association with coverage of specific vaccines was significant in one birth cohort and borderline or non-significant in another, but in general similar trends could be seen.

Table 2 Factors significantly ($p<0.05$) associated with incomplete vaccination[1] , non-vaccination[2] or invalid vaccination[3]

Factor[a]		Category with higher risk	Vaccine						
			DTP (+Hib)[d]	Polio[d]	DT-IPV	HBV[d]	MMR	MenC	HPV
Individual level	Age	Younger girls (vs. older)							Adolescent girls[2]
	School career	Delay or special education			Adolescents °1994[2]	Adolescents[1]	Adolescents[1]	Adolescents[2]	
Family level	Employment of the mother	Non-working (vs. working full-time)	Infants °2003[1,3]	Infants °2003[3]		Infants °2003[3]			
		Full-time (vs. part-time)				Adolescents °1991[1]	Adolescents °1991[1]	Adolescents °1991[2]	
	Family income[b]	Lowest category	Children[1,3]	Infants °2003[1] Children[1]	Children[2,3] Adolescents °1994[2]	Children[1] Adolescents °1994[1]	Children[2,3]	Children[2,3]	Adolescent girls[2]
	Birth order	4th or higher	Infants °2006[1]	Infants °2006[1]		Infants °2006[1]	Infants °2006[2]	Infants °2006[2]	
	Family type	Single or divorced	Infants °2006[1]	Infants °2006[1]	Adolescents °1994[2]		Adolescents °1991[1]		
		Foster parents[e]			Adolescents °1994[2]		Adolescents °1994[1]		
	Origin of the mother	Non-European			Adolescents °1994[2]	Adolescents[1]	Adolescents[1]	Adolescents °1991[2]	
		Non-Belgian	Infants °2006[1]	Infants °2006[1]		Infants °2006[1]		Adolescents °1994[2]	

(continued)

Table 2 (continued)

Factor[a]		Category with higher risk	Vaccine						
			DTP (+Hib)[d]	Polio[d]	DT-IPV	HBV[d]	MMR	MenC	HPV
	Educational level of the mother	Primary school (vs. higher)			Children[2,3]	Children[1,3]		Adolescents °1991[2]	
		University (vs. primary school)			Adolescents °1994[2]		Adolescents °1994[1]		
	Age of the mother	Younger	Infants °2006[1]	Infants °2006[1]		Infants °2006[1]	Infants °2006[2]	Infants °2006[2]	
	Employment of the father	Part-time/unemployed (vs. full-time)[f]					Adolescents °1991[1]	Adolescents °1991[2]	
	Cervical cancer screening mother	Non-screening mother (vs. screening mother)							Adolescent girls[2]
External factors[a]	Main vaccinator[c]	Paediatrician or family physician (vs. public health setting)	Infants[1,3] Children[1,3]	Infants[1,3] Children[1,3]		Infants[1,3] Children[1,3]	Infants[2,3] Children[1,3]	Infants[2,3]	

Degree of urbanization	City	Children[3]	Children[2,3]	
Reimbursement rules	Higher co-payment, less media advertising			Adolescent girls[2]
Information campaign	Personal information, letter not sent			Adolescent girls[2]

DTP diphtheria-tetanus-pertussis combined vaccine, *Hib* H. *influenzae* type b vaccine, *DT-IPV* diphtheria-tetanus-inactivated poliomyelitis vaccine, given as a school-age booster dose, *HBV* hepatitis B vaccine, *MMR* measles-mumps-rubella vaccine, *polio* poliomyelitis vaccine, *MenC* conjugated meningococcal group C vaccine, *HPV* human papillomavirus vaccine

Note: predictors for invalid vaccination were only assessed in infants °2003; incomplete vaccination was not assessed for HPV vaccination

Oral live polio vaccine was given to children °1997, whereas the inactivated vaccine was used for infants °2005/2008. Whole cell pertussis vaccines were used for children °1997, whereas acellullar vaccines were used for infants °2005/2008. Administration of Hib vaccines was not assessed in children °1997. Administration of DT-IPV vaccines was not assessed in adolescents °1991. Infants were surveyed at 18–24 months of age; children were 7–8 years of age; adolescents were 13–14 years of age; adolescent girls were 12–18 years of age. Birth year is mentioned if results were restricted to a specific birth cohort

[a]Note that the studies on HPV vaccination assessed uptake in a setting where the vaccines were only offered to eligible girls via private health care, whereas the other studies assessed vaccine uptake in a setting where vaccines were available both via public and private health care

[b]Note that family income was a predictor of valid MMR vaccination in infants °2003, but only the unknown income category was significantly different from the lowest income category

[c]Note that having several vaccinators involved was a significant predictor of being vaccinated with MMR vaccine for infants born in 2006 only

[d]In infants born in 2006, combined DTP-Hib-IPV-HBV vaccines were used

[e]Foster parents were only assessed separately in the analysis of adolescents born in 1994

[f]A part-time working father was a risk factor for meningococcal C vaccination, whereas an unemployed father was a risk for HBV vaccination

2.1.2 Vaccines Offered Only via a Private Health Care Setting

The second series of studies [5, 6] investigated predictors of vaccine uptake for one specific vaccine, namely the HPV vaccine, in the period it was recommended to adolescent girls by the SHC but offered only via the private health care setting with partial reimbursement (2007–2009). Information was obtained through analyses of HPV vaccine reimbursement claims of the National Alliance of Christian Mutualities (NACM), the largest sickness fund in Flanders. All female members aged 12–18 (°1989–1996; N = 117 151 in [2], N = 127 854 in [3]) and living in Flanders were selected from the membership files of the NACM. Initiation of HPV vaccination between January 2007 and June 2009 varied between 20 and 80 % depending on the year of birth (age) of the girls. These differences in vaccination coverage were mainly due to two factors. First, there were differences in the reimbursement rules (during certain periods of time and for certain birth cohorts the out-of-pocket cost for the vaccines was much lower, and eligibility rules were more advertised in the media). Second, the vaccine was partly reimbursed up until the age of 15 or later 18 years, so for the youngest girls in the study (born in 1995 and 1996) there was still a lot of time left after June 2009 to start vaccination. Besides these two main factors a higher probability of initiation of HPV vaccination was found for girls coming from families with higher incomes and for girls who were personally informed about their eligibility for reimbursement. Furthermore, the probability of initiation of HPV vaccination was found to be positively associated with cervical cancer screening of the mother in the years prior to the launch of HPV vaccines (factors affecting the probability of vaccination initiation are summarized in Table 2).

2.2 Parental Attitudes and Willingness to Pay

The main results with regard to parental attitudes are summarized in Table 3.

In the vaccination coverage study of 2005 additional questions were added to the questionnaires of both infants and adolescents to obtain information on parental attitudes and preferences with respect to multiple vaccine injections [5, 7]. The results were analysed separately for parents of infants and parents of adolescents. Willingness to pay (amount in euro) to avoid a concomitant injection and the maximum number of concomitant injections parents would allow during the same visit were used as a proxy of parental acceptance of concomitant injections. Parents of young children as well as those of adolescents gave preference to a maximum of two separate vaccine injections to be given at the same immunization visit. Parents also shared common attitudes on the amount of money they would pay to avoid concomitant injections. A significant proportion of parents of both infants and adolescents, 41.0 % and 38.8 %, respectively, were not willing to pay anything, whereas in both age groups the remaining parents mentioned a median amount of 20 euro to avoid a concomitant injection. However, extensive analysis using several regression methods to identify predictors of the attributed value and the allowed

Table 3 Predictors of different proxies for parental acceptance of concomitant vaccine injections (not vaccine specific). Being willing to pay to avoid a concomitant injection (WTP); amount (in euro) caregivers are willing to pay (amount WTP); number of concomitant injections caregivers would allow (number allowed); as assessed in parents of infants and adolescents in 2005

Predictor	Category with lower outcome	WTP Yes	Amount WTP	Number allowed
Educational level of the mother	Lowest (vs. secondary school)	Infants		
Employment of the father	Part-time or freelance (vs. full-time)	Infants		
	Not working (vs. full-time)	Adolescents		
Number of siblings	Lower number			Infants
Origin of the mother	Belgian vs. other European country		Infants	
	Non-European vs. Belgian			Infants
Main vaccinator	Well-baby clinic (vs. paediatrician)		Infants	
Number of concomitant injections parents would allow	Lower number	Adolescents		
WTP	Being willing to pay			Infants
Respondent's relation to the child	Mother vs grandparent[1]			Infants[2]
Child's vaccination status	Complete			Infants[2]
	Incomplete			Adolescents[3]

Note: Only factors and categories with significant odds ratios were plotted. Family income was a significant predictor of WTP in infants, but only if the unknown income category was compared to the categories with known income

[1]Grandparents accounted for less than 2 % of the respondents

[2]Comparing respondents who would allow an unlimited number of injections to those who would allow a limited number

[3]Comparing respondents who would allow more than two concomitant injections to respondents who would allow not more than two

number of concomitant injections (Table 3) explained only a small part of the variability in the answering behaviour and yielded some conflicting information; this suggests that the proxies we used are only rough indicators of parental attitudes on concomitant vaccines.

3 Discussion

In this chapter we summarized studies on predictors of infants' and adolescents' vaccine uptake and attitudes of parents towards vaccination in Flanders (Belgium). First, individual level characteristics, such as age and school career

were found to significantly affect vaccination coverage. Second, various family level characteristics such as family income, parental educational level or screening behaviour by the mother, were also significantly associated with vaccine uptake. A final set of predictors of vaccine uptake consisted of external factors such as main vaccinator, information campaigns or the reimbursement rules. Exploring relationships between vaccine uptake and these predictors can help to identify subgroups with higher risk of undervaccination who merit special attention. It can also be used to monitor existing vaccination programmes and to guide decisions on changes in these vaccination programmes. Information on parental attitudes towards different aspects of vaccination and vaccination programmes can further optimize these decisions. The results of the presented analyses suggest, in general, a need to monitor and support vaccinating activities of private vaccinators (paediatricians and family physicians) and to develop specific strategies for families in an unfavourable socio-economic situation, as well as for children in special education programmes. Interventions to increase vaccine uptake in infants should address the importance both of timely administration and of completion of the schedule, since similar risk factors were found for invalid and for incomplete vaccination. Apart from the socio-economical and individual predictors of vaccine uptake, documentation of vaccination is a major hurdle in the assessment of vaccination coverage, especially in older age groups, when vaccination is less an issue and is often scattered over different vaccine providers. A cornerstone for good documentation and vaccination practices throughout life is a centralized registration database, which is easily accessible for all vaccine providers and which takes into account safety and privacy issues.

Regular reassessment of vaccine coverage in different settings would provide the opportunity to detect and interpret trends over time. Targeted research (e.g. using a qualitative design) in known subgroups of undervaccinated children could add information on more specific hurdles for vaccination, out of which tailored strategies could be inferred. Ideally data on vaccination coverage should be complemented by studies designed to estimate the serological level of immunity in the target population, which is the indicator we are ultimately interested in when evaluating the performance of vaccination programmes. To have a better insight in parents' preferences regarding concomitant vaccine injections, sensitive quantifications using a more appropriate design (e.g. discrete choice experiments) would confer important additional insights.

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References

1. Hoppenbrouwers, K., Vandermeulen, C., Roelants, M., Boonen, M., Van Damme, P., Theeten, H., Depoorter, A.: Studie van de vaccinatiegraad bij jonge kinderen en adolescenten in Vlaanderen in 2008. Technical report, 2009. URL http://www.zorg-en-gezondheid.be/cijfersinfectieziekten_en_vaccinaties.aspx
2. Lefevere, E., Hens, N., De Smet, F., Van Damme, P.: BMC Public Health **11**, 470 (2011). doi: 10.1186/1471-2458-11-470. URL http://dx.doi.org/10.1186/1471-2458-11-470
3. Lefevere, E., Hens, N., Theeten, H., Van den Bosch, K., Beutels, P., De Smet, F., Van Damme, P.: Vaccine **29**, 8390–8396 (2011). doi: 10.1016/j.vaccine.2011.08.039. URL http://dx.doi.org/10.1016/j.vaccine.2011.08.039
4. Theeten, H., Hens, N., Vandermeulen, C., Depoorter, A.-M., Roelants, M., Aerts, M., Hoppenbrouwers, K., Damme, P.V.: Vaccine **25**, 4940–4948 (2007). doi: 10.1016/j.vaccine.2007.03.032. URL http://dx.doi.org/10.1016/j.vaccine.2007.03.032
5. Theeten, H., Hens, N., Aerts, N., Vandermeulen, C., Roelants, M., Hoppenbrouwers, K., Damme, P.V., Beutels, P.: Pediatr. Infect. Dis. J. **28**, 61–63 (2009). doi: 10.1097/INF.0b013e318184eea3. URL http://dx.doi.org/10.1097/INF.0b013e318184eea3
6. Theeten, H., Hens, N., Aerts, M., Vandermeulen, C., Roelants, M., Hoppenbrouwers, K., Damme, P.V., Beutels, P.: Vaccine **27**, 1964–1969 (2009). doi: 10.1016/j.vaccine.2009.01.096. URL http://dx.doi.org/10.1016/j.vaccine.2009.01.096
7. Theeten, H., Vandermeulen, C., Roelants, M., Hoppenbrouwers, K., Depoorter, A.-M., Van Damme, P.: Acta Paediatr. **98**, 1307–1312 (2009). doi: 10.1111/j.1651-2227.2009.01331.x. URL http://dx.doi.org/10.1111/j.1651-2227.2009.01331.x
8. Vandermeulen, C., Roelants, M., Theeten, H., Depoorter, A.-M., Van Damme, P., Hoppenbrouwers, K.: Pediatrics **121**, e428–e434 (2008). doi: 10.1542/peds.2007-1415. URL http://dx.doi.org/10.1542/peds.2007-1415

Part II
Modeling Behaviour Change in Response to Epidemic Threats

Modeling the Impact of Behavior Changes on the Spread of Pandemic Influenza

Sara Y. Del Valle, Susan M. Mniszewski, and James M. Hyman

Abstract We use mathematical models to assess the impact of behavioral changes in response to an emerging epidemic. Evaluating the quantitative and qualitative impact of public health interventions on the spread of infectious diseases is a crucial public health objective. The recent avian influenza (H5N1) outbreaks and the 2009 H1N1 pandemic have raised significant global concerns about the emergence of a deadly influenza virus causing a pandemic of catastrophic proportions. Mitigation strategies based on behavior changes are some of the only options available in the early stages of an emerging epidemic when vaccines are unlikely to be available and there are only limited stockpiles of antiviral medications. Mathematical models that capture these behavior changes can quantify the relative impact of different mitigation strategies, such as closing schools, in slowing the spread of an infectious disease. Including behavior changes in mathematical models increases complexity and is often left out of the analysis. We present a simple differential equation model which allows for people changing their behavior to decrease their probability of infection. We also describe a large-scale agent-based model that can be used to analyze the impact of isolation scenarios such as school closures and fear-based home isolation during a pandemic. The agent-based model captures realistic individual-level mixing patterns and coordinated reactive changes in human behavior in order to better predict the transmission dynamics of an epidemic. Both models confirm that changes in behavior can be effective in reducing the spread of disease. For example, our model predicts that if school closures are implemented for the

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duration of the pandemic, the clinical attack rate could be reduced by more than 50%. We also verify that when interventions are stopped too soon, a second wave of infection can occur.

1 Introduction

Pandemics are global epidemics and are often associated with a high morbidity and mortality burden. There have been three pandemic influenza outbreaks in the 20th history: the Spanish flu (1918–19), the Asian flu (1957–58), and the Hong Kong flu (1968–69) [32]. The 1918–1919 influenza pandemic (known as the Spanish flu) was the most devastating in recent history, where at least 20 million died [30]. In the United States, about 675,000 lives were lost to the Spanish flu with an estimated mean case fatality rate of 2% [52]. This case fatality rate is an order of magnitude larger than the case fatality rates observed in seasonal flu epidemics in normal years. Recurrent outbreaks of H5N1 around the world and the most recent pandemic (H1N1) 2009 suggest that a deadly pandemic is eminent.

Nearly half of the world's population resides in urban areas [50]. Air travel connects these urban centers in a global network where a new influenza strain can spread around the world in a few weeks, as recently experienced with pandemic (H1N1) 2009. In addition, influenza's short incubation period and the lack of a universal vaccine can increase the spread of influenza, posing a significant global challenge to public health officials. Mathematical models can help in meeting this challenge, if the model includes the most significant properties of the transmission dynamics. In particular, the model most include how people change their behavior in response to an epidemic threat.

Evidence suggests that in the presence of a deadly disease and lack of pharmaceutical interventions, people will change their behavior to avoid infection [15, 19, 42]. Recent studies have evaluated the impact that non-pharmaceutical interventions, such as school closures, social distancing, and travel restrictions, could have on the spread of the next influenza pandemic [13, 14, 21, 24]. However, none of these studies have incorporated intentional changes in individual behavior, such as avoiding gatherings, increasing hygiene, or staying home. Furthermore, these studies have assumed that these non-pharmaceutical interventions would remain in effect for the duration of the pandemic. Typically, people resume their normal behaviors due to lack of resources or as the perceived risk declines [27]. Recent studies on the impact of basic public health measures implemented during the 1918 pandemic [6, 27] indicate that non-pharmaceutical interventions did not last for the duration of the pandemic.

Mathematical models for the spread of infectious diseases have been extensively used to gain insights into the transmission dynamics of infectious diseases. Several approaches have been used for these studies including simple compartmental models [31, 44], network models [35], and agent-based models [18, 24, 34, 48].

These models have provided new insights on important issues such as the effects of drug resistance [5, 46], treatment [34, 40], vaccination [3, 45], non-pharmaceutical interventions [11, 15] and on the overall dynamics of infectious diseases [28].

Diseases often spread through person-to-person contacts; therefore, realistic mixing patterns can be crucial to accurately predicting the path and severity of the disease [16]. The course of an epidemic through a population is determined by the interactions among individuals and the process of transmitting a pathogen is a stochastic (random) process based on the length of time the individuals are in contact with each other and the strength of the contact. Agent-based models can capture this realistic contact structure and allow the simulation to explore how contact networks and different demographic characteristics affect disease transmission.

Several studies have shown the importance of population structure when modeling disease spread [20], but only a few studies have incorporated realistic mixing populations [18, 24]. The accurate representation of population heterogeneity is one of the greatest challenges of epidemic modeling. While substantial progress has been made over the years with the introduction of different mixing functions [29] and mixing matrices [2] for compartmental models, they are still far from achieving a good approximation to real world scenarios. In recent years, new approaches that incorporate more realistic contact structures have been developed to allow for nonrandom interactions among populations [4, 22, 48, 54]. For example, Zaric [54] compared random and nonrandom mixing patterns for network epidemic models and showed that different mixing assumptions led to different epidemic outcomes. In particular, they found that random mixing generally results in a greater number of new infections than nonrandom mixing. Similarly, Bansal et al. [4] used several real and simulated datasets of human contact networks to analyze their impact on disease spread. They concluded that homogeneous-mixing models are appropriate for host populations that are nearly homogeneous. However, network models are more appropriate to better capture and predict disease spread through heterogeneous host populations. Furthermore, Fukś et al. [22] used an agent-based model of Southern and Central Ontario to investigate the spatial correlations of disease spread. They concluded that spatial correlations were difficult to destroy if neighborhood sizes were inhomogeneous. Finally, Stroud et al. [48] showed a strong correlation between local demographic characteristics and pandemic severity. This study used an agent-based model of Southern California with a heterogeneously mixing population and concluded that the average household size in a census tract was strongly correlated with the clinical attack rate.

Here, we use a simple mathematical model to show how behavioral changes can be easily introduced into epidemiological models. In addition, we use a large-scale agent-based model to assess the potential impact of temporary and permanent behavioral changes including school closures in containing a pandemic influenza and analyze how these changes affect the contact structure and transmission dynamics.

2 Methods

We will consider two approaches to incorporate behavior changes in a mathematical model. We first describe a simple system of five ordinary differential equations (ODEs) to describe disease dynamics based on the Kermack–McKendrick susceptible-infected-recovered model (SIR) [31]. We extended this model by using the approaches introduced in Del Valle et al. (2005) [15]. The second approach is based on a stochastic agent-based model, object-oriented platform for people in infectious epidemics (OPPIE). This is an extension of the Los Alamos Epidemic Simulation System (EpiSimS) [16, 18, 48] and includes dynamic behavior changes.

2.1 Ordinary Differential Equation Model

In our ODE model, the population is divided into two subgroups: a group that does not change its behavior or has *normal* behavior (subscript n) and a group that modifies its *behavior* in response to an outbreak (subscript b). People move back and forth between the two groups (reducing susceptibility or infectivity) depending on the behavior adopted. Individuals in each activity group are characterized by their epidemiological status: susceptible, S_n and S_b and infectious individuals, I_n and I_b; the transfers are shown diagrammatically in Fig. 4. Because we are primarily interested in the effectiveness of changes in behavior for a single outbreak, we use a closed system with no migration in or out of the population, and births and natural deaths are not included in the model.

We define t_0 as the beginning of the epidemic. Movement of individuals between the two groups depends upon disease incidence in the population. It is assumed that a certain fraction of the population will change their behavior to protect themselves against infection or reduce their chances of spreading the disease. Let $\varphi_{S_b} S_n$ and $\varphi_{I_b} I_n$ be the transfer rates from the S_n and I_n classes to the S_b and I_b classes, respectively, and $\varphi_{S_n} S_b$ and $\varphi_{I_n} I_b$ be the transfer rates from the S_b, and I_b classes to the S_n and I_n classes, respectively. The rate coefficients are modeled by step functions given by:

$$\varphi_i = \begin{cases} 0, t < \tau \\ c_i, \ \tau < t < \tau_{max} \\ 0 \ t > \tau_{max} \end{cases}$$

for i $= S_n, I_n, S_b$, and I_b, where the parameter c is a positive constant that determines the rate of movement and τ is the time that determines when the new behavior is adopted.

Using the transfer diagrams in Fig. 1, we obtain the following system of differential equations:

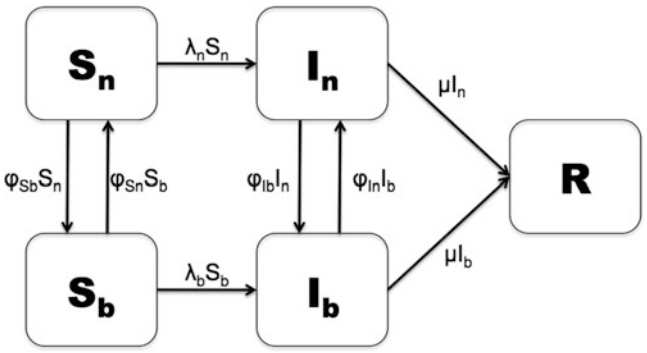

Fig. 1 Schematic relationship between people who adopt a new behavior in response to an epidemic and people who do not change their behavior. The arrows that connect the boxed groups represent movement of individuals from one group to an adjacent one. Susceptible individuals (S_n or S_b) can become infected (I_n or I_b) at rates λ_n or λ_b; infected individuals recover at a rate μ; and people change their behavior based on the transfer rates φ_{S_b}, φ_{I_b}, φ_{S_n}, or φ_{I_n}

$$
\begin{aligned}
\frac{dS_n}{dt} &= -(\varphi_{S_b} + \lambda_n)S_n + \varphi_{S_n} S_b \\
\frac{dI_n}{dt} &= -(\varphi_{I_b} + \mu)I_n + \varphi_{I_n} I_b + \lambda_n S_n \\
\frac{dS_b}{dt} &= -(\varphi_{S_n} + \lambda_b)S_b + \varphi_{S_b} S_n \\
\frac{dI_b}{dt} &= -(\varphi_{I_n} + \mu)I_b + \varphi_{I_b} I_n + \lambda S_b \\
\frac{dR}{dt} &= \mu(I_n + I_b)
\end{aligned} \tag{1}
$$

where λ_n (for normal behavior) and λ_b (for modified behavior) are the forces of infection. λ_n and λ_b incorporate the probability of transmission per contact, β, the reduced number of contacts because of symptomatic infection, θ, and $1 - \eta_j$ (j = s or i), which accounts for the effectiveness of the behavior in reducing either susceptibility (η_s) or infectivity (η_i). β is defined as the susceptibility of the population multiplied by the infectivity of the disease multiplied by the average number of contacts an individual has per day. The forces of infection for both groups are shown by:

$$
\begin{aligned}
\lambda_n &= \beta \left[\left(\frac{\theta I_n}{\rho} \right) + (1 - \eta_i) \left(\frac{\theta I_b}{\rho} \right) \right] \\
\lambda_b &= \beta \left[(1 - \eta_s) \left(\frac{\theta I_n}{\rho} \right) + (1 - \eta_i)(1 - \eta_s) \left(\frac{\theta I_b}{\rho} \right) \right]
\end{aligned} \tag{2}
$$

where $\rho = N - (1-\theta)(I_n + I_b)$ and N is the total population $(S_n + S_b + I_n + I_b + R)$. In the forces of infection, η_i is incorporated into the $\theta I_b/\rho$ infectious fractions because individuals in the I_b class have adopted a new behavior and η_s is incorporated into the infectious fractions in λ_b because individuals in the susceptible class (S_b) have also adopted a new behavior. These forces of infection and appropriate initial conditions complete our model formulation.

2.2 The Agent-Based Model

The OPPIE simulation platform is an agent-based model that combines the demographic-based population of a region, a network of specific business and home locations, and the movement of individuals between locations with daily itineraries. We simulated the spread of an influenza epidemic using a synthetic population constructed to statistically match the 2000 US Census population demographics of Southern California at the census tract level. There are 20 million individuals living in six million households, with an additional one million locations representing actual schools, businesses, shops, and social recreation addresses. This synthetic population only represents individuals reported as household residents; thus, visiting tourists, guests in hotels, and travelers in airports are not explicitly included.

Each individual has a schedule of activities based on the National Household Transportation Survey (NHTS) [37]. A schedule specifies the type of activity, the starting and ending time, and the location of each assigned activity. There are six types of activities: *home*, *work*, *shopping*, *social recreation*, *school*, and *other*. The time, duration, and location of activities determine which individuals mix together at the same location at the same time, which is relevant for airborne transmission.

Each location is geographically located using the Dun & Bradstreet commercial database. Each building is subdivided based on the number of activities available at that location. There are one or more buildings per activity that are further subdivided into rooms or mixing places. Schools have classrooms, workplaces have workrooms or offices, and shopping malls have shops. Typical room sizes can be specified; for example, for workplaces the mean workgroup size varies by standard industry classification (SIC) code. The number of rooms in each building is computed by dividing the peak occupancy by the appropriate mixing group size. We used two data sources to estimate the mean workgroup by SIC including a study on employment density [53] and a study on commercial building usage from the Department of Energy [36]. Based on these two data sources workgroup sizes range from 3.1 for transportation workers to 25.4 for health service workers. The average workgroup size over all types of work is 15.3. For the analyses presented here, the average mixing group sizes are 8.5 at a school, 4.4 at a shop, and 3.5 at a social recreation venue.

2.2.1 Disease Progression Model

Airborne diseases spread primarily from person to person during close proximity through contact, sneezing, coughing, or via fomites. In OPPIE, an opportunity for disease spread between two individuals occurs when they occupy a mixing location together. Whether or not a susceptible individual becomes infected is based on how long they co-occupy within a mixing place, the presence of infectious individuals, a high-level description of the activity they are engaged in, and their age.

A location represents a street address, and a room or mixing place represents a specific place where people have face-to-face interactions. When an infectious person is in one of these mixing locations with a susceptible person for some time, we estimate a probability of disease transmission, which depends on the variables identified above.

A susceptible person j has a dimensionless susceptibility multiplier S_j and an infectious person i has an infectious multiplier I_i. The probability that the susceptible individual j becomes infected during an activity is computed as:

$$P_j = 1 - e^{-\sum_i T S_j I_i t_{ij}} \tag{3}$$

where T is the average transmissibility per unit time, t_{ij} is the duration of contact, and the sum extends over all infectious people that occupied the room with individual j.

Disease progression of the epidemic is modeled as a Markov chain consisting of five main epidemiological stages: uninfected, latent (non-infectious), incubation (partially infectious), infectious, and recovered. Infected individuals start in the incubation stage and remain there for a period of between 0 and 0.5 days, 0.5 or 1.0 day, before transitioning to the symptomatic or recovered stages, respectively. The average incubation time is 1.9 days and average duration of the symptomatic stage is 4.1 [34]. The disease model assumes that 50% of adults and seniors, 75% of students, and 80% of preschoolers will stay home within 12 hours of the onset of influenza symptoms. These people can then transmit disease only to household members or visitors. Based on previous studies [34], 33.3% of infections are assumed to be subclinical. Individuals in the subclinical stage are only half as infectious as those in the symptomatic stages and continue their normal activities as if they were not infected. The infection rate for children is assumed to be double than for adults. All scenarios were analyzed for the same set of transmission parameters where the population was initially seeded with 100 people infected, all in the incubation stage.

2.2.2 Baseline Assumptions

The Homeland Security Council released the National Strategy for Pandemic Influenza for the United States, which suggests that the emergence of a new influenza virus could have a clinical disease attack rate of 30% in the overall

population [49]. Based on this attack rate, we constructed a baseline scenario under the assumption of no specific intervention to contain the pandemic and an infection attack rate of 45% with a clinical attack rate of 30%.

2.2.3 School Closure Assumptions

Protecting children during an influenza pandemic is important since illness rates are typically highest among school-aged children [38]. Closing schools limits students' contacts and has the potential to block paths of spread between families and neighborhoods [1]. Several studies have analyzed the impact of school closures [8,21,24]; however, these studies only investigated the impact of sustaining a school closed during the entire epidemic. School closures in OPPIE are implemented as a general closure of selected activity locations. Based on the Center for Disease Control and Prevention pandemic guidelines [9], closures in OPPIE follow a steplike function and are specified with a start and stop time; the activity to close; and a single location or a fraction of all locations of the specified activity type that will be closed. During the time a closure is in effect, anyone whose activity schedule would have taken them to one of the closed locations will stay home during that time instead. Scheduled after-school activities are not affected by a school closure.

2.2.4 Fear-Based Home Isolation Assumptions

Fear-based home isolation consists of people staying home as a reaction to an epidemic crisis. Some of these people may be considered the "worried well". The news of increasing numbers of people becoming ill, or seeing friends and family fall ill, is strong motivation to avoid potential infectious situations. Surprisingly, none of the recent studies on pandemic influenza have incorporated the impact of this type of behavioral change. We assume that people isolate due to fear at a level that follows the pattern of the epidemic [6, 27]. This is implemented with a specification of start, peak, and end times with corresponding fractions of the population that will be isolating at those times, along with a minimum and maximum contiguous duration per individual. We assume that people who choose to stay home will only self-isolate for 7–14 days at a time. People isolate on an individual basis, not on a household basis, so there might be households in which some members of the family are isolating due to fear and others are going about their normal activities. Fear-based home isolation begins when a percentage of the population is symptomatic (e.g., 0.1%). The number of people self-isolating increases linearly until reaching a maximum near the epidemic peak day. After this day, the stay-home rate begins to drop linearly with time, until no fear-based home isolation is occurring by a selected end day.

2.2.5 Strain-Specific Vaccine Assumptions

Currently, vaccine manufactures need an estimated 5–8 months to develop a strain-specific egg-based vaccine [47]. Based on seasonal influenza vaccine production, we estimate U.S. production at four million doses per week; thus, we assume that a limited number of vaccines, enough to cover 0.67% of the population per week, will be available five months after the emergence of pandemic influenza. We further assume that two doses of pandemic vaccine are required to attain an immune response of 80% seropositivity after 42 days from the first dose [33]. Those who are vaccinated and become sick are only 20% as infectious as those who become sick without the vaccine. In all of the scenarios where a strain-specific vaccine is considered, the strain-specific vaccine is distributed as soon as it becomes available. Vaccine is distributed to households at random until supplies run out; 95% of the selected household members are vaccinated, and 5% either refuse treatment or cannot be found.

3 Results

Here we show how we use both models to analyze the impact that behavioral changes may have on disease transmission. In particular, we look at the impact of some generic behavior for the ODE type model and school closures and fear-based home isolation for the agent-based model.

3.1 Ordinary Differential Equation Results

We recognize that large agent-based simulations may require significant infrastructure such as high performance computing; therefore, we analyze a simple ODE model and show how behavioral changes can modify disease dynamics.

We used the model presented in Sect. 2.1 and analyzed the impact that temporary behavioral changes (e.g., school closures) may have on the spread of an airborne infection. We use a population of 10,000 people and start the simulation with one infected person. We assume that some generic behavior is implemented for two weeks (14 days) starting on day 25. Furthermore, we assume that the behavior reduces susceptibility and infectivity by 50%, that is, $\eta_s = 0.5$ and $\eta_i = 0.5$. In addition, we assume that θ, a reduction in contact rates due to symptomatic infection, is 0.8. Finally, we assume that β, the probability of infection, is 0.4. Figure 2 shows the epidemic curves as a function of time for S_n, S_b, I_n, and I_b. Not that as people change their behavior, the disease spread slows down. Since behavioral changes are only temporary and do not provide a permanent cure to the disease, the virus eventually infects everyone in the population (due to homogeneous assumptions).

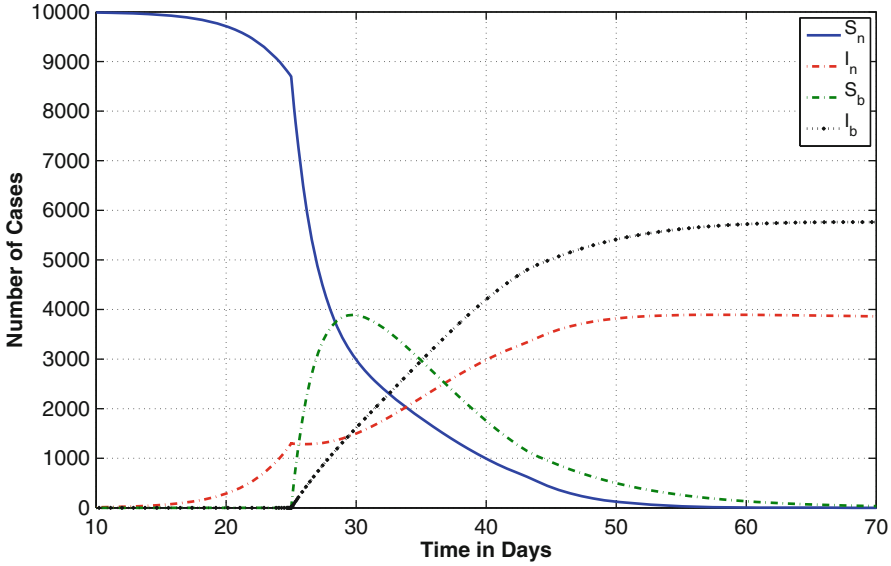

Fig. 2 *Epidemic curves* for various groups within the population including S_n, S_b, I_n, and I_b. Note that as the changes in behavior are implemented (starting on day 25), the disease transmission slows down

3.2 Agent-Based Model Results

3.2.1 Baseline Simulation

The baseline scenario was constructed with no specific intervention to contain the pandemic and an infection attack rate of 45% with a clinical attack rate of 30%. A key quantity in epidemiology is the basic reproduction number (denoted by R_0) defined as the average number of secondary cases generated by a primary infectious case in a completely susceptible population [2]. Hence, the R_0 concept only applies to the case of newly emergent infectious agents or situations when the disease in question has not been observed in a given population for a long period of time, so that the population is essentially entirely susceptible. This concept applies to most pandemics, particularly to the influenza pandemic of 1918 for which the mean R_0 has been estimated to range from 1.5 to 5.4, depending on the specific location and pandemic wave considered [10]. For consistency with historical pandemics [23,34], we considered a moderately severe pandemic strain with an R_0 of 1.8, which is in agreement with the transmissibility baseline assumed in other modeling studies [21, 23, 34]. OPPIE tracks who infects whom and so the value of R_0 was calculated using the average number of secondary infections generated by the index cases.

Table 1 Results for the baseline and various durations of 100% school closures

	Baseline	5-month 1st wave	5-month 2nd wave	8-month 1st wave	8-month 2nd wave	11-month
Clinical attack rate (%)	30.6	14.1	12	14.1	8.5	14.1
Pandemic duration (days)	150[a]	190[b]	350[a]	190[b]	465[a]	300[a]
Mortality per 100,000	614	279	240	282	164	281
Population vaccinated (%)	0	0	15.7	0	25.5	13.1

[a]When the number of newly infected cases has reached zero
[b]When the number of newly infected people has reached its lowest point before ramping up again

3.2.2 School Closures and Vaccination

School closures can provide an effective way to reduce the spread of the epidemic. We assumed that schools close when 0.1% of the population is symptomatic (day 33), and they remain closed for 5, 8, or 11 months. Table 1 shows that in the absence of any interventions, the model predicts a 30.6% clinical attack rate and 614 influenza-related deaths per 100,000 persons in the population. However, our results show that if schools remain closed for 11 months, the clinical and mortality attack rate would be reduced by more than 50%.

In Fig. 3, we show the symptomatic percentage of the population as a function of time for the baseline and for 100% school closures for 5, 8, and 11 months. School closures might be relaxed after 5 and 8 months, if a strain-specific vaccine becomes available. In the 5 month school closure scenario, schools reopen on day 183 when 0.0007% (14,238 people) is infected; in the 8 month scenario, schools reopen on day 273 when 0.00003% (721 people) of the population is infected. However, if schools close for the duration of the pandemic (in this case 11 months), the disease dies out and no second wave is generated. Unlike previous studies that have shown that the benefit provided by school closures is maintained after schools reopen [25], our simulation results show that, given the limited number of vaccine doses, if schools reopen too early a new infection wave appears, resulting in an increased number of new cases. Nevertheless, even in the presence of infection waves, the overall clinical attack rate for these three scenarios of school closures is lower than the baseline. Although school closures prolong the epidemic due to the reduction in the number of contacts, they benefit society by spreading the number of hospitalizations over two waves, which is crucial in order to maintain health-care services operational. Our results show that school closures for the duration of the pandemic (up to 11 months) are the most effective strategy in containing the pandemic and reducing morbidity and mortality. Furthermore, the 11 month strategy also reduces the number of vaccinations needed to contain the pandemic.

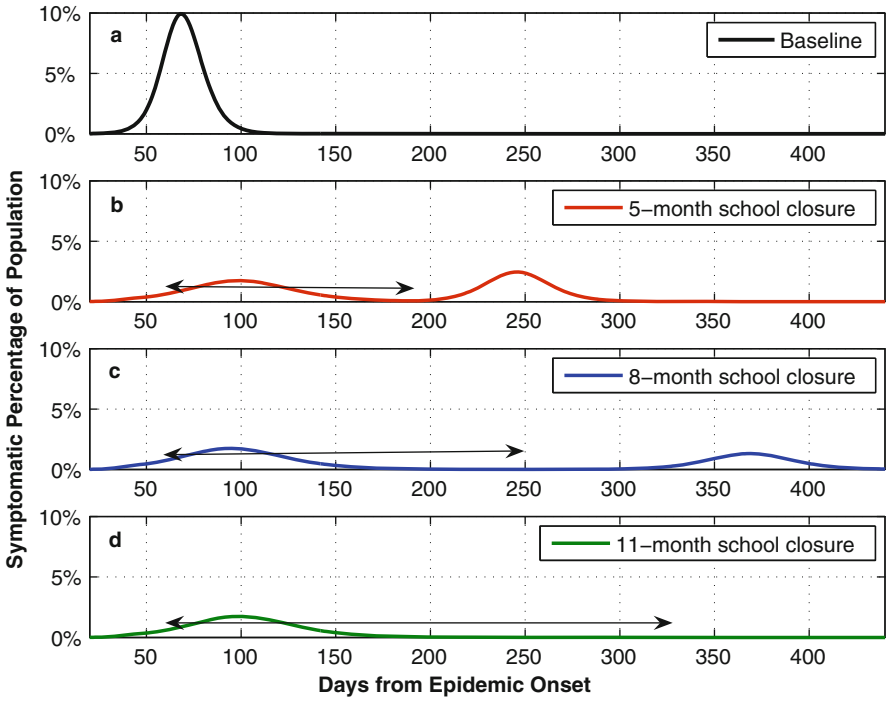

Fig. 3 Symptomatic percentage of the population as a function of time for the baseline scenario and three school closure scenarios. (**a**) shows the simulated epidemic curve for the baseline scenario, (**b**) shows the results for a 5-month closure scenario, (**c**) shows the results for an 8-month closure scenario, and (**d**) shows the results for the 11-month 100% closure scenario. The *arrows* indicate the time when school closures are in effect. Note that as the interventions are relaxed (schools reopen), new infection waves can appear (panels (**b**) and (**c**))

3.2.3 Fear-Based Home Isolation and Vaccination

In Table 2, we illustrate the simulation results for various levels of fear-based home isolation. When the percentage of population self-isolating at home, due to fear, is 15%, the clinical attack rate and death rate decrease, but the percentage of infections generated at home increases. When the number of people self-isolating is greater than 50%, the epidemic is partitioned into two infection waves and the number of infected people increases.

Figure 4 shows a comparison of the effective reproduction number and the epidemic dynamics for the baseline and 50% fear-based home isolation. $R_{\text{effective}}$ captures the effects of public health interventions and depletion of the susceptible population as the epidemic progresses. Note that $R_{\text{effective}}$ drops below 1 when the number of susceptibles declines, but as fear-based home isolation is relaxed and the social contact networks return to normal, $R_{\text{effective}}$ increases. In general, we observe that even if a small fraction of the population reduces their interactions for a

Table 2 Results for the baseline and various levels of fear-based home isolation

	Baseline	15%	30%	50% 1st wave	50% 2nd wave	60% 1st wave	60% 2nd wave
Clinical attack rate (%)	30.6	25.9	20.5	13	9.6	7.6	18.2
Pandemic duration (days)	150[a]	211[a]	300[a]	184[b]	372[a]	161[b]	340[a]
Mortality per 100,000	614	517	411	251	199	150	364
Population vaccinated (%)	0	2.8	5.9	0	17.8	0	13.3
Infections generated at home (%)	58.4	62.2	65.8	65	65	62.9	62.9

[a]When the number of newly infected cases has reached zero
[b]When the number of newly infected people has reached its lowest point before ramping up again

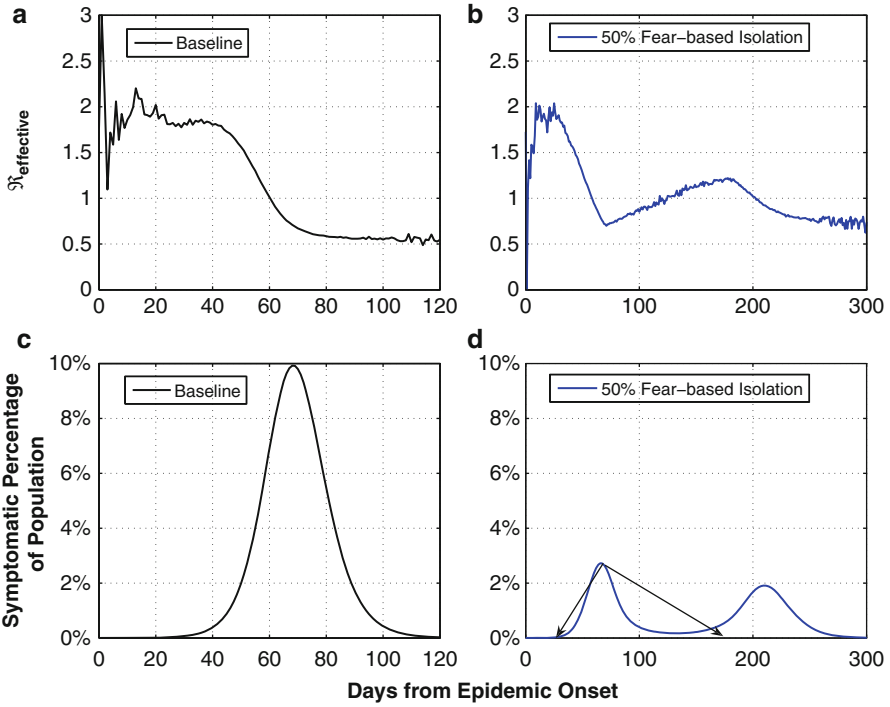

Fig. 4 Epidemic dynamics for the baseline and 50% fear-based home isolation for 5-months. (**a**) and (**b**) show the effective reproduction number as a function of time for the baseline and 50% fear-based home isolation, respectively. (**c**) and (**d**) show the symptomatic percentage of the population for the baseline and the 50% fear-based home isolation scenario

week or two, morbidity and mortality can be reduced, but the epidemic is prolonged; however, temporal compliance of large fractions of people can create susceptible populations, resulting in waves of infection [6, 27, 41].

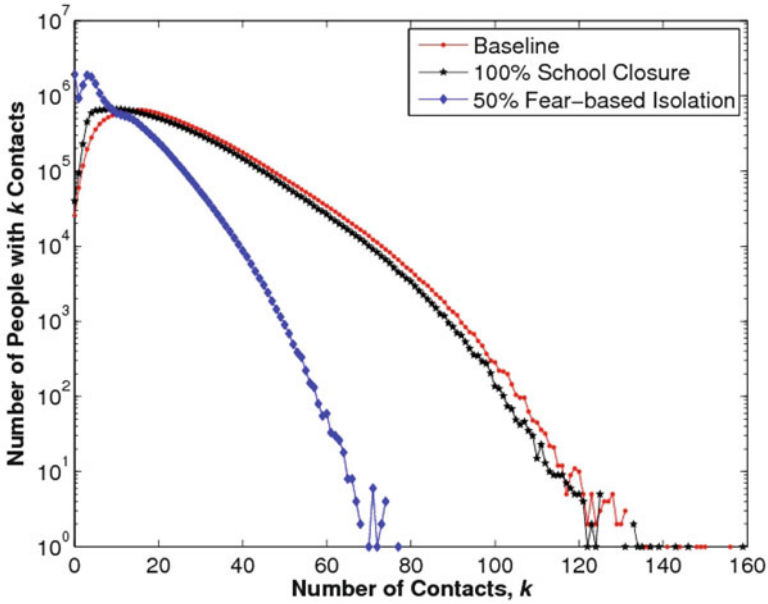

Fig. 5 Degree distribution of the population in Southern California under three different scenarios for a typical day. On average, each individual has 22.5, 19.9, and 8 contacts per day for the baseline, 100% school closure scenario (5-month), and 50% fear-based home isolation scenario, respectively

3.2.4 Impact on Social Contact Network

Population mixing information is key to provide good approximation on the path of the disease and devise effective intervention strategies. Here, we apply tools from social network epidemiology [35,39,43] to study how changes in behavior affect the contact network and, as a result, disease transmission. The social contact network emerges from the simulation as individuals move through their daily activities and come into and out of contact in rooms [11]. We extracted the degree distribution of the social contact structure in the absence of disease during a random day for the baseline, 100% school closure scenario, and at the peak of the 50% fear-based home isolation scenario. Figure 5 depicts the population distribution in Southern California under the three scenarios for a typical day. On average, each individual has 22.5, 19.9, and 8 contacts per day for the baseline, 100% school closure scenario, and 50% fear-based home isolation scenario, respectively. We observe that the average number of contacts per day decreased for the school closure and fear-based home isolation scenarios when compared to the baseline. Note that the average number of people contacted per person can provide an estimate of how many people can potentially acquire infection from one index case. Furthermore, we found that closing schools would be less effective in breaking the social contact network than fear-based home isolation. This finding might be due to the fact that school closures

imply partial home isolation; individuals affected by this intervention still perform other scheduled activities, except for school-related activities. While fear-based home isolation assumes that people affected by this intervention are completely cut off from the rest of the population, our results show that reactive changes in population contact rates can have a dramatic impact on the overall contact structure.

4 Discussion

We used two types of modeling approaches to show that coordinated or reactive behavioral modifications can have a significant effect not only in reducing disease burden but also on the qualitative dynamics of influenza transmission. Although vaccination would be the best means for controlling influenza, a strain-specific vaccine will not be available until 5–8 months after the emergence of a new pandemic influenza and current production capabilities are insufficient to cope with demand. Antivirals share important features that could make them useful during a pandemic [34], although most countries do not have enough antivirals stockpiled and current distribution strategies may not allow for rapid dissemination of drugs. Behavioral modifications have the potential to slow down the spread of the pandemic in the absence of pharmaceutical interventions.

We argue that models that use social contact networks and human behavior are better able to capture the dynamics of infectious-disease transmission than models that ignore human behavior or use homogeneous mixing. We showed how easy one can incorporate behavioral changes in traditional ODE epidemiological models and how simple assumptions can change the dynamics of disease transmission.

The emergent degree distribution of the baseline social network is in agreement with contact patterns observed in small convenience samples [17, 51]. Although we cannot compare the emergent contact patterns in the presence of school closures and fear-based home isolation due to lack of data, our simulation results are useful in providing estimates of the effects of behavioral changes on disease burden and gain insights into potential qualitative effects on the transmission dynamics (e.g., multiple waves of infection). The simulations suggest that fear-based home isolation at moderate levels (less than 50%) can have an impact on breaking transmission paths; however, its impact on the social contact network is highly sensitive to the duration that this intervention is in effect.

Our simulations show that if 100% of the schools close when 0.1% of the population is ill and they remain closed for the duration of the pandemic, the clinical attack rate could be reduced by more than 50%, when compared with the baseline. However, if schools reopen before the pandemic is over, a second wave is likely to appear and increase morbidity and mortality; thus, the parameters associated to a school closing policy should depend on the actual pandemic profile. For example, our results suggest that a temporary school closure policy may not be successful in

the sense that secondary waves of infection could be triggered if the school closure policy is suspended when the pandemic is still running its course.

The appearance of a second wave may imply a failed intervention strategy [41]; however, our results suggest that the overall clinical attack rate when a school closure intervention strategy is implemented is still lower than that obtained from the baseline scenario. Temporary school closures may have benefits beyond reducing morbidity and mortality, such as maintaining health-care services by spreading the number of hospitalizations over two waves. However, school closures indirectly contribute to absenteeism when parents must miss work to care for their children at home. Therefore, recommendations on school closures must be planned in advance to reduce the social and economic impact of absenteeism.

Fear-based home isolation can be effective in reducing morbidity and mortality and slowing transmission. The effectiveness of fear-based home isolation is determined by the fraction of the population that voluntarily withdraws from their daily activities for a week or two. We showed that as the number of people isolating at home increases, the clinical attack rate decreases. However, when the fraction of people self-isolating is over 50% (e.g., the intervention is too strong [26]) a second infection wave appears if home isolation is relaxed, leading to a larger clinical attack rate. It may not be feasible in reality for a large fraction of the population to self-isolate for a week or two; however, even if a small fraction of the population self-isolates, it can have a dramatic impact on reducing morbidity and mortality.

One of the most striking results of our study is the fact that temporary behavioral modifications have the potential to generate waves. This result raises an interesting question about the role that behavioral changes played in previous pandemics, since there were some temporary public health measures during the 1918 pandemic [6, 7, 12, 27]. There is a potential for multiple infection waves if public health measures are relaxed before the epidemic is over. Perhaps the most illustrative example of secondary waves is the 2002–2003 SARS epidemic in Toronto, Canada, where a secondary wave of infection occurred following a relaxation of infection-control precautions that were also associated with temporary increases in nosocomial transmission events [41]. The potential role that behavior changes may have played on the multiple wave pandemic profile observed during the 1918–1919 influenza pandemic in many regions of the world should not be discarded [6, 12, 27].

Early detection of index cases and early dissemination of information to the public are critical to empowering the population to make rational decisions, such as self-isolation. Capturing human behavior can have a profound influence in the predictions of future disease spread and the resources needed to contain an outbreak [19]. Modeling studies such as the one presented here could prove useful in providing estimates of the effects of changes in human behavior for future pandemic guidelines.

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References

1. Ackerman, E., Elveback, L.R., Fox, J.P.: Simulation of Infectious Disease Epidemics. CC Thomas, Springfield, Illinois (1988)
2. Anderson, R.M., May, R.M.: Infectious Diseases of Humans. Oxford University Press, Oxford (1991)
3. Bansal, S., Pourbohloul, B., Meyers, L.A.: PLoS Med. e387 (2006)
4. Bansal, S., Grenfell, B.T., Meyers, L.A.: J. R. Soc. Interface **4**, 879 (2007)
5. Blower, S.M., Porco, T.C., Darby, G.: Nature Med. **4**, 673 (1998). doi: 10.1038/nm0698-673
6. Bootsma, M.C.J., Ferguson, N.M.: Proc. Natl. Acad. Sci. USA **104**, 7588 (2007). doi: 10.1073/pnas.0611071104
7. Caley, P., Philp, D.J., McCracken, K.: J. R. Soc. Interface **6**, 631 (2008). doi: 10.1098/rsif.2007.1197
8. Cauchemez, S., Valleron, A.J., Boëelle, P.Y., Flahault, A., Ferguson, N.M.: Nature **452**, 750 (2008). doi: 10.1038/nature06732
9. Centers for Disease Control and Prevention (CDC). Interim pre-pandemic planning guidance: Community strategy for pandemic influenza mitigation in the United States Early, targeted, layered use of nonpharmaceutical interventions. http://www.flu.gov/planning-preparedness/community/community_mitigation.pdf. Cited 4 Apr 2012
10. Chowell, G., Nishiura, H.: Phys. Life Rev. **5**, 50 (2008). doi: 10.1016/j.plrev.2007.12.001
11. Chowell, G., Hyman, J.M., Eubank, S., Castillo-Chavez, C.: Phys. Rev. E 68(6 Pt 2), 066102 (2003). doi: 10.1103/PhysRevE.68.066102
12. Chowell, G., Ammon, C.E., Hengartner, N.W., Hyman, J.M.: J. Theor. Biol. **241**, 193 (2006). doi: 10.1016/j.jtbi.2005.11.026
13. Colizza, V., Barrat, A., Barthelemy, M., Valleron, A., Vespignani, A.: PLoS Med. **4**, e13 (2007). doi: 10.1371/journal.pmed.0040013
14. Cooper, B.S., Pitman, R.J., Edmunds, W.J., Gay, N.J.: PLoS Med. **3**, e212 (2006). doi: 10.1371/journal.pmed.0030212
15. Del Valle, S., Hethcote, H., Hyman, J.M., Castillo-Chavez, C.: Math. Biosc. **195**, 228 (2005). doi: 10.1016/j.mbs.2005.03.006
16. Del Valle, S.Y., Hyman, J.M., Hethcote, H.W., Eugank, S.G.: Soc. Networks **29**, 539 (2007). doi: 10.1016/j.socnet.2007.04.005
17. Edmunds, W.J., O' Calaghan, C.J., Nokes, D.J.: Proc. R. Soc. B **22**, 264 (1997). doi: 10.1098/rspb.1997.0131
18. Eubank, S.G., Guclu, H., Kumar, V.A., Marathe, M.V., Srinivasan, A., Toroczkai, Z., Wang, N.: Nature **429**, 180 (2004). doi: 10.1038/nature02541
19. Ferguson, N.: Nature **446**, 733 (2007). doi: 10.1038/446733a
20. Ferguson, N.M., Keeling, M.J., Edmunds, W.J., Gani, R., Grenfell, B.T., Anderson, R.M., Leach, S.: Nature **425**, 681 (2003). doi:10.1038/nature02007
21. Ferguson, N.M., Cummings, D.A., Cauchemez, S., Fraser, C., Riley, S., Meeyai, A., Iamsirithaworn, S., Burke, D.S.: Nature **437**, 209 (2005). doi: 10.1145/1315843.1315857
22. Fukś, H., Lawniczak, A.T., Duchesne, R.: Eur. Phys. J. B **50**, 209 (2006). doi: 10.1140/epjb/e2006-00136-7
23. Gani, R., Hughes, H., Fleming, D., Griffin, T., Medlock, J., Leach, S.: Infect. Dis. **11**, 1355–1362 (2005)
24. Germann, T.C., Kadau, K., Longini, I.M. Jr., Macken, C.A.: Proc. Natl. Acad. Sci. USA **103**, 5935 (2006). doi: 10.1073/pnas.0601266103

25. Glass, K., Barnes, B.: Epidemiology **18**, 623 (2007). doi: 10.1097/EDE.0b013e31812713b4
26. Handel, A., Longini, I.M., Antia, R.: Proc. R. Soc. B **274**, 833 (2007). doi: 10.1098/rspb.2006.0015
27. Hatchett, R.J., Mecher, C.E., Lipsitch, M.: Proc. Natl. Acad. Sci. USA **104**, 7582 (2007). doi: 10.1073/pnas.0610941104
28. Hethcote, H.W.: SIAM Rev. **42**, 599 (2000). 10.1137/S0036144500371907
29. Isham, V., Mdley, G.: Models for Infectious Human Diseases: Their Structure and Relation to Data. Cambridge University Press, Cambridge (1996)
30. Johnson, N.P., Mueller, J.: Bull. Hist. Med. **76**, 105 (2002). doi: 10.1353/bhm.2002.0022
31. Kermack, W.O., McKendrick, A.G.: Proc. R. Soc. Series A **115**, 700 (1927). 10.1098/rspa.1927.0118
32. Kilbourne, E.D.: Emerg. Infec. Dis. **12**, 9 (2006). doi: 10.3201/eid1201.051254
33. Lin, J., Zhang, J., Dong, X., Fang, H., Chen, J., Su, N., Gao, Q., Zhang, Z., Liu, Y., Wang, Z., Yang, M., Sun, R., Li, C., Lin, S., Ji, M., Liu, Y., Wang, X., John, W., Feng, Z., Wang, Y., Yin, W.: Lancet **368**, 991 (2006). doi: 10.1016/S0140-6736(06)69294-5
34. Longini, I.M., Halloran, M.E., Nizam, A., Yang, Y.: Am. J. Epidemiol. **159**, 623 (2004). doi: 10.1093/aje/kwh092
35. Meyers, L.A., Pourbohloul, B., Newman, M.E.J., Skowronski, D.M., Brunham, R.C.: J. Theor. Biol. **232**, 71 (2004). doi: 10.1016/j.jtbi.2004.07.026
36. Michaels, J.: Commercial buildings energy consumption survey. (2003). http://www.eia.doe.gov/emeu/cbecs/cbecs2003/detailed_tables_2003/detailed_tables_2003.html. Cited 12 June 2012
37. National Household Travel Survey (NHTS). http://www.bts.gov/programs/national-household-travel-survey. Cited 4 April 2012
38. Neuzil, K.M., Hohlbein, C., Zhu, Y.: Arch. Pediar. Adolesc. Med. **156**, 986 (2002)
39. Newman, M.E.J.: Phys. Rev. E **66**, 016128 (2002). doi: 10.1103/PhysRevE.66.016128
40. Nuno, M., Chowell, G., Gumel, A.: J. R. Soc. Interface **22**, 505 (2007). doi: 10.1098/?rsif.2006.0186
41. Ofner-Agostini, M., Wallington, T., Henry, B., Low, D., McDonald, L.C., Berger, L., Mederski, B., SARS Investigative Team, Wong, T.: Investigation of the second wave (phase 2) of severe acute respiratory syndrome (SARS) in Toronto, Canada. What happened? Can. Commun. Dis. Rep. **34**, 1–11 (2008)
42. Pang, X., Zhu, Z., Xu, F., Guo, J., Gong, X., Liu, D., Liu, Z., Chin, D.P., Feikin, D.R.: J. Am. Med. Assoc. **290**, 3215 (2003)
43. Reed, J.M., Keeling, M.J.: Proc. R. Soc. B **270**, 699 (2003). doi: 10.1098/rspb.2002.2305
44. Ross, R.: The Prevention of Malaria. John Murray, London (1911)
45. Smith, D.J., Forrest, S., Ackley, D.H., Perelson, A.S.: Proc. Natl. Acad. Sci. USA **96**, 14001 (1999). doi: 10.1073/pnas.96.24.14001
46. Stilianakis, N.I., Perelson, A.S., Hayden F.G.: J. Infect. Dis. **177**, 863 (1998). doi: 10.1086/515246
47. Stohr, K., Esveld, M.: Science **306**, 2195 (2004). doi: 10.1126/science.1108165
48. Stroud, P.D., Del Valle, S.Y., Sydoriak, S.J., Riese, J., Mniszewski, S.: J. Artif. Soc. Soc. Simulat. **10**(4), 9 (2007)
49. US Homeland Security Council (HSC), National Strategy for Pandemic Influenza Implementation Plan. http://www.flu.gov/planning-preparedness/federal/pandemic-influenza-oneyear.pdf. Cited 4 Apr 2012
50. United Nations (UN), Department of Economic and Social Affairs, Population Division, Urban Population Development and the Environment (2007), http://www.un.org/esa/population/publications/2007-PopDevt/2007-PopDevt-Urban.htm. Cited 4 Apr 2012
51. Wallinga, J., Teunis, P., Kretzschmar, M.: Am. J. Epidemiol. **164**, 936 (2006). doi: 10.1093/aje/kwj317

52. Woodson, G.: 2005 Preparing for the Coming Influenza Pandemic. http://earthsky.org/health/grattan-woodson-interview Cited 4 Apr 2012
53. Yee, D., Bradford, J.: Employment density study, Canadian METRO Council Technical Report (1999)
54. Zaric, G.S.: Healthcare Manage. Sci. **5**, 147 (2002). doi: 10.1023/A:1014489218178

Uncoordinated Human Responses During Epidemic Outbreaks

Piero Poletti, Bruno Caprile, Marco Ajelli, and Stefano Merler

Abstract Uncoordinated human behavioral responses triggered by risk perception can alter the evolution of an epidemic outbreak further and beyond control measures imposed by public authorities. In fact, spontaneous behavioral changes could develop as a defensive response during the spread of an epidemic, thereby impacting the epidemic dynamics and affecting timing and overall number of cases. In this chapter, a model coupling the classic SIR disease transmission model with an imitation dynamics process is introduced which accounts for the diffusion of different behaviors in the population as a response to the epidemic threat. A detailed analysis of the model identifies the main determinants leading to remarkable alterations in infection dynamics in both risk perception and diffusion of human behavioral patterns. Empirical evidence points to the need of incorporating human behavior in prediction models informing public health decisions.

1 Introduction

Mechanisms able to account for spontaneous behavioral changes in response to perceived risk are increasingly important as they have the potential for improving predictions about the spread of emerging epidemics. The aim of this chapter is to analyze the main determinants in both risk perception and diffusion of human behavioral patterns leading to remarkable alterations in infection dynamics.

In particular, a model accounting for human behavioral response to the risk of infection is introduced. The approach is fairy general to be applied to the description of epidemic outbreaks caused by different diseases (e.g., due to influenza, smallpox, SARS). The effectiveness of human self-protection is investigated by considering

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behavioral changes during the spread of a generic, influenza-like infection. The role of the key parameters regulating the mechanism of spontaneous self-protection is analyzed along with the interplay between risk perception and the disease transmission process. As a practical application, the effect played by risk perception during the 2009 H1N1 pandemic in Italy is discussed.

1.1 Evidence of Uncoordinated Behavioral Changes

During an epidemic outbreak, individuals may change their behavior in order to reduce the risk of infection, especially when serious consequences for individual health are implied. A population-based survey reported that more than 75 % of respondents would avoid public transportation and 20–30 % would try to avoid crowded environments as precautionary actions in response to a hypothetical influenza pandemic [22]. During the 2009 H1N1 influenza, an initial high level of anxiety about the pandemic has been observed [11] and different behavioral changes triggered by the perceived risk of infection have been reported [7, 21, 23–25]. In Australia, after the first pandemic wave, individuals "reported increasing hand-washing (46 %) and covering cough and sneezes (27 %)" to reduce the risk of infection [24]. In the USA, data collected on public response to H1N1 influenza from May 2009 to June 2009 suggest that "16 to 25 % of Americans had avoided places where many people are gathered, like sporting events, malls, or public transportation and 20 % had reduced contact with people outside [their] household as much as possible" [25]. Furthermore, larger uncoordinated behavioral changes have been detected for more severe epidemics. For instance, an 80 % reduction in travel to and from Hong Kong has been reported during the 2003 SARS crisis [9]. This empirical evidence highlights that behavioral response occurs when a new infectious disease emerges, although it is hard to quantify its impact on the epidemic spread.

1.2 Evolutionary Game Theory and Epidemic Modeling

Human behavioral change in response to the risk of infection can be accounted for by modeling the diffusion of fear as a parallel infection. In this case, the "recovery from fear" occurs at a constant rate, regardless the current state of the epidemic and the behavior adopted by the individuals. However, individuals may or may not reduce risky behaviors on the basis of the current risk perception of the epidemic. The approach considered in this chapter is based on evolutionary game theory [12], which allows considering a symmetric mechanism regulating spontaneous behavioral changes. Different behaviors adopted in the population are

represented by a given set of strategies. The adoption of self-protection is assumed to be driven by the perceived convenience of different behaviors, dependent on the epidemic dynamics.

2 The Model

The disease transmission process is based on an SIR scheme, where susceptible individuals may adopt two mutually exclusive behaviors, *"normal"* b_n and *"altered"* b_a, on the basis of the perceived risk of infection. We assume that individuals adopting the *altered* behavior are able to reduce the risk of getting infected by reducing the number of potentially infectious contacts and, in turn, the force of infection to which they are exposed. This defensive response accounts for both reduction in physical contacts and, more in general, all self-prophylaxis measures which can reduce the transmission probability during these contacts. For instance, a reduction in the number of contacts can be achieved by avoiding crowded environments or by limiting travels, whereas a reduction in transmission probability can occur as a consequence of an increased wariness in common activities (e.g., the behavioral goals recommended by the WHO for reducing influenza transmission, such as washing hands frequently or respecting cough/respiratory etiquette).

In the model, spontaneous behavioral changes occur on the basis of cost/benefit considerations. This assumption perfectly fits the language of evolutionary game theory, in which behaviors adopted by individuals correspond to strategies played in a suitable game, with certain expected payoffs.

All individuals pay a cost for the risk of infection, which we assume to depend linearly on the perceived prevalence $M(t)$ and to be higher for individuals adopting the *normal* behavior (b_n) than for those adopting the *altered* behavior (b_a). However, individuals playing b_a pay an extra, fixed, cost because they are limiting their usual activities. Therefore, the payoffs associated with b_n and b_a result respectively:

$$P_n(t) = -m_n M(t), \quad P_a(t) = -k - m_a M(t)$$

The *altered* behavior gives the advantage of reducing the risk of infection ($m_n > m_a$), but the extra cost associated to it (k) implies that the *normal* behavior is the most convenient one when the perceived prevalence M is small (or in absence of disease). Which behavior is more convenient to adopt clearly depends on the status of the epidemic. The balance of the payoff between the two possible behaviors is determined by the cost associated to the risk of infection and on the perceived prevalence of infections in the population (M(t)). The latter is modeled by assuming a fading memory mechanism (such in [1, 6]) altering the perception of the risk of infection on the basis of the number of cases occurred over a certain (past) period of time.

The diffusion of strategies in the population is modeled as an imitation process [4, 12] based on the idea that individuals change strategy as they become aware that their payoff can increase by adopting a different behavior. By introducing the variables S, I, and R (describing the fraction of susceptible, infective, and recovered individuals, respectively) and by introducing the variable x (describing the fraction of individuals adopting the *normal* behavior), the system governing this process can be written as follows:

$$\begin{cases} \dot{S} &= -\beta IS[x+q(1-x)] \\ \dot{I} &= \beta IS[x+q(1-x)] - \gamma I \\ \dot{R} &= \gamma I \\ \dot{M} &= \beta IS[x+q(1-x)] - \nu M \\ \dot{x} &= x(1-x)(q\beta I - \beta I) + \rho x(1-x)(1-mM)S \end{cases} \tag{1}$$

where β is the transmission rate; $1/\gamma$ is the average duration of infectivity period (here corresponding to the generation time); q represents the reduction of the risk of infection to which individuals adopting the *altered* behavior are exposed; ν weighs the decay of the perceived prevalence; ρ essentially represents the speed of the imitation process with respect to the pathogen transmission dynamics; $m = (m_n - m_a)/k$ defines the risk threshold for determining which behavior would represent the most convenient choice.

Basically, the last equation of the system accounts for the diffusion of the two different behaviors in the population. The first term of the equation accounts for a natural selection embedded into the transmission process that favors individuals reducing the risk of infection ($q\beta I - \beta I < 0$); the second term represents the imitation process and accounts for spontaneous changes in individual behaviors, based on the balance between the payoffs associated to the two different behaviors (i.e., $1 - mM$). Behavioral change driven by the imitation dynamics occurs depending on the difference between the payoffs of the two possible behaviors, the perceived prevalence, the level of the risk threshold, and the speed of the imitation process. The latter is in general different from the speed of the disease transmission process as imitation is based on the diffusion of information. Details on the derivation of the last equation in System 1 can be found in [19] for a model comprising behavioral changes possibly occurring among infective individuals and for different symptomaticity levels of the infection.

2.1 Basic Reproduction Number

The basic reproduction number R_0 is defined as the average number of secondary infections that results from a single infectious individual in a fully susceptible population. For the System 1, R_0 can be computed using the next-generation technique [5], and it results to be $R_0 = [x+q(1-x)]\beta/\gamma$. R_0 can thus be interpreted

as a weighted sum of two basic reproductive numbers: the reproductive number for individuals adopting the *normal* behavior (namely the fraction x), i.e., $R_0^n = \beta/\gamma$ and the reproductive number for individuals adopting the *altered* behavior (namely the fraction $1-x$), i.e., $R_0^a = q\beta/\gamma$. Therefore, R_0 depends on the fraction of individuals in the population who are currently adopting either *normal* or *altered* behavior.

3 Behavioral Changes During a "Generic" Influenza-Like Infection

In this section, parameters characterizing the disease transmission process are taken from reliable estimates available for the 2009 H1N1 pandemic influenza. Specifically, R_0 is assumed to be 1.4, and the generation time is taken equal to 2.8 days [3, 10, 16].

3.1 Baseline Scenario

The effect of possible spontaneous behavioral responses to the risk of infection on the epidemic spread is investigated, starting from a *baseline* configuration and by varying one by one the parameters. This baseline represents the simple case where the perceived prevalence M is exactly the prevalence of infections I ($\gamma = \nu$) and at the beginning of the epidemic the perceived risk of infection is zero ($M(0) = 0$). Moreover, as an illustrative scenario, values of parameters related to human behavioral response are taken in such a way that (a) the adoption of the *altered* behavior reduces by 15 % the number of potentially infectious contacts, i.e., $q = 0.85$; (b) the *altered* behavior becomes more convenient when the prevalence becomes larger than the 1 % of the population, i.e., $1/m = 0.01$; (c) the delay between the time at which the *altered* behavior becomes convenient and the time at which more than 50 % of the population becomes responsive is about 5 days, i.e., $\rho = 10$. The initial conditions considered in this section are $S(0) = 1 - 10^{-3}$, $I(0) = 10^{-3}$, $x(0) = 1 - 10^{-6}$, and $R(0) = M(0) = 0$.

The resulting dynamics of System (1) is shown in Fig. 1. After an initial growth of the epidemic, the perceived prevalence reaches the prevalence threshold $1/m$ and the *altered* behavior becomes more convenient. As a consequence when the *altered* behavior became widely adopted in the population, which occurs after few days, the epidemic growth rate reduces remarkably. As the prevalence decreases below the threshold, the *normal* behavior becomes more convenient and its diffusion produces a fat tail in the infection dynamics.

The timing of the behavioral response is characterized by parameters m and ρ. The former describes how the perceived prevalence M is weighted in the payoff functions, i.e., in the balance of the cost associated to the risk of infection and the

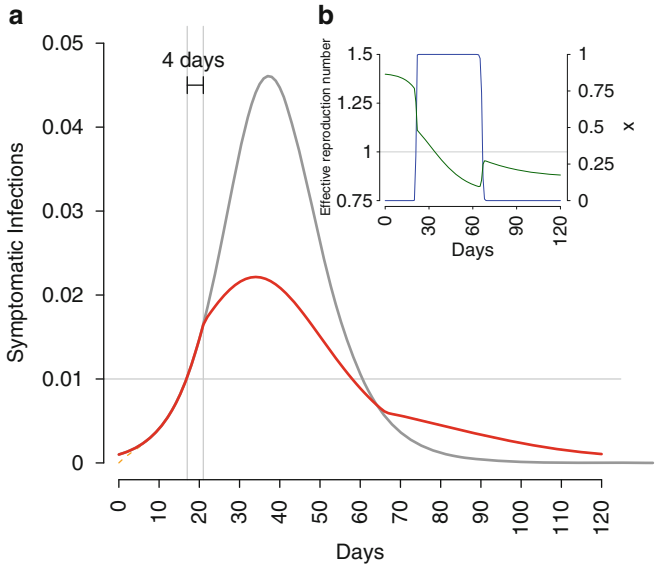

Fig. 1 (**a**) Daily prevalence of infection in the case of no responsiveness of the population ($q = 1$ *bold gray line*) and in the baseline scenario ($q = 0.85$, *bold red line*). The *horizontal gray line* represents the prevalence threshold $1/m$. The behavioral response appears about 4 days after the perceived prevalence $M(t) = I(t)$ crosses the threshold $1/m$ producing a lower increase in the prevalence of infection. (**b**) The dynamics of $1 - x$ (*blue line*, scale on the *left*) and the effective reproductive number over time (*dark green line*, scale on the *right*)

cost of a self-protection strategy. The latter represents the speed of the imitation process with respect to the disease transmission timescale. As a matter of fact, $1/m$ defines the threshold for the perceived prevalence above which individuals reducing contacts have a larger payoff; the larger m, the earlier the *altered* behavior is perceived as the most convenient choice. On the other hand, ρ drives the delay (embedded in the imitation dynamics) between the time at which a strategy becomes more convenient and the time at which the strategy is adopted by the majority of the population. In sum, the time at which the transition between the two possible behaviors occurs is driven by m, while the duration of this transition is driven by ρ; these two parameters together define the *responsiveness* of the population to an epidemic outbreak.

3.2 *Effectiveness of Human Self-protection*

The effectiveness of human self-protection is analyzed in terms of: (1) final epidemic size (defined as the total number of infections at the end of the epidemic); (2) daily peak prevalence; (3) peak day.

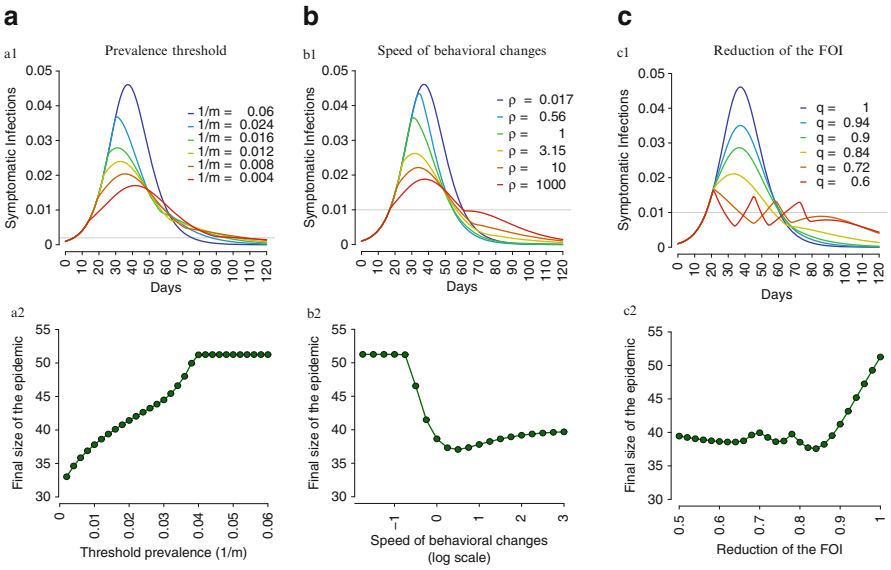

Fig. 2 (**a**) Daily prevalence of infections ($a1$), final epidemic size ($a2$) as obtained for different values of the prevalence threshold $1/m$. Other parameters as in the baseline scenario. (**b**) As (a) but for different values of the speed of behavioral changes ρ. (**c**) As (a) but for different values of the reduction factor q

As mentioned above, a major responsiveness of the population to an infection corresponds to a small prevalence threshold (large values of m) and to large values of ρ. The responsiveness of the population is related to time at which the behavioral response starts to affect the population behavior. As the population responsiveness increases, a larger reduction in the final epidemic size and in the daily peak prevalence is observed (see Fig. 2a and b). However, if the prevalence threshold $1/m$ is larger than the maximum prevalence of infections, or the imitation process is too slow (i.e., for small values of ρ), the human response never takes place and the epidemic spreads following the dynamics of an SIR model driven by R_0^n. An unreachable prevalence threshold represents the situation in which the epidemic is not perceived sufficiently severe to trigger a behavioral response of the population. This happens when $1/m$ is larger than $I^p = 1 - \frac{1}{R_0^n} + \frac{1}{R_0^n} \log \frac{1}{R_0^n}$, i.e., the largest possible daily peak prevalence, which is reached when all individuals adopt the *normal* behavior throughout the whole course of the epidemic.

The size of reduction in contagious contacts associated to the *altered* behavior has a strong impact on the epidemic dynamics. A larger reduction of the risk of infection is enacted by individuals adopting the *altered* behavior when smaller values of q are considered. As q decreases, the final epidemic size and the daily peak prevalence reduce as well (see Fig. 2c).

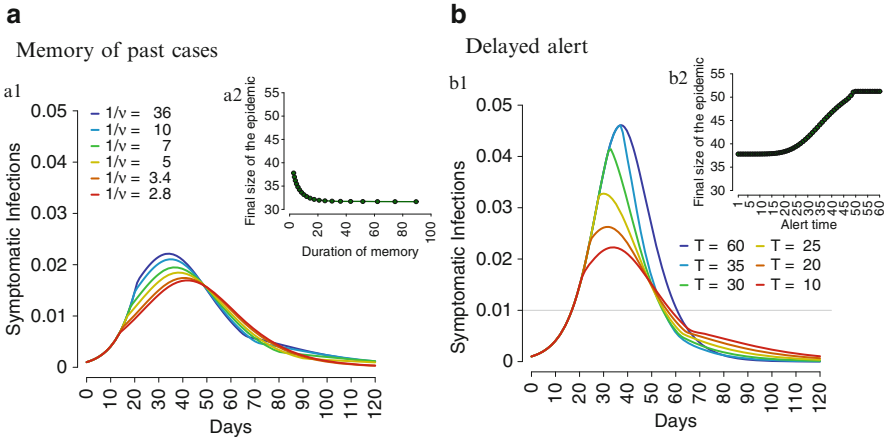

Fig. 3 (**a**) Daily prevalence of infections (*a1*), final epidemic size (*a2*) as obtained for different values of the average memory length $1/\nu$. Other parameters as in the baseline scenario. (**b**) As (a) but for different values of the alarm time T (in days)

At this point three interesting aspects are worth highlighting:

1. Even a small reduction in the number of contagious contacts enacted by the population can remarkably alter the spread of the epidemic.
2. A threshold exists for q such that for smaller values of q a larger impact of behavioral changes on the final epidemic size, the daily peak prevalence, and the peak day does not occur. Indeed, in terms of the final epidemic size and the peak day, a reduction of 100 % in the number of potentially infectious contacts (corresponding to $q = 0$, i.e., total isolation) produces the same effects obtained by considering a reduction of 25 % ($q = 0.75$).
3. For small values of q, the model accounts for multiple epidemic waves. A detailed discussion on the conditions for observing such a pattern can be found in [17].

3.3 Risk Perception and Information Diffusion

In Sects. 3.1 and 3.2 the perceived prevalence M at time t is assumed to be exactly the prevalence I at time t (i.e., $\nu = \gamma$). However, individuals may explore the convenience of different behaviors taking into account infections occurred over a (past) period of time. This case is investigated by considering $1/\nu > 1/\gamma$. As a matter of fact, the perceived risk of infection associated to every single new infection is larger when $1/\nu > 1/\gamma$ is considered. Therefore, it is not surprising that a longer memory duration leads to a larger diffusion of the *altered* behavior and implies a decrease in the daily peak prevalence and the final epidemic size, and a delay in the epidemic spread (see Fig. 3a).

A misperception of risk may occur when the population becomes aware of a new epidemic outbreak after a period of time since the emergence of the epidemic. This situation can be investigated by assuming that the perceived prevalence is initially equal to zero for a certain period of time, T. Figure 3b shows that the effectiveness of human response diminishes when a larger delay is considered. In particular, daily peak prevalence and final epidemic size increase as T increases and, no relevant effects on the outbreak can be detected when the "alert" takes place too late.

4 The 2009 H1N1 Pandemic in Italy

In March 2009, a new influenza virus emerged in Mexico giving rise to a pandemic that spread worldwide [10]. Early in the course of the pandemic, the population was very concerned about the event [15, 21]. Did this affect the behavior of the population and, consequently, alter the dynamics of the epidemic?

As most European countries, Italy experienced one single pandemic wave during fall-winter 2009 and no substantial activity was detected during the summer. However, the weekly influenza-like-illness (ILI) incidence is characterized by an initial slow exponential increase (September–mid-October 2009) followed by a sudden and sharp increase of the growth rate (mid-October). Over the whole period schools remained open [8] and only moderate mitigation measures were enacted (e.g., antiviral treatment of severe cases) [14]. This allows us to investigate an "uncontrolled" epidemic, not affected by "heavy" public health interventions or by school closure. On the other hand, since the emergence of the pandemic the Italian population was exposed to a massive information campaign on the risks possibly associated to the pandemic, which may have contributed to alter the perceived risk.

4.1 The Effect of Risk Perception During the 2009 Pandemic

Two different phases, characterized by two distinct exponential growth rates, can be appreciated in Italy (especially when data are plotted in logarithmic scale) by observing the ILI incidence as reported by the surveillance system during the 2009 H1N1 pandemic (see green points in Fig. 4a and its subpanel).

The observed pattern cannot be reproduced by a classic SIR model, unless one considers a time-dependent transmission rate, switching from a low transmission level during the first four weeks to a higher level for the rest of the epidemic. However, this model would not be able to explain the reason of the sudden change in the transmissibility potential.

On the contrary, the model introduced in this chapter perfectly fits the observed ILI incidence (see red lines in Fig. 4a and its subpanel) and provides a plausible explanation of the mechanisms responsible for the observed evolution of the ILI incidence. Indeed, the estimated parameter configuration obtained by fitting ILI

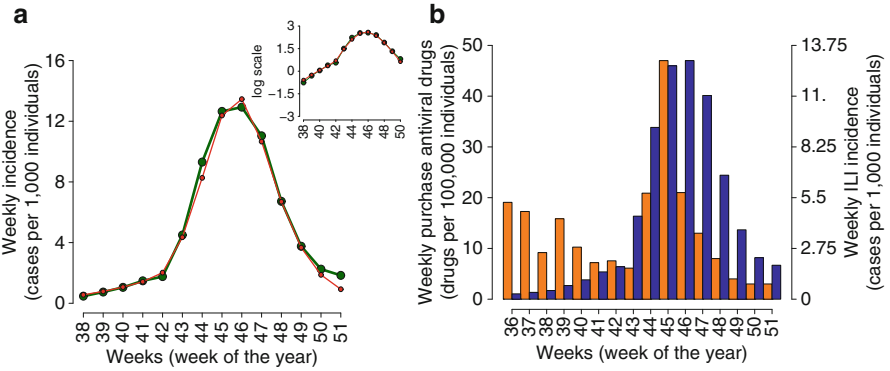

Fig. 4 (**a**) Weekly ILI incidence as reported to the surveillance system (*green*) and weekly incidence simulated by the model (*red*). Sub-panel shows the same curves in a logarithmic scale. Parameter values used in the simulation are set as follows. The generation time $1/\gamma$ is assumed 2.5 days according to [10]; $S(0) = 0.9$ according to a serological survey on the Italian population [20]; $x(0) = 10^{-8}$ and $m = 0.1$ assumed; $M(0) = 10.5$, $I(0) = 0.001243$, $\rho = 66$, $q = 0.84$, $\nu = 0.005$, $\beta = 0.59$, fitted; the estimated under reporting factor is 16.9 %, in good agreement with the range 18–20.2 % estimated in [2]. (**b**) Weekly purchase of antiviral drugs (*orange*, scale on the left axis) and weekly ILI incidence as reported to the surveillance system (*blue*, scale on the right axis) during the 2009 pandemic, in Italy

incidence entails an initial overestimation of the perceived risk (which decreases over time), along with an initial diffusion of the *altered* behavior in the population, which in turn is replaced by the *normal* behavior during the course of the epidemic. In fact, at the beginning of the pandemic, the simulated population is led to adopt the *altered* behavior by a high level of perceived risk of infection (as in the presence of a well-sustained circulation of the virus) and, as a consequence, the growth rate of the epidemic results lower than what would have been observed in a population adopting the *normal* behavior. On the other hand, a decrease in the perceived risk of infection is observed, despite the (slow) increase in the actual number of cases. In fact, the latter depends on the combination of two opposite phenomena: the increase of new infections and the decline (slowed by the memory mechanism) of the perceived prevalence, which was overestimated in the early phases of the epidemic. As the perceived prevalence goes below the risk threshold $1/m$, the *normal* behavior starts to spread quickly in the population as the most convenient strategy to be adopted through the subsequent course of the epidemic. This leads to a sudden change in the growth rate of the epidemic which is triggered by an increase of R_0. Model simulations show that the two distinct exponential growth phases observed for ILI incidence correspond to an initial diffusion of the *altered* behavior in the population, which determines an epidemic spread driven by R_0^a, and a second phase characterized by the diffusion of the *normal* behavior, where the spread is driven R_0^n. The best estimate for R_0^a is 1.24 and for R_0^n is 1.48. Estimates of R_0^n, i.e. the basic reproductive number for a population in which the normal behavior

is widely adopted, are in good agreement with those obtained for the 2009 influenza pandemic [2, 3, 10, 16].

The model explains the observed ILI incidence only if an initial (persistent) diffusion of the *altered* behavior in the population is considered. Specifically, an initial perceived risk of infection above the risk threshold, a long-lasting memory (able to keep the *altered* behavior as apparently more convenient over a relevant period of time), and a fast imitation process (enough to produce a sudden change in the force of infection) are required.

4.2 Antiviral Drugs Purchase and Perceived Risk

By fitting the model to the observed ILI incidence, our investigation identifies an initial overestimation of the risk as the main determinant of the influenza dynamics reported in Italy in the 2009. The same result is suggested by other empirical evidences, such as the temporal pattern of drug purchases.

As shown in Fig. 4b, during the fall the purchase of antiviral drugs complied with the observed ILI temporal dynamics; on the contrary, until mid-October an excess of antiviral drug purchase can be observed, suggesting an initial overestimation of the risk of infection. Specifically, when the 2009 pandemic arrived in Europe at the end of April, the weekly number of antiviral drugs sold jumped suddenly to more than 12 doses per 100,000 individuals per week [13], while the maximum weekly number of antiviral drugs sold during the 2008–2009 influenza season was less 2 doses per 100,000 individuals per week. Moreover, the purchase of antiviral drugs reached a peak of about 35 doses per 100,000 individuals per week at the end of July, despite no substantial ILI activity was detected in Italy during the summer.

The concern about the pandemic might have amplified the purchase of antiviral drugs, likely due to the information campaign about the use of antivirals for treating H1N1 infections. This example provides an empirical evidence that the Italian population have actively enacted spontaneous defensive response measures aimed at reducing the risk of infection in response to the high perceived risk. A discussion on this topic, including other (empirical) sources of information supporting the hypothesis of an initial overestimation of the risks of the pandemic, is developed in [18].

5 Conclusion

Spontaneous human behavioral changes triggered by the perceived risk of infection can remarkably alter the spread of an epidemic, leading to different epidemic dynamics. In particular, if changes in behavioral patterns are fast enough, they can

have a remarkable effect in reducing the daily prevalence of infection and the final epidemic size. In addition, human response may also lead to quite rich epidemic dynamics including, for example, the occurrence of multiple epidemic waves. Our performed investigation singles out the main determinants of human behavior and risk perception leading to remarkable alterations of the dynamics of an epidemic outbreak. First, if the perceived risk associated to an epidemic is sufficiently large, even a small decrease in the number of potentially infectious contacts can remarkably reduce the impact of an epidemic. Second, the disease spread is highly sensitive to how rapidly people adopt self-protecting behavioral patterns. Third, when the population becomes aware only late of a new epidemic outbreak, the effectiveness of human response reduces. However, when the mechanism regulating the spread of information about the disease is sufficiently fast, spontaneous social distancing is always effective.

Finally, our analysis shows that an initial overestimation of risk can delay the epidemic spread, leading to sudden changes in the transmissibility potential and, in turn, to a (somewhat unexpected) sharp increase in the growth rate of an emerging epidemic, as it might have happened in Italy during the 2009 H1N1 pandemic.

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References

1. Ajelli, M., Iannelli, M., Manfredi, P., Ciofi degli Atti, M.L.: Vaccine **26**(13), 1697 (2008)
2. Ajelli, M., Merler, S., Pugliese, A., Rizzo, C.: Epidemiol. Infect. **139**(1), 68 (2011)
3. Baguelin, M., Hoek, A.J.V., Jit, M., Flasche, S., White, P.J., Edmunds, W.J.: Vaccine **28**(12), 2370 (2010)
4. Bauch, C.T.: Proc. R. Soc. B **272**, 1669 (2005)
5. Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J.: J. Math. Biol. **28**(4), 365 (1990)
6. d'Onofrio, A., Manfredi, P., Salinelli, E.: Theor. Popul. Biol. **71**, 301 (2007)
7. Eastwood, K., Durrheim, D.N., Butler, M., Jones, A.: Emerg. Infect. Dis. **16**(8), 1211 (2010)
8. European Commission. Organisation of school time in Europe, Primary and general secondary education, 2009/10 school year (2009)
9. Ferguson, N.M., Cummings, D.A., Fraser, C., Cajka, J.C., Cooley, P.C., Burke, D.S.: Nature **442**, 448 (2006)
10. Fraser, C., Donnelly, C.A., Cauchemez, S., Hanage, W.P., Van Kerkhove, M.D., Hollingsworth, T.D., Griffin, J., Baggaley, R.F., Jenkins, H.E., Lyons, E.J., Jombart, T., Hinsley, W.R., Grassly, N.C., Balloux, F., Ghani, A.C., Ferguson, N.M., Rambaut, A., Pybus, O.G., Lopez-Gatell, H., Alpuche-Aranda, C.M., Bojorquez Chapela, I., Palacios Zavala, E., Espejo Guevara, D.M., Checchi, F., Garcia, E., Hugonnet, S., Roth, C.: The WHO Rapid Pandemic Assessment Collaboration. Science **324**(5934), 1557 (2009)
11. Funk, S., Gilad, E., Watkins, C., Jansen, V.A.A.: Proc. Natl. Acad. Sci. USA **106**(16), 6872 (2009)
12. Hofbauer, J., Sigmund, K.: Evolutionary Games and Population Dynamics. Cambridge University Press, Cambridge (1998)
13. Istituto Superiore di Sanitá. FluNews Aggiornamento epidemiologico settimanale numero 14, 25–31 January 2010. (2010). (In Italian)

14. Istituto Superiore di Sanitá. FluNews Aggiornamento epidemiologico settimanale numero 22, 22–28 March 2010. (2010). (In Italian)
15. Jones, J.H., Salathé, M.: PloS One **4**, e8032 (2009)
16. Munayco, C.V., Gomez, J., Laguna-Torres, V.A., Arrasco, J., Kochel, T., Fiestas, V., Garcia, J., Perez, J., Torres, I., Condori, F., Nishiura, H., Chowell, G.: Eurosurveill **14**(32), 19299 (2009)
17. Poletti, P., Caprile, B., Ajelli, M., Pugliese, A., Merler, S.: J. Theor. Biol. **260**(1), 31 (2009)
18. Poletti, P., Ajelli, M., Merler, S.: PLoS One **6**(2), e16460 (2011)
19. Poletti, P., Ajelli, M., Merler, S.: Math. Biosci. **238**, 80 (2012)
20. Rizzo, C., Rota, M.C., Bella, A., Alfonsi, V., Declich, S., Caporali, M.G., Ranghiasci, A., Lapini, G., Piccirella, S., Salmaso, S., Montomoli, E.: Vaccine **28**(10), 3558 (2010)
21. Rubin, G.J., Amlot, R., Page, L., Wessely, S.: Br. Med. J. **339**, b2651 (2009)
22. Sadique, M.Z., Edmunds, W.J., Smith, R.D., Meerding, W.J., de Zwart, O., Brug, J., Beutels, P.: Emerg. Infect. Dis. **13**(9), 1307 (2007)
23. Schwarzinger, M., Flicoteaux, R., Cortarenoda, S., Obadia, Y., Moatti, J.: PLoS One **5**(4), e10199 (2010)
24. Seale, H., Heywood, A.E., McLaws, M., Ward, K.F., Lowbridge, C.P., Van, D., MacIntyre, C.R.: BMC Infect. Dis. **10**(1), 99 (2011)
25. SteelFisher, G.K., Blendon, R.J., Bekheit, M.M., Lubell, K.: N. Engl. J. Med. **365**, e65 (2010)

The Talk of the Town: Modelling the Spread of Information and Changes in Behaviour

Sebastian Funk and Vincent A.A. Jansen

Abstract Changes in host behaviour can influence the course of a disease outbreak. These changes can be triggered not only by public campaigns and mass media reporting, but also by person-to-person communication and influence from peers. Here, we describe a model in which awareness of the presence of a disease can spread in a population and influence the spread of the disease itself through protective measures that people can take. We describe the dynamics of disease spread, focusing, in particular, on the relation between awareness and proximity of disease in the network.

1 Human Behaviour and Infectious Diseases

Human behaviour is intricately linked with the spread of infectious diseases [1, 2]. After all, transmission of an infectious disease depends on *contact* of some sort, either with another infected individual or with an environmental reservoir. The rate of transmission depends on the intensity and rate with which we make such contacts. For instance, the rate of transmission of a sexually transmitted disease is linked to the behaviour that governs the frequency with which sexual contacts, or the change in sexual partners. An element of human behaviour is therefore contained in any mathematical model for an infectious disease, in a way that may be as simple as a fixed *contact rate* in a traditional susceptible-infected-recovered (SIR) model [3].

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There are situations, however, in which it may become desirable to model behaviour *explicitly*, that is, to include it in the model dynamics and allow it to change over time. Such situations arise, for example, when behaviour depends on overall prevalence of a disease (so-called *prevalence-elastic* behaviour), on information which is communicated concurrently with the spread of an infection or on extrinsic factors such as perceived adverse vaccine effects [4] or severe outcomes associated with a given disease. In these cases, behaviour can be an important source of heterogeneity in the population, it can change over time, and it can both affect and be affected by the dynamics of the disease itself.

While it might be impossible to model the behaviour of an *individual*, it has been suggested that *collective* human behaviour can be described using computational and mathematical models [5]. These have been applied, for example, in sociology [6], economics [7] and anthropology [8] and to crowd behaviour [9, 10] and vehicle traffic [11]. In order to study the collective behavioural response to the spread of an infectious disease, one needs to consider the following questions:

- *What causes people to act?* We are all exposed to a variety of sources of information and have different tendencies to act on them. Collectively, are we more likely to respond to public health messages or to be influenced by the behaviour of our peers? Does it influence us to perceive high prevalence of the disease in our neighbourhood? It is known that humans tend to overestimate the risk of extreme outcomes [12]. How does this influence our response to an outbreak of a given disease? All of these factors will depend on the specific disease, the media and public health response and a variety of other cultural and historical factors. It remains an open challenge to identify common patterns in the answer, any of these questions.
- *How do the behavioural reactions influence the disease dynamics?* Depending on the disease being studied, behavioural changes can have an impact on the dynamics of the disease in a variety of ways. For airborne diseases, individual behaviour that has the potential to affect the dynamics of the disease can range from social distancing or voluntary quarantine to wearing face masks, hygienic practice, usage of prophylactic or other medication and vaccination. Beyond these, more extreme measures such as mass flight from an area in which a disease is present or the erection of road blocks to stop a disease from expanding geographically have occurred in history. All of these have the potential to influence the epidemiology of an infectious disease in different ways.

In the light of this wide range of possibilities for behavioural influences and outcomes, it is important to identify their common elements, in order to understand the overall influence of human behaviour on infectious diseases. Previously [2], we suggested to distinguish between *prevalence-based* behaviours, based on information directly related to the disease prevalence, or *belief-based* behaviours based on information not directly related to disease prevalence. Belief-based behaviour can have its own dynamics independently of the disease dynamics, as the behaviour can be copied from one person to the next. This is the case, for example, for behavioural

changes that are based on the spread of some sort of information, be it a rumour, awareness or fear. Moreover, we suggested to distinguish whether individuals source their social neighbourhood for (*local*) information to act on or behaviour to imitate, or whether they act on publicly available (*global*) information. Lastly, for the influence on disease dynamics, we suggested to distinguish whether a given behaviour would change the state of an individual with respect to a disease (e.g., by turning someone from being susceptible to being immune via vaccination), whether it would change the parameters of spread itself (e.g., by leading to speedier recovery from infection), or modify the contact structure between individuals (e.g., if people avoid contact with those infected). Of course, all these distinctions are somewhat arbitrary, and in reality our reactions will rarely fit perfectly in either of these categories.

2 The Spread of Awareness

Ideas, innovations, rumours or a cultural practice can spread in a way not entirely dissimilar from the spread of a disease: those who have not yet been "infected" (i.e., convinced or informed) can become so by coming in some form of (not necessarily physical) contact with someone who has [13, 14]. The spread of rumours or ideas has been described as "infection of the mind" [15] or "thought contagion" [16]. The analogy between the spread of information and communicable diseases seems to have been first proposed by Landau [17] and later, independently, by Kendall [18] and Goffman and Newill [19]. Generally, studies on models of rumours have concentrated on similar questions to epidemic models, that is the probability of it affecting a large part of the population and the fraction which hears of it over a given period of time. The work of Landau [17] is based on the epidemic model of Kermack and McKendrick [20] and considers cases where probability of transmission depends on the age of the rumour or the time since a given spreader heard it first. A similar model was proposed by Landahl [21], who had individuals transmit a message an average of f times, f being a function of time. The stochastic model of Daley and Kendall [22, 23] added a "stifler" class for those who carry the rumour, but have lost interest and no longer spread it, just as Goffman and Newill [13, 19, 24] did in their deterministic models.

After the flurry of activity on models of rumour spreading in the 1950s and 1960s, interest resurged in the past 10 years, in line with increasing interest in network theory. A number of studies applied variants of the model of Daley and Kendall [23] to different network settings [25–28] to study the interplay between topology and model dynamics. Nekovee et al. [15] extended this to include the possibility that individuals lose interest or forget about the rumour. Agliari et al. [29, 30] proposed a model in which the information contained in the rumour decays as it spreads through the population, an idea we will get back to in the following.

3 Spreading Awareness and Behavioural Changes

We are interested in a situation where people change their behaviour upon becoming *aware* of the presence of a disease. In particular, we want to investigate what happens when awareness can *spread*, in the sense outlined in Sect. 2. We understand this to be awareness of the (perceived) presence of the disease and assume people to change their behaviour once they become aware, by protecting themselves from getting infected. We consider a scenario where first-hand information originates via acutely infected cases but subsequently spreads independently of the disease.

There is anecdotal evidence that this kind of word-of-mouth and person-to-person spread of awareness can occur when an infectious disease is around. From the lepers' bell to notes on a nursery door, from the millions of text messages exchanged during the outbreak of severe acute respiratory syndrome (SARS) in Ghuangzhou in 2003 [31], to online health fora [32] and the exchange of twitter messages concerning vaccination against pandemic influenza H1N1 [33], examples for the exchange of information relating to the presence of an infectious disease are numerous.

In our model (see box below for details), we consider the population to be connected in a *contact network*; that is, any two members of the population are connected if they could potentially transmit the disease between each other. In addition, people are connected on a second network over which awareness spreads. Connections can be present over both networks or only on one of them, that is, people could be connected on an online forum but not be able to transmit disease between each other because they never get into contact, or vice versa, or they could be connected on both networks.

Lastly, we assume the *quality* of information, or the probability of individuals to act on it, to decay as it spreads in the population (Fig. 1), an idea first formulated by Agliari et al. [29, 30]. This reflects that we are interested in local and timely information, which will lose its value both with time and (network) distance.

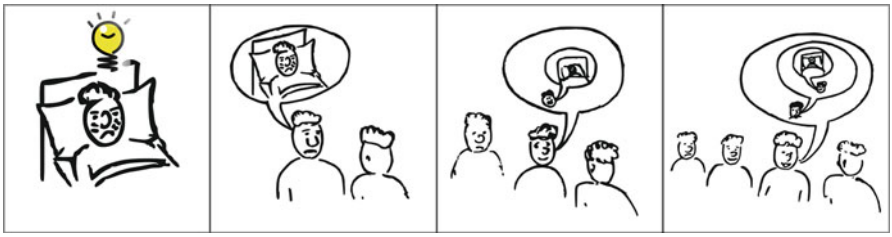

Fig. 1 A model of awareness spread with decay of information. *Left to right*: awareness originates in an infected case. As it spreads from person to person, the level of awareness gets updated with the distance from the source and in this way loses some quality, in the sense that it will cause less of an incentive to change the behaviour of the recipient

Mathematical Details of the Model

As described in [34], we divide the population of size N into susceptibles (S), infected (I) and recovered (R) [3]. Further, we divide the population according to the level of awareness they possess, here understood as awareness that the disease is present nearby. The level of awareness is denoted i, with $i = 0$ denoting the highest level of awareness, decreasing as i increases. Awareness spreads at rate α and is lost (forgotten) at rate λ. Each time awareness is passed on to someone else, its level increases by 1 (in other words, a bit of quality is lost every time awareness is passed on). The infection spreads at base rate β, and recovery from disease occurs at rate γ. Susceptibles of awareness level i are assumed to reduce their susceptibility (i.e., their infection rate) by a factor ρ^i, so that $0 < \rho < 1$ is the decay constant of awareness. New generation arises in infected individuals at rate ω.

The resulting set of equations is (see also Fig. 2)

$$\frac{dI_0}{dt} = -\gamma I_0 - \lambda I_0 + \omega(I - I_0)$$

$$\frac{dR_0}{dt} = +\gamma I_0 - \lambda R_0$$

$$\frac{dS_{i>0}}{dt} = -(1-\rho^i)\beta\frac{S_i}{N}I - \alpha\frac{S_i}{N}\left(\sum_{j=0}^{i-2} N_j\right) + \alpha\frac{N_{i-1}}{N}\left(\sum_{j=i+1}^{\infty} S_j\right) - \lambda S_i + \lambda S_{i-1}$$

$$\frac{dI_{i>0}}{dt} = (1-\rho^i)\beta\frac{S_i}{N}I - \gamma I_i - \alpha\frac{I_i}{N}\left(\sum_{i+1}^{i-2} N_j\right) + \alpha\frac{N_{i-1}}{N}\left(\sum_{j=i+1}^{\infty} I_j\right) - \lambda I_i + \lambda I_{i-1} - \Omega I_i$$

$$\frac{dR_{i>0}}{dt} = +\gamma I_i - \alpha\frac{R_i}{N}\left(\sum_{j=0}^{i-2} N_j\right) + \alpha\frac{N_{i-1}}{N}\left(\sum_{j=i+1}^{\infty} R_j\right) - \lambda R_i + \lambda R_{i-1}$$

where $I = \sum_i, I_i$, $S_0 = 0$ and $N_i = S_i + I_i + R_i$.

4 Dynamics of the Model

In the following, we describe the phenomena observed in simulations of the model. Readers interested in analytical backing of these results are referred to [34].

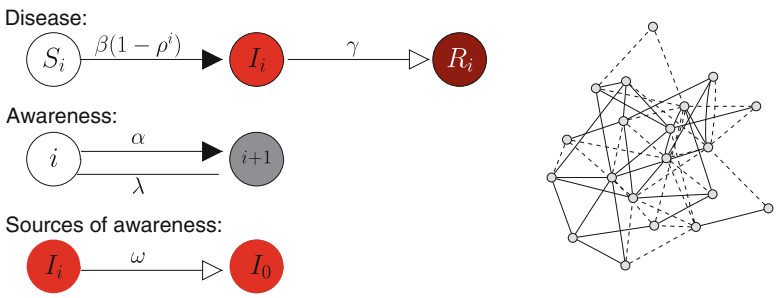

Fig. 2 *Left*: Schematic diagram of the model. Transitions marked occur within nodes (*empty caps*) or across the disease (*solid*) or awareness (*dashed*) network (*solid caps*). *Right*: A network with two types of edges (disease, awareness)

4.1 Relative Timescales of Spread

The dynamic interaction between awareness and disease that results from our model depends highly on the relative timescales of the two processes. If awareness spreads much faster than disease, it will reach its final distribution amongst the population before the disease spreads widely. In this case, awareness provides merely a uniform backdrop that is static on short timescales. This is the scenario we would expect for information disseminated by the mass media in response to an outbreak of a novel disease. If, on the other hand, the disease spreads much faster than awareness, it will encounter an unaware population which only retrospectively might receive information on the outbreak. In other words, this situation is similar to one in which awareness does not exist at all. In both of these cases, there is no need to model the dynamical interaction of awareness and disease explicitly, and any impact of awareness on spread can be subsumed in the parameters of the disease model.

If, on the other hand, both spread on similar timescales, the effect of the dynamic interaction between awareness and disease becomes more sensitive to the details of network and spatial structure, as we will describe in the following sections.

4.2 Local Quenching of Disease Outbreaks

If disease and awareness operate on similar timescales, the dynamical interplay between the two can result in them having a strong impact on each other, with network structure and overlap becoming more important. Let us first assume that the networks of both infection and awareness are the same. In that case, as soon as awareness originates in those infected and spreads in the population, it starts to quench the outbreak locally because high-quality information (which has a high tendency of changing the behaviour or people) is near the outbreak itself.

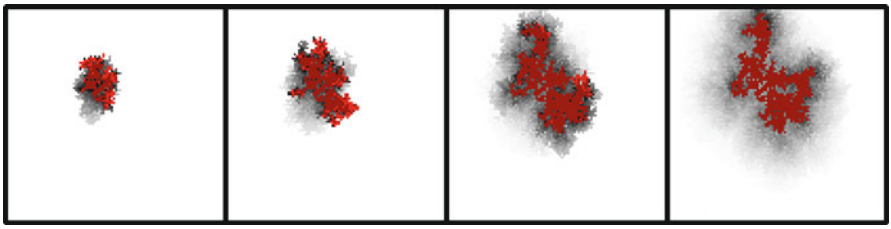

Fig. 3 Snapshots from a simulation of the disease-awareness model on a triangular lattice, progressing in time from left to right. The *red patch*, in the centre is where the disease has reached, with *bright red* indicating those currently infected surrounded by susceptibles in *white to dark grey*, with increasing awareness levels the darker they are plotted. In the *rightmost panel*, the outbreak has stopped

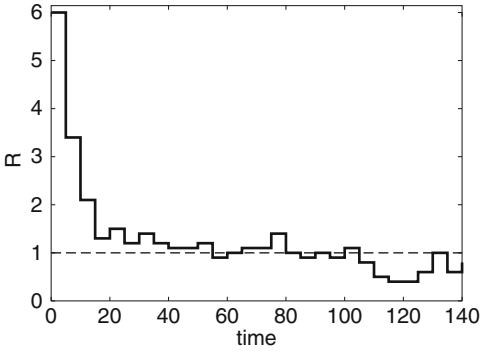

Fig. 4 Change of the effective reproductive number R in time in a simulated outbreak on a triangular lattice, starting with a single infected individual

This results in a lot of awareness appearing around infected cases, which can slow down an outbreak until the disease reaches another unaware part of the population, or it can even stop an outbreak altogether (Fig. 3).

If the behavioural reaction is not strong enough to stop an initial outbreak completely in its tracks while, on the other hand, it is strong enough to slow down the spread of the disease locally, the course of the outbreak is changed: if we follow the reproductive number R over time, it moves around 1 for a long time during the outbreak instead of declining monotonically, as would be expected without the effect of the behavioural response (Fig. 4). This is not dissimilar from patterns observed for the influenza pandemic of 1918, where similar variation of R in time has been attributed to the possible impact of individual reactions [35], or the irregular pattern in the epidemic tail of the 2001 UK foot and mouth disease epidemic [36]. The changing dynamics are reflected in the spatiotemporal pattern which changes from a simple diffusive spread with radial outward progression from the source of the outbreak to a much more irregular, patchy shape, characteristic of critical phenomena (Fig. 3) [37].

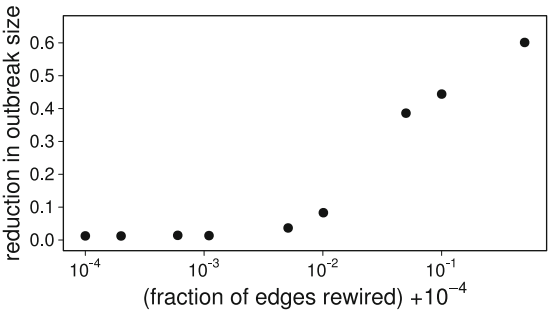

Fig. 5 Relative reduction in outbreak size in simulations of the disease-awareness model on a triangular lattice, with a part of the disease edges randomly rewired, given as (mean outbreak size with awareness)/(mean outbreak size without awareness). The averages are over 100 simulations on a lattice of 10,000 nodes

4.3 The Importance of Clustering and Network Overlap

The local quenching of outbreaks described in Sect. 4.2 can only occur when there exists a notion of locality in the population in which disease and awareness spread. For this to be the case, the network needs to possess a *clustered* structure. In network science, clustering traditionally denotes the probability for there to be a connection between two individuals who are both connected to a third individual (or, the probability of two friends of someone to be friends amongst themselves). Here, we mean, more generally, the fact that the distribution of shortest paths from a given individual to other individuals in the networks has a steep slope or, in other words, that very few individuals are close (only a few hops on the network away), while most are distant (many hops away).

This alone, however, is not enough to guarantee a strong impact of the spread of awareness on outbreaks. For this, we need the networks over which awareness and disease spread to display a strong degree of overlap, in the sense that contacts on one network need to be contacts on the other, too. This guarantees that the individuals closest to those infected (which also act as sources of high-quality information) are the ones with the best information. Clustered structure then allows this information to be spread to individuals who themselves are not distant from the source of infection, protecting these before the disease can get to them.

This effect can be observed clearly when considering the model on an (overlapping) triangular lattice (i.e., a very clustered structure with a strong sense of locality) in which some of the disease edges are randomly rewired. As a consequence of this rewiring, the potentially infectious connections of an infected node have a certain probability of pointing to a region in the disease network which is not local to that node on the awareness network. If that is the case, the disease can escape regions of the network where it is locally suppressed as people around an infected cluster protect themselves. The greater the probability of such escape, the weaker the effect that awareness spread can have in containing outbreaks (Fig. 5).

5 Conclusions

We have described the dynamics of a model for the concurrent spread of an infectious disease and awareness to its presence and assumed this awareness to be the trigger for behavioural reactions. Local interactions between disease and awareness only become relevant when the two spread on similar timescales. In that case, we can observe local quenching of disease outbreaks as those that are most at risk become aware and protect themselves. When this happens, the spatial progression of an outbreak changes from a simple diffusive process to a situation where small outbreaks flare up before they get contained locally. This effect is the strongest when the networks over which infection and awareness spread are overlapping and clustered. If this is not the case, for example, when the infection can escape to unaware populations with a certain probability, the behavioural reactions become less effective in quenching outbreaks.

Whether any of this happens in reality remains an open question. While all parts of our model have been informed by anecdotal evidence, it can be quite difficult to quantify the different components and their relative impact. Still, there are some things to be learnt from the kind of study we present here. Recent studies of health behaviour show that the structure of networks of influence can play a role in how such behaviours become adopted in a population [32]. Here, we show that, if people are indeed influenced by their peers, it is the interplay between the network of influence with the network of infection that determines the effect on outbreaks. Moreover, if behavioural reactions can change the epidemiology of a given disease, one must be careful in extrapolating from observations in a disease-free situation to one where a disease is present. How exactly peer and media influence, the particularities of any given infectious disease and the type and strength of behavioural reactions interact is notoriously difficult to establish. Still, it seems that innovative theoretical approaches used hand in hand with careful observational studies, for example, using the digital traces we leave in our online interactions, have a role to play in shedding some light on what shapes our reactions to disease outbreaks and how this, in turn, can affect the fate of an outbreak itself.

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References

1. McNeill, W.H.: Plagues and Peoples. Anchor Press, Garden City (1976)
2. Funk, S., Salathé, M., Jansen, V.A.A.: J. R. Soc. Interface **7**(50), 1247 (2010). DOI 10.1098/rsif.2010.0142
3. Anderson, R.M., May, R.M.: Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford (1991)

4. Jansen, V.A.A., Stollenwerk, N., Jensen, H.J., Ramsay, M.E., Edmunds, W.J., Rhodes, C.J.: Science **301**(5634), 804 (2003). DOI 10.1126/science.1086726
5. Goldstone, R.L., Janssen, M.A.: Trends Cogn. Sci. **9**(9), 424 (2005). DOI 10.1016/j.tics.2005.07.009
6. Macy, M.W., Willer, R.: Annu. Rev. Sociol. **28**(1), 143 (2002). DOI 10.1146/annurev.soc.28.110601.141117
7. Kirman, A., Zimmermann, J.B.: Economics with heterogeneous interacting agents. Lecture Notes in Economics and Mathematical Systems. Springer, Heidelberg (2001)
8. Kohler, T.A., Gumerman, G.G. (eds.): Dynamics in human and primate societies: agent-based modeling of social and spatial processes. Santa Fe Institute Studies on the Sciences of Complexity. Oxford University Press, Oxford (2000)
9. Helbing, D., Farkas, I., Vicsek, T.: Nature **407**(6803), 487 (2000). DOI 10.1038/35035023
10. Helbing, D., Keltsch, J., Molnár, P.: Nature **388**(6637), 47 (1997). DOI 10.1038/40353
11. Wilson, R.E., Philos. T. R. Soc. A **366**(1872), 2017 (2008). DOI 10.1098/rsta.2008.0018
12. Lichtenstein, S., Slovic, P., Fischhoff, B., Layman, M., Combs, B.: J. Exp. Psychol. **4**(6), 551 (1978)
13. Goffman, W.: Nature **212**, 449 (1966). DOI 10.1038/212449a0
14. Bettencourt, L.M., Cintrón-Arias, A., Kaiser, D.I., Castillo-Chávez, C.: Physica A **364**, 513 (2006). DOI 10.1016/j.physa.2005.08.083
15. Nekovee, M., Moreno, Y., Bianconi, G., Marsili, M.: Physica A **374**(1), 457 (2007). DOI 10.1016/j.physa.2006.07.017
16. Lynch, A.: J. Ideas **2**, 3 (1991)
17. Landau, H., Rapoport, A.: Bull. Math. Biophys. **15**(2), 173 (1953)
18. Kendall, D.: Publ. Inst. Statist. Univ. Paris **6**, 307 (1957)
19. Goffman, W., Newill, V.A.: Nature **204**, 225 (1964). DOI 10.1038/204225a0
20. Kermack, W.O., McKendrick, A.G.: Proc. R. Soc. A **115**, 700 (1927)
21. Landahl, H.: Bull. Math. Biophys. **15**(3), 367 (1953)
22. Daley, D.J., Kendall, D.G.: Nature **204**(4963), 1118 (1964). DOI 10.1038/2041118a0
23. Daley, D., Kendall, D.: J. Inst. Math. Appl. **1**, 42 (1965). DOI 10.1093/imamat/1.1.42
24. Goffman, W., Newill, V.A.: Proc. R. Soc. A **298**(1454), 316 (1967). DOI 10.1098/rspa.1967.0106
25. Zanette, D.H.: Phys. Rev. E **64**(5), 050901 (2001). DOI 10.1103/PhysRevE.64.050901
26. Zanette, D.H.: Phys. Rev. E **65**(4), 041908 (2002). DOI 10.1103/PhysRevE.65.041908
27. Moreno, Y., Nekovee, M., Vespignani, A.: Phys. Rev. E **69**(5), 055101 (2004). DOI 10.1103/PhysRevE.69.055101
28. Moreno, Y., Nekovee, M., Pacheco, A.F.: Phys. Rev. E **69**(6 pt 2), 066130 (2004). DOI 10.1103/PhysRevE.69.066130
29. Agliari, E., Burioni, R., Cassi, D., Neri, F.M.: Phys. Rev. E **73**(4), 046138 (2006). DOI 10.1103/PhysRevE.73.046138
30. Agliari, E., Burioni, R., Cassi, D., Neri, F.M.: Phys. Rev. E **75**(2), 021119 (2007). DOI 10.1103/PhysRevE.75.021119
31. Tai, Z., Sun, T.: New Media Soc. **9**(6), 987 (2007)
32. Centola, D.: Science **329**(5996), 1194 (2010). DOI 10.1126/science.1185231
33. Salathé, M., Khandelwal, S.: PLoS Comput. Biol. **7**(10), e1002199 (2011). DOI 10.1371/journal.pcbi.1002199
34. Funk, S., Gilad, E., Watkins, C., Jansen, V.A.A.: Proc. Natl. Acad. Sci. USA **106**(16), 6872 (2009). DOI 10.1073/pnas.0810762106
35. Nishiura, H.: Theor. Biol. Med. Model **4**, 20 (2007). DOI 10.1186/1742-4682-4-20
36. Keeling, M.J., Woolhouse, M.E., Shaw, D.J., Matthews, L., Chase-Topping, M., Haydon, D.T., Cornell, S.J., Kappey, J., Wilesmith, J., Grenfell, B.T.: Science **294**(5543), 813 (2001). DOI 10.1126/science.1065973
37. Stollenwerk, N., Jansen, V.: Population Biology and Criticality. Imperial College Press, London (2011)

Modeling Contact and Mobility Based Social Response to the Spreading of Infectious Diseases

Nicola Perra and Alessandro Vespignani

Abstract We present here a set of prototypical mechanisms aimed at modeling the social adaptation and response triggered in the population by the knowledge of the spreading of an infectious disease. We define models that couples the spreading of information and behavioral changes with the spreading of the infectious disease by considering the local and non-local prevalence-based information available to individuals in the population. The behavioral changes are modeled both as the onset of effective social distancing and contact reduction as well as changes in the mobility patterns of individuals. The defined models exhibit a rich phase space with multiple epidemic peaks and threshold behavior. In addition, we show that in specific cases the change of mobility pattern may counterintuitively enhance the disease spreading. The class of models presented here can be used in the case of data-driven computational approaches to analyze scenarios of social adaptation and behavioral change.

In the last years we have witnessed formidable advances in the data-driven modeling of the spreading of infectious diseases. The growing abundance of demographic, census, and mobility data is allowing the development of highly detailed models aiming at providing both a conceptual understanding and quantitative scenario analysis of infectious disease spreading. For a long time these modeling approaches have assumed that the network of contacts that exists at the beginning of an outbreak remain fixed throughout the outbreak, rather than change in real time as the outbreak itself spreads. For instance, infected individuals hide, run away, and generally destroy the regular patterns of interaction present at regular time. Some of these new patterns of interaction, such as staying at home or off mass transit, might temporarily stifle the diseases spread through the network. Other patterns

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like fleeing can facilitate the spread to whole new populations. The coevolution of the social network with the spread of the disease therefore is at the heart of understanding the social epidemiological nature of disease spread.

In this context, self-initiated changes in behavior induced by transmission of information about the disease both from the media and the local environment (friends, colleagues, etc.) is one of the prime mechanism of social adaptation to the spreading of an infectious diseases. The awareness of each individuals to the prevalence of the disease can transform in the "fear" of the disease and alter the behavioral patterns of individuals. The ensuing behavioral changes can be grouped in to two major reactions mechanisms: (i) People can decide to avoid social contacts with infected individuals, to avoid crowded spaces, and to prevent children from attending school generating a social distancing effect that reduces the transmissibility of the disease. (ii) In order to reduce their risk to get sick, people can also decide to change their mobility patterns either canceling specific trips or changing the path to reach destination according to the information concerning the prevalence of the diseases in different areas. These self-initiated measures affect the local contagion process as well as the diffusion pattern of the disease by changing the level of contact and the mobility rate of individuals. At the modeling level these two social responses unfold in a different way. Social distancing can be modeled as an intrapopulation phenomena reflected in the change of contact rates of individuals. Mobility responses affects mostly the inter-population coupling defined by the exchange of individuals among different subpopulations in geographically structured models. Finally, other types of changes in the behaviors could be imposed by authorities through the closure of schools, churches, and public offices, bans on public gatherings, and travel restrictions. Due to the availability of public data on these imposed phenomena they have been intensively studied. Instead, self-initiated behavioral changes are elusive to modeling because of the difficulty involved in quantifying these changes and an overall lack of relevant data.

Here we want to provide a brief review of recent results we have obtained at level of intra-population dynamics and in the framework of metapopulation models describing collections of subpopulations linked by intercommunity mobility. We can easily imagine the information about the disease as a competing spreading process acting on the same time scale of the pathogen spread. The contact structure as well as the coupling patterns can be simultaneously modified changing the global unfolding of the disease. The study of these societal phenomena and their effects on the spreading is extremely hard due the feedback mechanisms induced by the change of behaviors. For this reason models have looked so far at contact- and diffusion-based behavioral changes separately. Indeed, the understanding of the effects induced by all possible change in behaviors can be reached just after the characterization of the single phenomena.

Modeling the infectious disease with a simple SIR model in which individuals can be either susceptible, infected or recovered, we present a general framework to study contact-based behavioral changes in isolated subpopulations. In particular we present the definition and characterization of two models that incorporate different societal reactions based on the local and nonlocal prevalence-based information

about the disease available to individuals in the population. We then consider mobility-based behavioral changes in a system of connected subpopulations. In this case different societal reactions triggering changes in the mobility behavior of individuals are studied and characterized within the framework of metapopulation approaches. We provide a theoretical and numerical analysis of the various mechanisms involved and uncover a rich phenomenology of the behavior-disease models that includes epidemics with multiple activity peaks and transition points. Furthermore, although the aim of such a self-initiated behavior is to prevent an individual's exposure to the disease, we show that it may lead to the unanticipated effect of facilitating the disease spread to new locations. This abundance of different dynamical behaviors clearly shows the importance of the behavior-disease perspective in the study of realistic progressions of infectious diseases and provides a chart for future studies and scenario analyses in data-driven epidemic models.

1 Single Population: Contact-Based Behavioral Changes

We approach the analysis of behavioral changes due to the spreading of diseases considering first the intra-population dynamics. We consider a single isolated, unstructured population characterized by N individuals. All the effects due to the contacts among individuals in different subpopulations are for the moment neglected. In particular, we consider the general extension of the SIR model where a new class of individuals, S^F, is introduced. The label F stands for "fear" characterizing individuals that fear the disease and self-initiate social distancing measures in order to reduce the likelihood of contagion [1,2]. In this class of models the spread of the disease is coupled with the spread of the fear of the disease within the population. The unfolding of the fear contagion process depends on the source and type of information to which individuals are exposed [3,4].

Among the many different mechanisms governing the transitions of individuals into and out the compartment S^F, we review two basic interaction schemes. The first mechanism is prevalence-based. Individuals enter in the compartment S^F by interacting with infected individuals. The awareness of the presence of sick persons triggers the transition in the new compartment and the consequent reduction in the contacts. The second mechanism, instead, is belief-based. Individuals enter the new compartment interacting either with infected individuals as in the previous case or with people already in the S^F compartment. The presence of individuals fearing the disease is able to trigger further transitions in this compartment. The fear is able to self-sustain its spread in this case as more and more individuals change their behaviors because others did.

The basic infectious disease evolution is described using the SIR model [5]. In this model individuals are partitioned into compartments according to their disease status. At each time step t, three different compartments are defined: $S(t)$, $I(t)$, and $R(t)$ representing the number of susceptible, infected and recovered individuals in the population. For diseases characterized by a time scale much

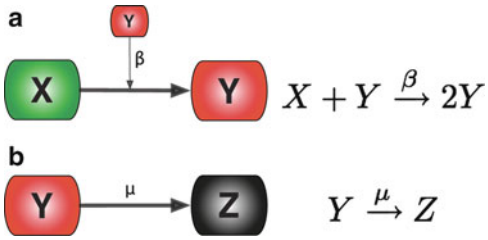

Fig. 1 Schematic representation of the two types of transitions that will be recurrent in the different models presented. In panel (**a**) we show the first in which individuals in compartment X interact with individuals in class Y, represented by the *small square*, becoming Y themselves with rate β. In general the compartment inducing the transition of individuals in X could be any other compartment in the model, for example, M, different from the end-point of the transition. In panel (**b**) we show the second type. This is a spontaneous transition with rate μ in which an individual in compartment Y spontaneously moves to compartment Z

smaller respect to the average lifetime of individuals, we can then consider the population as constant, i.e., $N = S(t) + I(t) + R(t)$ for each time step. The evolution of the disease is defined by two simple classes of transitions represented in Fig. 1. In the first one, a susceptible individual interacts with an infectious one acquiring the infection with transmission rate β. This transition depends then on the internal structure of the population and on the contacts patterns. In the second one, an infected individual recovers spontaneously from the disease with rate μ entering in the recovered compartment. Individuals in this class are immune of the disease. The two transitions can be represented as:

$$S + I \xrightarrow{\beta} 2I, \tag{1}$$

$$I \xrightarrow{\mu} R. \tag{2}$$

Influenza-like illness usually can be easily transmitted, even without direct contacts. A typical simplification used to model this type of diseases considers the mixing between individuals as homogenous: each pair of individuals has the same probability of interaction. According to this assumption, the larger the number of infectious individuals the higher the probability of transmission of the infection. The force of infection can be then defined in terms of a mass action law [6], $\lambda_{S\to I} = \beta I(t)/N$.

The local spreading of the disease is characterized by its basic reproductive number R_0. This quantity is defined as the average number of secondary infected cases generated by a primary infected individual in a fully susceptible population. In the limit of homogeneous mixing, only if on average each infected is able to produce at least one other infected individual the disease will be able to spread. The basic reproductive number of the SIR model is simply $R_0 = \frac{\beta}{\mu}$. The reproductive number defines the threshold of the epidemic process. The populations will experience an outbreak just if the disease transmission rate is larger than the recovery rate, i.e.,

$\beta > \mu$. In this case the epidemic generate a number of infected individuals larger than those who recover, leading initially to an exponential increase in the overall number of infectious individuals $I(t)$.

1.1 The New Compartment: S^F

The self-initiated behavioral changes are modeled adding a new compartment, S^F, to the basic SIR structure [7].This describes individuals, still susceptible and healthy, that change their behavior reducing the number contacts or that implement other social distancing measures [1, 3, 8–14].

These actions raise the level of protection from the disease reducing the transmission rate of the infection. For individuals in the class S^F the force of infection is thus reduced by a resiling of the transmissibility β to $r_\beta \beta$ with $0 \leq r_\beta < 1$. The transition from S^F to I is then:

$$S^F + I \xrightarrow{r_\beta \beta} 2I. \tag{3}$$

The force of infection for individuals in the new compartment is $\lambda_{S^F \to I} = r_\beta \beta I(t)/N$. The crucial parameter is r_β that modulates the level of protection from the contagion due to the self-induced behavioral changes.

When the epidemic starts to decline, it is natural to assume that individuals relax the adopted behavioral changes returning to regular social behavior. This translates into a transition $S^F \to S$. There are different possible mechanisms that can account for this process [1, 3, 11, 13, 15]. Individuals can simply lose interest in the disease and spontaneously recovery from fear, or they can interact with other individuals that are recovered or healthy and decide to change their behavior. In the last case we can define two different transitions:

$$S^F + S \xrightarrow{\mu_F} 2S \tag{4}$$

and

$$S^F + R \xrightarrow{\mu_F} S + R, \tag{5}$$

regulated by two mass-action laws: $\lambda^A_{S^F \to S} = \mu_F S(t)/N$ and $\lambda^B_{S^F \to S} = \mu_F R(t)/N$.

The new compartment S^F allows in a very simple way the inclusion of social distancing in the system. A variety of scenarios can be considered in the modeling of the phenomena that induce susceptible individuals to change their behavior moving in the compartment S^F. In the next section we will describe two basic mechanisms studying their effects on the disease unfolding [7].

1.2 Local Prevalence-Based Behavioral Changes

The first mechanism we consider for the generation of individuals with fear of the disease is prevalence-based. The fear of the disease is simply coupled with the spread of the virus in the population [1, 3, 7, 11]. In this scenario susceptible individuals change their behavior interacting with infectious individuals. The larger the number of sick and infectious individuals, the higher the probability to adopt behavioral changes. The fear contagion process is modeled introducing a new transition

$$S + I \xrightarrow{\beta_F} S^F + I, \tag{6}$$

where β_F is the transmission rate of the awareness/fear of the disease. In analogy with the previous interactions, this processes is characterized by a mass-action law of the form $\lambda^I_{S\to S_F} = \beta_F I(t)/N$.

Considering the basic structure of a SIR model and adding the transitions (3), (4), (5) and (6) (see Fig. 4 for a schematic representation) we can write the set of differential equation for this model as

$$\begin{aligned}
d_t S(t) &= -\beta S(t)\frac{I(t)}{N} - \beta_F S(t)\frac{I(t)}{N} + \mu_F S^F(t)\left[\frac{S(t)+R(t)}{N}\right],\\
d_t S^F(t) &= -r_\beta \beta S^F(t)\frac{I(t)}{N} + \beta_F S(t)\frac{I(t)}{N} - \mu_F S^F(t)\left[\frac{S(t)+R(t)}{N}\right],\\
d_t I(t) &= -\mu I(t) + \beta S(t)\frac{I(t)}{N} + r_\beta \beta S^F(t)\frac{I(t)}{N},\\
d_t R(t) &= \mu I(t).
\end{aligned} \tag{7}$$

To better understand the equations let us consider the negative flows. The first term of the first equation in (7) takes into account susceptible individuals who through interaction with infected ones become sick. The second term takes into account susceptible individuals who through interaction with infected ones change their behavior. The first term of the second equation takes into account individuals in compartment S^F who through interaction with infected individuals enter in the compartment I. This transition is reduced by a factor r_β due to the protection that they gain. The last term in the second equation takes into account people with fear of the disease who through social interaction with healthy and recovered individuals, move back to compartment S. The first term in the third equation takes into account the spontaneous recovery of infected individuals.

The system of equations in (7) is characterized by different regimes according to the initial conditions and the value of the parameters selected. It is natural to assume that the initial population is fully susceptible except for a few infected individuals. This translates in fixing, $S^F(t=0) = R(t=0) = 0$. It is easy to prove [7] that if the disease spreading is faster than the fear spreading ($\beta_F \ll \beta$,), the model reduces to the classic SIR with basic reproductive number $R_0 = \beta/\mu$. Instead, if fear spreads

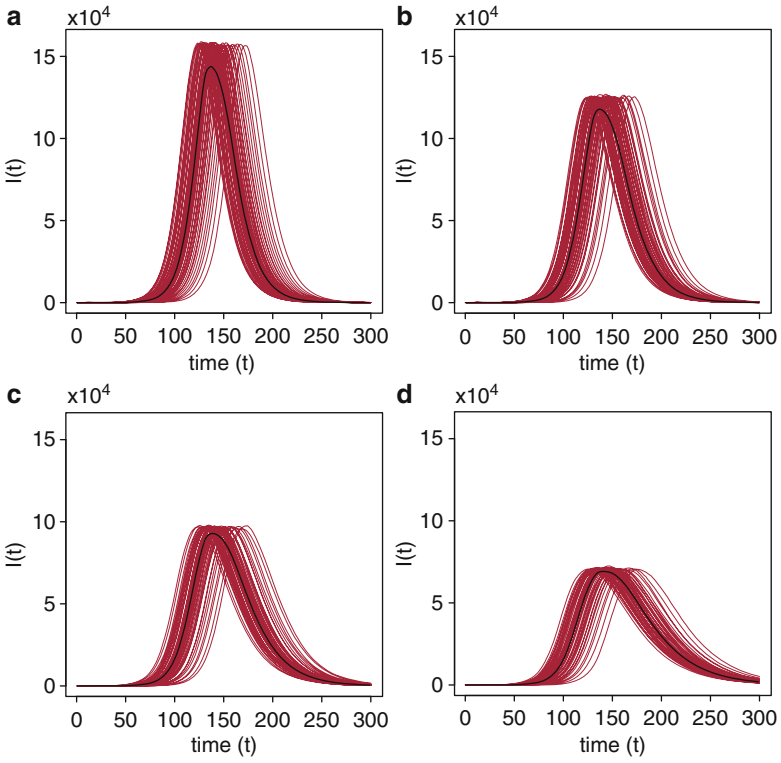

Fig. 2 Medians of $I(t)$ for the for baseline (SIR model without fear of contagion) and three realizations of the model for different values of β_F. In particular in panel (**a**) is plot the baseline SIR model with the same disease parameters. In panel (**b**) is considered $\beta_F = 1\ \text{day}^{-1}$. In panel (**c**) $\beta_F = 2.5\ \text{day}^{-1}$. In panel (**d**) $\beta_F = 5\ \text{day}^{-1}$. The peak time is the same for all the scenarios and how the number of infected individuals at peak is reduced as β_F increases. The other relevant parameter are $\mu_F = 0.5\ \text{day}^{-1}$, $r_\beta = 0.5$, $\mu = 0.1\ \text{day}^{-1}$, $N = 10^6$, and $R_0 = 2$. The medians are evaluated using 5×10^3 stochastic runs

much faster than the disease, $\beta_F \gg \beta$, even a small number of infected individuals is able to trigger a rapid transition in the compartment S^F. The epidemic in this case is equivalent to the spreading of a disease with an effective reproductive number $R_0^F = r_\beta \beta/\mu = r_\beta R_0$.

In the intermediate region in which the two transmission rates are comparable, $\beta_F/\beta \sim \mathcal{O}(1)$, the spread of the fear does not significantly affect the timing or the size of the disease. As showed in Fig. 2 in this region fear simply produces a mild reduction in the epidemic size.

Moving in a different phase space by increasing the value of β_F, an interesting region characterized by multiple peaks emerges. This is important not only from a mathematical point of view but also for practical reasons. In historical data from the 1918 pandemic multiple epidemic peaks were observed [15–17]. These

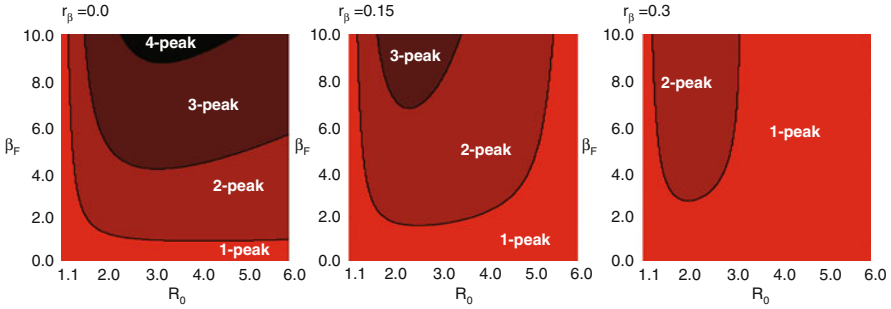

Fig. 3 **Model I** Phase diagram of infection waves on R_0-β_F plane. We display the regions of parameter space on R_0-β_F plane exhibiting different number of disease activity peaks for three different values of $r_\beta = 0,\ 0.15,$ and 0.3, where we have fixed $\mu = 0.1\ \text{day}^{-1}$, $\mu_F = 0.1\ \text{day}^{-1}$ and $N = 10^6$. The phase diagram has been obtained by numerical integration of the deterministic equations in Eq. (7)

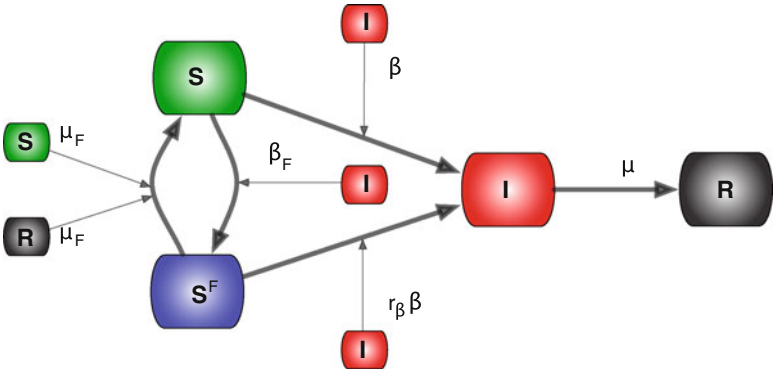

Fig. 4 **Model I.** Schematic representation of Model I

cannot be created by the simple SIR mechanisms. Adding some components to the model is necessary. Changes in the behaviors during that period have been often associated to the emergence of multiple waves of infections. The presence of multiple peaks can be qualitatively understood considering that after the first wave of infection individuals start leaving the compartment S^F returning to the S state. In this compartment they are less protected from the disease. If the number of infected individuals at this stage is not too small and if there is still a large enough pool of individuals susceptible to the infection a second wave might emerge.

The analysis of the phase diagram of the model as a function of the parameter R_0-β_F identifies the regions where multiple peaks are observed. In Fig. 3 the multiple peak region for three different values of r_β is shown. As this parameter increases, the region in which multiple peaks are encountered shifts to smaller

values of R_0 and larger values of β_F. Fixing r_β, increasing values of β_F increase the number of infection peaks while an increase in R_0 leads to a decrease in the number of peaks.

By increasing the value of β_F to larger and larger values, the spread of the fear contagion becomes increasingly rapid with respect to the spread of the disease. It is natural to think in this regime that the reproductive number of the disease is characterized by the S^F class. We then have two different scenarios:

1. If $r_\beta \beta/\mu > 1$, then the epidemic size is given by that of an SIR model with $\beta \to \beta r_\beta$.
2. If $r_\beta \beta/\mu < 1$, then fear completely stops the spreading of the disease.

At the end of the disease epidemic the system enters the so-called "disease-free" stage. This region of the phase space is described by

$$(S, S^F, I, R) = (S_\infty, S^F_\infty, 0, R_\infty). \tag{8}$$

In this model there is one only disease-free state characterized by

$$(S, S^F, I, R) = (N - R_\infty, 0, 0, R_\infty). \tag{9}$$

The model does not allow an endemic state of fear. Fear can only be produced by the presence of infected people. As soon as the infection dies out, people recover from their fear of the disease by interacting with the susceptible and recovered individuals and become susceptible themselves.

1.3 Local Belief-Based Behavioral Changes

The contagion process governing the spread of the fear may also occur by the contact with individuals who have already acquired fear/awareness of the disease [7]. The fear contagion process therefore can also progress according to the following process:

$$S + S^F \xrightarrow{\alpha\beta_F} 2S^F, \tag{10}$$

where the transmission rate is $\alpha\beta_F$, with α modulating the ratio between the fear spreading rate by contacting infected individuals and contacting individuals with fear of the disease. The transition rate is defined by the mass-action law $\lambda^{III}_{S\to S^F} = \alpha\beta_F S^F(t)/N$. This transition is a self-reinforcing process in which individuals might enter the compartment S^F simply by interacting with people in this compartment: fear generates fear. In this model people could develop fear of the infection both by interacting with infected persons and with people already concerned about the disease. A new parameter, $\alpha \geq 0$, is necessary to distinguish between these two interactions. These processes are different in their nature. In general individuals

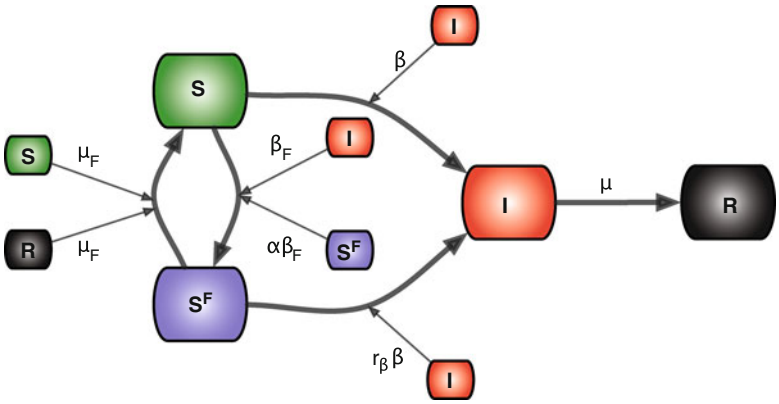

Fig. 5 Model III. Schematic representation of Model III

who contact infected people are more likely to acquire the fear of the disease than those who interact with individuals which also fear the disease. For this reason it is natural to fix $0 \leq \alpha \leq 1$.

In the limit in which no infected individuals are present in the population the S^F compartment can only grow through the interaction $S + S^F \xrightarrow{\alpha\beta_F} 2S^F$. The early stage of this process is analogous to an SIS-like model as long there is at least one initial individual in the fear compartment, i.e., $S^F(t=0) = 1$ [7]. In this case it is possible to define the reproductive number of the fear contagion process as

$$R_F \equiv \alpha \frac{\beta_F}{\mu_F}. \tag{11}$$

In isolation, the fear contagion process is analogous to the reproductive number of an SIS or SIR model with transmission rate $\alpha\beta_F$. However, in the general case the spread of the fear of infection is coupled with the actual disease spread. As schematically presented in Fig. 5, the complete set of equations is

$$\begin{aligned}
d_t S(t) &= -\beta S(t)\frac{I(t)}{N} - \beta_F S(t)\left[\frac{I(t)+\alpha S^F(t)}{N}\right] + \mu_F S^F(t)\left[\frac{S(t)+R(t)}{N}\right],\\
d_t S^F(t) &= -r_\beta \beta S^F(t)\frac{I(t)}{N} + \beta_F S(t)\left[\frac{I(t)+\alpha S^F(t)}{N}\right] - \mu_F S^F(t)\left[\frac{S(t)+R(t)}{N}\right],\\
d_t I(t) &= -\mu I(t) + \beta S(t)\frac{I(t)}{N} + r_\beta \beta S^F(t)\frac{I(t)}{N},\\
d_t R(t) &= \mu I(t).
\end{aligned} \tag{12}$$

In the case in which the disease spreads faster than the fear of it, then the reproductive ratio is $R_0 = \beta/\mu$. In the opposite case the reproductive ratio is

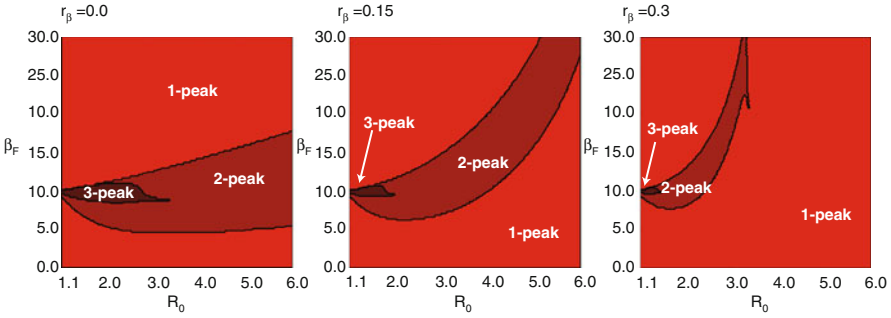

Fig. 6 Phase diagram of infection waves on R_0-β_F plane. We display the regions of parameter space on R_0-β_F plane exhibiting different number of disease activity peaks for three different values of $r_\beta = 0,\ 0.15,$ and 0.3, where we have fixed $\mu = 0.4\,\text{day}^{-1}$, $\mu_F = 0.5\,\text{day}^{-1}$, $\alpha = 0.05$ and $N = 10^6$. The phase diagram has been obtained by numerical integration of the deterministic equations in Eq. (12)

governed by the compartment S^F so that $R_0^F = r_\beta R_0$ and the epidemic size will be reduced depending on the value of r_β. In this latter case, if $r_\beta R_0 < 1$, then the protection from infection gained in the compartment S^F causes the disease to fade out.

In the early stages of the epidemic the set of equations can be linearized and the equations for S^F compartment is given by

$$S^F(t) \sim \frac{\beta_F}{\mu(R_0-1)-\mu_F(R_F-1)} \times \left[e^{\mu(R_0-1)t} - e^{\mu_F(R_F-1)t}\right]. \tag{13}$$

Two different regions in the parameter space are then identified: one in which the rate of increase of fear is dominated by its own contagion process, $\mu_F(R_F-1) > \mu(R_0-1)$, and one in which the rate of the local belief-based spread is dominated by the disease, $\mu(R_0-1) > \mu_F(R_F-1)$. In the first case the fear spreads independently of the value of R_0, and the epidemic size will be reduced due to the protection that individuals gain in the S^F compartment [7].

The new interaction, although intuitively simple, significantly complicates the dynamic behavior of the model. In particular within several regions of the parameter space we observe two or more epidemic peaks (see Fig. 6). This non-trivial behavior can be easily understood. Fear reinforces itself until it severely depletes the reservoir of susceptible individuals, causing a decline in new cases. As a result people are lured into a false sense of security and return back to their normal behavior (recovery from fear) causing a second epidemic peak that can be even larger than the first [15–17].

Residual Collective Memory of the Disease and Its Effect on Epidemic Resurgence

At the end of the disease epidemic the system enters the disease-free stage. Setting $I(t) = 0$ and the epidemic size to R_∞ is possible to show that the model allows for two different disease-free equilibriums depending on the value of a parameter $\gamma \equiv R_F \left(1 - \frac{R_\infty}{N}\right) - 1$ [7]. In particular, for

$$\gamma \leq 0 \Rightarrow (S_\infty, S^F_\infty, I_\infty, R_\infty) = (N - R_\infty, 0, 0, R_\infty), \tag{14}$$

where fear dies along with the disease, and the one given by

$$\gamma > 0 \Rightarrow \left(S_\infty, S^F_\infty, I_\infty, R_\infty\right) = \left(\frac{R_\infty}{R_F - 1}, N - \frac{R_F R_\infty}{R_F - 1}, 0, R_\infty\right), \tag{15}$$

where fear and behavioral changes persist even after the end of the disease epidemic. The condition $R_F > 1$ is necessary but not sufficient in order to have an endemic state of fear, while $R_F \leq 1$ is sufficient to avoid an endemic state of fear. Unfortunately, the parameter γ is an implicit function of the whole dynamics through the epidemic size R_∞.

The presence of an endemic state associated to long lasting fear and the altered social behavior, a societal memory of the disease, is a quite interesting features of the model induced by the fear's self-reinforcement. In this model fear is able to sustain its presence in the population if the effective reproductive number of the local belief-based spread is larger than unity even if the disease dies out. Unfortunately, this argument cannot be used to fix the range of parameters in the phase space with these properties since any linearization at these stages of the compartments is not suitable.

Furthermore, the possibility of having an endemic state of fear indicates that an event localized in time is capable of inducing long lasting modifications to social behavior with interesting consequences. In the case of a second epidemic, the presence of part of the population already in the compartment S^F reduces the value of the basic reproduction number. The societal memory of the first outbreak increases the resistance in the population against the spread of the second outbreak in a non-trivial way. This is an important result that confirms how an endemic state of behavioral change in the population reduces the likelihood and impact of a second epidemic outbreak. We note that such a state will inevitably fade out on a long time scale. This can be modeled with a spontaneous transition $S^F \to S$ acting on a time scale longer than the epidemic process itself.

Discontinuous Transition in the Epidemic Prevalence

In the first model the epidemic size was significantly reduced just for large values of β_F. When belief-based behavioral changes are added, the reduction is characterized by a rich behavior as shown in Fig. 7. In this plot the fraction of the final number

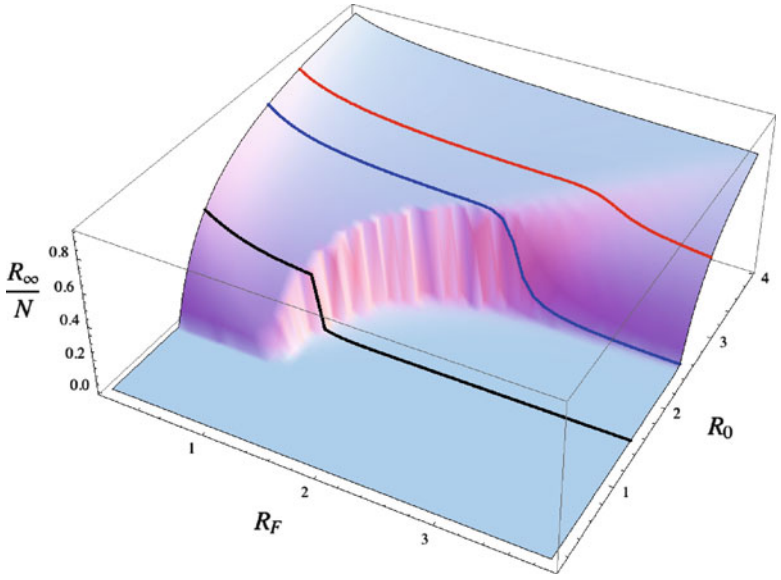

Fig. 7 Reduction of the epidemic size as a function of R_F and R_0. The three lines are curves of R_∞/N as a function of R_F, keeping R_0 constant are considered. In particular, $R_0 : 1.5, 2.5, 3$ which correspond to *solid black*, *blue*, and *red lines*, respectively. The value $R_0 = 2.5$ is a special case that leads to $R_0 r_\beta = 1$. It divides the phase space in two different regions. All the values of R_0 below are characterized by $R_0 r_\beta < 1$. In this case for large values of R_F the model is reduced to an SIR with reproductive number $R_0 r_\beta$ below 1 and the epidemic is halted. Interestingly, this behavior starts in an intermediate regime of R_F. There is a critical value R_F^* of R_F above which (i.e., $R_F > R_F^*$) the epidemic size is zero. This transition happens with a jump, as shown by the *solid black line*. All the values of R_0 above 2.5 are instead characterized by $R_0 r_\beta > 1$. Also in this case the model is reduced to an SIR with reproductive number $R_0 r_\beta$ for large values of R_F, but in this case this value is above 1. This results in a epidemic size that is always nonzero. In this region of parameters no jumps are present (see the *dashed line*). The other parameters used are $r_\beta = 0.4$, $\mu = 0.4\,\text{day}^{-1}$, $\mu_F = 0.5\,\text{day}^{-1}$, $N = 10^6$, and $\alpha = 0.05$

of recovered individuals at the end of the epidemic is shown as a function of R_F and R_0, keeping fixed the other parameters. The self-reinforcement mechanism creates a more complicated phase space that allows for a jump in the epidemic size as R_F increases above a critical value R_F^* (see the black line in Fig. 7). This behavior, typical of the first-order phase transitions in cooperative systems, signals a drastic change in the dynamical properties of the behavior-disease model. If $R_F < 1$, then obviously the fear of the disease is not able to affect a large fraction of the population and the disease spreads as usual in the population, affecting at the end of its progression R_∞ individuals. If $R_F > 1$ we face two different scenarios or two different regions of R_0 separated by the blue line in Fig. 7:

- In the case that $R_0 r_\beta > 1$ (i.e., the red line in Fig. 7) the generation of a finite fraction of individuals in the S^F compartment is not able to halt the epidemic.

The behavioral changes are not enough to bring the reproductive number below the epidemic threshold and R_∞ decreases smoothly because of the epidemic progress with a progressively lower effective reproductive number.

- If $R_0 r_\beta \leq 1$, (i.e., the black line in Fig. 7) the individuals that populate the S^F compartment keep the spread of the epidemic below the threshold. In principle, the state $R_\infty = 0$ and $S^F = N$ would be possible. In general, the process needs to start with infectious individuals that trigger the first transitions $S \to S^F$ and therefore a small number of R_∞ individuals are generated. However, there will be a R_F^* at which the growth of the fear contagion process is faster than the growth of the epidemic with a small R_∞. At this point the fear contagion process is accelerated by the growth of individuals in S^F while the epidemic spread is hampered by it. The S^F is quickly populated by individuals while the epidemic stops, generating a very small number of R_∞. This generates a jump in the amount of individuals that experience the infection as a function of R_F. The value at which the transition occurs also depends on the other parameters of the model including R_0 and r_β.

The self-reinforcing mechanism that characterized this model clearly creates non-trivial behaviors in the dynamics. In particular strong reductions in the cumulative number of infected individuals associated with discontinuous transition are observed. Even more, in the case of a second epidemic, the memory of the system shifts the reproductive number towards smaller values. These results show how simple modifications of the basic SIR model that accounts for change in the behavior of individuals might have critical effects in the unfolding of the disease.

2 Coupled Subpopulations: Mobility-Based Behavioral Changes

Considering a system of many subpopulations connected by human mobility, we now focus on a different type of behavioral changes. The epidemic dynamics happening inside each subpopulations is now coupled by the movement of individuals to the other subpopulations. In the previous sections we considered local behavioral changes that affect just the internal dynamics (reaction) of a single isolated population. Now we consider mobility-based changes in the behavior that act on the diffusion of individuals. Indeed, during the outbreak of an acute infectious disease, it is natural to expect self-initiated human behavioral changes and variations of individuals' mobility patterns. Obviously the extent of behavioral change depends on the risk as perceived by individuals that concerns the severity of the disease, prevalence of it within the population, and the information available on the disease. As discussed before, behavioral changes have been shown [18] to modify the disease state of individuals [3, 19], model parameters [12], and contact structure [20]. Human responses to the presence of a disease might have a direct

impact on mobility and traveling habits, since avoiding infected areas is a natural attitude of individuals and more drastic reactions such as not traveling at all may spontaneously arise, as documented in recent epidemics. In the following we present a general framework based on the metapopulation approach that includes two different self-initiate diffusion-based changes in individuals behavior [21]. In order to fully characterize their effects in the spreading, we neglect internal changes in the behavior as those discussed in Sect. 1.

2.1 Metapopulation Approach

This framework is extensively used to describe sets of spatially structured interacting subpopulations as a network whose links denote the mobility of individuals across subpopulations [6]. Each subpopulation consists of a number of individuals that are divided into several classes according to their dynamical state with respect to the modeled disease—for instance: susceptible, infected, removed, etc. The internal compartmental dynamics models the contagion dynamics by considering that people in the same subpopulation are in contact and may change their state according to their interactions and the disease dynamics. Subpopulations also interact and exchange individuals due to mobility from one subpopulation to another. Figure 8 shows a schematic representation of the metapopulation system. The global invasion threshold, R^*, marks the point beyond which a local outbreak reaches other subpopulations and spreads throughout the metapopulation system. The global invasion threshold not only depends on the infection parameters but also on the mobility rates of individuals and the property of the mobility network of individuals [22, 23]. This quantity thus differs from the single population epidemic threshold, R_0 that defines just the local spreading.

Dynamics in these systems have been intensively studied considering fully Markovian dynamics for the movement of individuals among subpopulations, and more recent analyses have focused on the analytical description of models with recurrent patterns [21–24]. In the following we consider a general scenario in which individuals have memory of their original subpopulations, which they return to after having reached their destination location. More explicitly, we define a population of size N now partitioned into V subpopulations. An individual is assigned its origin subpopulation—its *home*—among the V subpopulations. The subpopulations are interconnected by edges that represent the mobility connections among subpopulations. We can therefore conceptualize the metapopulation system as a network made of V nodes with assigned degree distribution $P(k)$ that defines the probability that any given subpopulation is connected to k other subpopulations.

The mobility of the population can be modeled in different ways depending on the required level of realism. A simple scheme reads as follows for every time step each of the N_i individuals ($N = \sum_i N_i$) of subpopulation i travels with probability λ_{ij} to the subpopulation j. These probabilities and the selected paths encode the

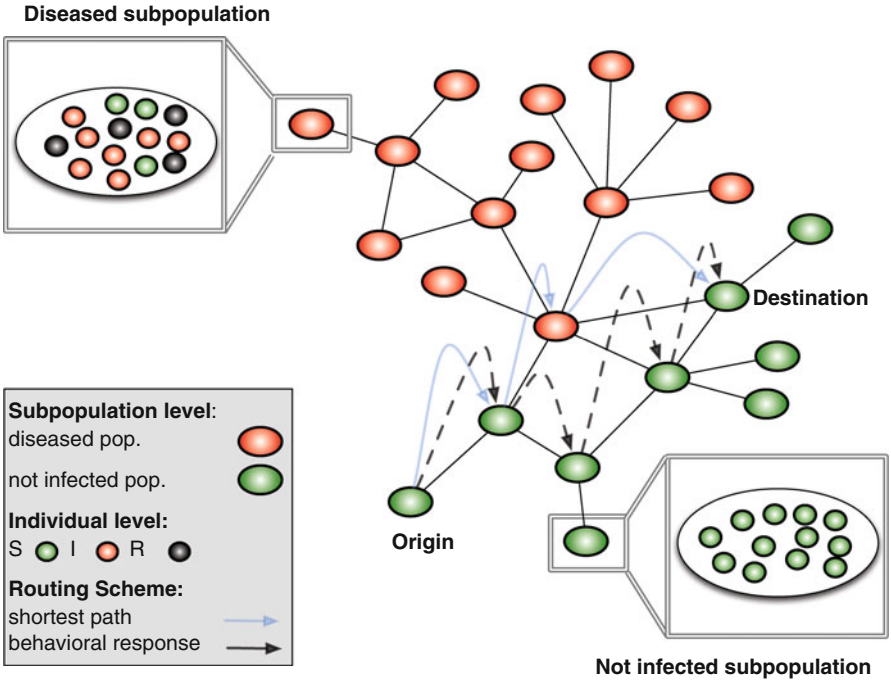

Fig. 8 Schematic representation of the metapopulation system. A population of individuals is divided into V subpopulations connected with each other following a heterogeneous network. Within each subpopulation, individuals are classified according to their dynamical status as susceptible (S), infected (I) and removed (R). In absence of behavioral changes (*blue arrows*), individuals move from a subpopulation to another at a rate λ following the shortest path connecting both subpopulations. The discontinuous arrows represent the second mechanisms of behavioral reaction in which people travel avoiding places with high prevalence at the cost of larger diffusion paths

details of the mobility. In realistic scenarios they are data driven. For example, the probability of selecting a destination can be set to be proportional to the total traffic of that node and the mobility scheme could be traffic-based. Individuals in this case follow paths to the destination proportionally to the actual traffic. In other cases the path can be fixed to be the shortest path between source and destination. In the following we consider the last case and a scenario in which the basic departure probability is fixed for all subpopulations i.e., $\lambda_{ij} = \lambda$. All travelers spend a time τ at their destinations before coming back home. The length of stay can be fixed or extracted from distributions built from real data. The intra-population epidemic dynamics is modeled using the basic SIR model. It is possible to analytically derive the invasion threshold within these settings. For details we refer the readers to reference [21].

2.2 Variation in Departure Probabilities

In the first behavioral reaction mechanism, individuals react to prevalence-based information about the disease. In particular, the probability $\lambda_{ij}(t)$ of traveling from subpopulation i to subpopulation j at time t is related to the level of infection at the destination subpopulation. One of the simplest possibility is considering that, the higher the incidence of the infection at the destination, the less likely the individual will engage in traveling. This translate in setting the probabilities of traveling as:

$$\lambda_{ij}(t) = \lambda \left(1 - \frac{I_j(t)}{N_j(t)}\right). \tag{16}$$

In the beginning when the number of infected individuals is zero in the large majority of subpopulations the probability of moving from i to j is equivalent to the baseline when no behavioral changes are considered i.e. λ. When the disease start to spread and the number of infected individuals in the diseased subpopulation increases, the departure probabilities start to deviate from the baseline. Mechanisms similar to this have been observed in real cases. In the recent H1N1 pandemic, for example, a consistent decline in the number of passengers arriving at airports in Mexico both domestically and internationally have been registered.

In Fig. 9 we show the results of this mechanism against the baseline in which no behavioral changes are implemented. The plot shows the behavior of the density of infected subpopulations D/V at the end of the global epidemic as a function of both the basic reproductive number R_0 and the traveling diffusion rate λ. The results readily show that the metapopulation system exhibits an invasion threshold which is independent of human behavioral changes. This feature of the model can be traced back to the fact that the behavioral changes are prevalence based. Analogously to the basic reproductive number, the invasion threshold is determined by the average number that each infected subpopulation will generate in a fully susceptible metapopulation system. Clearly in this regime the prevalence-based behavioral changes are irrelevant and the threshold value is thus not affected. Not surprisingly when the departure probabilities are reduced, the fraction of diseased subpopulations at the end of the outbreak decreases with respect to the null case. This kind of response is beneficial for the populations. The reason for the reduction in D/V is rooted in the effective reduction of the mobility rate of individuals, which leads to a smaller exposure of susceptible individuals to the disease both while traveling and at home. Of course the effect is much more evident for large value of the mobility rate λ and reproductive number R_0.

2.3 Variation in the Mobility Paths

The second mobility-based behavioral change model (see Fig. 8 for a schematic representation) induces changes in traveling routes. Specifically, any individual who is traveling from an origin (subpopulation i) to a destination (subpopulation j)

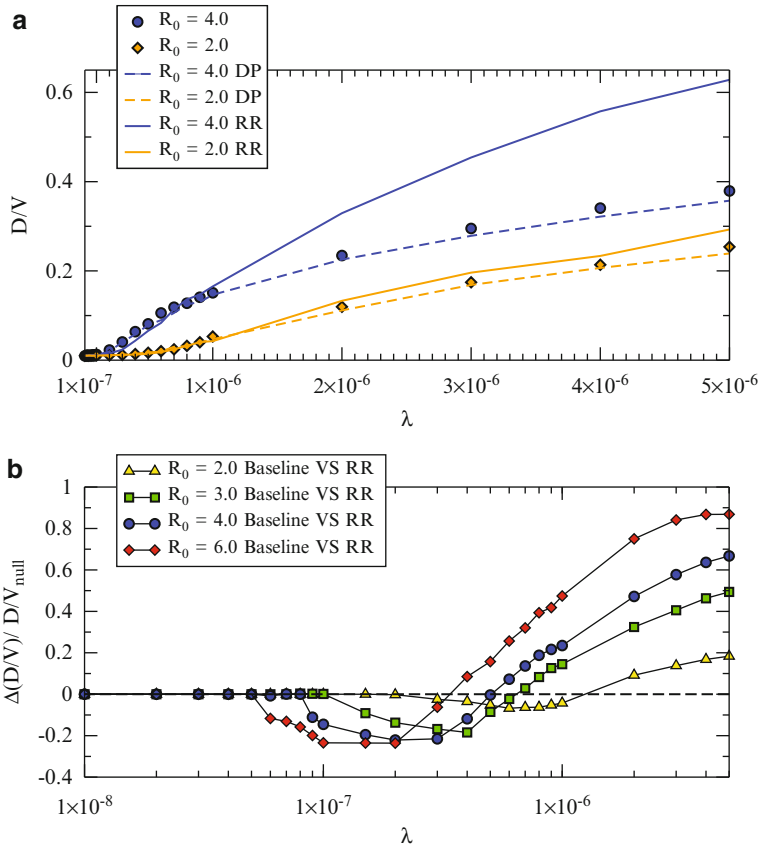

Fig. 9 The figure compares the fraction of diseased subpopulations D/V when behavioral reaction mechanisms are active with the situation in which such behavioral responses are not taken into account. (**a**) Shows the dependency of D/V with the mobility rate λ for random scale-free networks generated according to the uncorrelated configuration model [25]. Symbols represent the results obtained when individuals do not react to the presence of the disease. The rest of the results correspond to the mechanisms of behavioral changes: "DP" stands for "departure probability" and represents the mechanism in which individuals decide whether or not to travel; "RR" (re-routing) corresponds to the case in which people travel while trying to minimize the risk of infection avoiding subpopulations with high prevalence at the cost of long travel paths. The results confirm that the invasion threshold is independent of behavioral changes and that the latter has a significant impact on the invasion dynamics of the metapopulation. The points are the averages among at least 100 stochastic runs and considers $\mu = 0.04$ and $h = 0.1$. (**b**) we report the relative difference of subpopulations experiencing an outbreak in the RR and baseline scenarios as a function of λ. It is possible to see the nonlinear behavior that first induce a decrease—close to the invasion threshold—and then a sharp increase in the number of affected subpopulations

attempts to avoid traversing infected subpopulations, except when the next move leads to its destination. This process is obviously not deterministic and it consists of a trade-off between the risk associated with visiting a given subpopulation and

the increase of the travel path length to the final destination. In this model the risk perception associated with the visit of a given subpopulation is dependent on the prevalence of the disease in that subpopulation. However, staying away from infected subpopulations has the associated cost of traveling through alternative routes. Individuals move to the neighboring subpopulation l that minimizes the cost function

$$c_l(t) = h\delta_l + (1-h)\frac{I_l(t)}{N_l(t)}, \tag{17}$$

where δ_l is the change in distance to the destination, which can only take values -1 if node l is in the shortest path to the destination, 0 if it is at the same distance to the destination than the actual node, and +1 otherwise. The parameter h tunes the force of the behavioral response and for $h = 1$ the shortest path is always followed, whereas $h = 0$ corresponds to a path minimizing the risk of traversing infected areas.

As shown in Fig. 9, this second type of behavioral adaptation defines an interesting dynamic of the epidemic diffusion. As in the previous mechanism the invasion threshold is not changed. Indeed, in the early stages of the spreading, the number of infected individuals is small and individuals follow the shortest path to their destination. As shown in Fig. 9b for values of the parameter R_0 and λ that bring the system just above the invasion threshold, the rerouting of individuals on different paths leads to a reduction of the outbreak probability in the subpopulations along the origin-destination path. This leads to a final reduction of the subpopulations experiencing an outbreak. This is an interesting phenomena due to the effects induced by the rerouting mechanism [21]. Indeed, when the h mechanism is active, the number of individuals going through a node in the shortest path between an origin and a destination decreases due to the rerouting of individuals induced by the risk aversion mechanism. This implies that a smaller number of individuals goes through that node lowering the probability of outbreak in each sub-population that depends on the reproductive number R_0 and the number of traveling individuals [21]. However, for increasing R_0 and λ this probability saturates to one and all subpopulations visited on the original and the rerouted path experience an outbreak. In this regime the number of subpopulations affected by the epidemic is much larger than in the case without behavioral changes. This is a very interesting phenomenon in which the behavioral changes that were put in place to reduce the risk of infection actually give a negative global effect. This is due to the fact that, trying to minimize the risks to get sick, individuals change their route visiting places that otherwise would have not been visited, therefore contributing to a wider spread of the disease. The network is explored more efficiently and the disease can spread much faster.

3 Discussion

We have presented two general approaches, intra-population and inter-population, to model the effect of self-induced behavioral changes induced in a population by the awareness and risk perception to the spreading of an infectious disease. These two approaches looked at different scales and aspects of the same problem. The first approach considers a single isolated population and two different mechanisms modeling the contact-based behavioral changes. Interestingly these simple models exhibit a very interesting and rich spectrum of dynamical behaviors. Both mechanisms show multiple peaks in the incidence curve. In the belief-based model we find a disease-free equilibrium is present where the population acquires a memory of the behavioral changes induced by the epidemic outbreak. This memory is contained in a stationary (endemic) prevalence of individuals with self-induced behavioral changes. Furthermore, a discontinuous transition in the number of infected individuals at the end of the epidemic is observed as a function of the transmissibility of fear of the disease contagion.

The second approach considers a metapopulation system where two different mechanisms of mobility-based behavioral changes have been presented. In the first model individuals reduce their mobility in order to reduce the risk of contagion. This basic mechanism translates in a reduction of the number of infected subpopulation. In the second model instead individuals keep traveling but change their routes in order to minimize their risk. The results show that the disease spreading, as given by the number of subpopulations with local outbreaks, increases when travelers decide to bypass the subpopulations with a high number of infected individuals. Indeed, the increased flow of individuals going through alternative paths brings the infection to new subpopulations that would otherwise be infected by other subpopulations. This constitutes a very interesting finding, as one can think of the whole process in terms of a social dilemma; individuals adopt a sort of selfish behavior by avoiding highly infected spots, but as a consequence, the disease invades a larger fraction of the subpopulations in the metapopulation system. Thus, what is beneficial at the individual level, turns out to have a negative impact on the whole population, especially in the cases where the epidemic has pervaded the system (large R_0 and λ).

The results presented here points out the importance and relevant effects of behavioral changes in the modeling of infectious diseases. The extension of the models in which both contact- and mobility-based changes are considered at once are the obvious next step. However, the nontrivial dynamic behavior of the models emphasizes the importance of calibrating those features by appropriate choices of parameter values. Unfortunately, in many cases we lack the data necessary for calibrating the behavioral models. The availability of real-world, quantitative data concerning behavioral changes in populations affected by epidemic outbreaks is therefore the major roadblock to the integration of behavior-disease models. Any progress in this area certainly has to target novel data acquisition techniques and basic experiments aimed at gathering these data.

References

1. Epstein, J.M., Parker, J., Cummings, D., Hammond, R.A.: PLoS ONE **3**(12), e3955 (2008)
2. Lynch, A.: J. Ideas **2**, 3 (1991)
3. Funk, S., Gilad, E., Watkins, C., Jansen, V.: Proc. Natl Acad. Sci. **106**, 6872 (2009)
4. DeFleur, M.L., Ball-Rokeach, S.: Theories of Mass Communication. Longman, NY (1989)
5. Kermack, W., McKendrick, A.: P. Roy. Soc. Lond. A Mat. **115**, 700 (1927)
6. Keeling, M.J., Rohani, P.: Modeling Infectious Diseases in Humans and Animals. Princeton Univeristy Press, New Jersey (2008)
7. Perra, N., Balcan, D., Gonçalves, B., Vespignani, A.: Towards a Characterization of Behavior-Disease Models. PLoS ONE **6**(8):e23084. doi:10.1371/journal.pone.0023084 (2011)
8. Fenichel, E., Castillo-Chavez, C., Ceddia, M., Chowell, G., Gonzalez Parrae, P., Hickling, G.J., Holloway, G., Horan, R., Morin, B., Perrings, C., Springborn, M., Velazquez, L., Villalobos, C.: Proc. Natl. Acad. Sci. USA **108**, 6306 (2011)
9. Chen, F., Jiang, M., Rabidoux, S., Robinson, S.: J. Theor. Biol. **278**, 107 (2011)
10. Poletti, P., Ajelli, M., Merler, S.: PLoS ONE **6**(2), e16460 (2011)
11. Poletti, P., Caprile, B., Ajelli, M., Pugliese, A., Merler, S.: J. Theor. Biol. **260**, 31 (2009)
12. Coelho, F., Codeço, C.: PLoS Comput. Biol. **5**(7), e1000425 (2009)
13. Bagnoli, F., Lio, P., Sguanci, L.: Phys. Rev. E **76**, 061904 (2007)
14. Crosby, A.W.: Cambridge University Press, Cambridge (1990)
15. Bootsma, M., Ferguson, N.: Proc. Natl. Acad. Sci. **104**, 7588 (2007)
16. Hatchett, R., Mecher, C., Lipsitch, M.: Proc. Natl. Acad. Sci. **104**, 7582 (2007)
17. Markel, H., Lipman, H., Navarro, J., Sloan, A., Michalsen, J., Stern, A., Cetron, M.S.: J. Am. Med. Assoc. **298**, 6 (2007)
18. Funk, S., Salathé, M., Jansen, V.A.A.: J. R. Soc. Interface **7**, 1247 (2010)
19. Eames, K.: J. R. Soc. Interface **6**, 811 (2009)
20. Gross, T., D'Lima, C.J.D., Blasius, B.: Phys. Rev. Lett. **96**, 208701 (2006)
21. Meloni, S., Perra, N., Arenas, A., Gomez, S., Moreno, Y., Vespignani, A.: Modeling human mobility responses to the large-scale spreading of infectious diseases, Scientific Reports 1, **62**, doi:10.1038/srep00062 (2011)
22. Colizza, V., Vespignani, A.: J. Theor. Biol. **251**, 450 (2008)
23. Colizza, V., Vespignani, A.: Phys. Rev. Lett. **99**, 148701 (2007)
24. Balcan, D., Vespignani, A.: Nature Phys. **7**, 581–586 (2011)
25. Catanzaro, M., Boguña, M., Pastor-Satorras, R.: Phys. Rev. E **71**, 027103 (2005)

Incorporating Human Behaviour in Epidemic Dynamics: A Modelling Perspective

Istvan Z. Kiss

Abstract The past few years have seen the development of a suite of extended epidemic models that take into account the "active" nature of individuals and/or population. Many models start from the natural premise that individuals are not "passive" but, on the contrary, receive and process information about potential or ongoing epidemics. Therefore, risk perception and behaviour change play a major role in shaping and changing the outcome of an epidemic. Incorporating such aspects into classical epidemic models poses many challenges. First of all, there are many open questions about how information is generated, its availability locally and globally, its routes of dissemination and diminishing returns of "old" information. All these factors lead to a significantly extended state space with many more variables and parameters compared to standard epidemic models. Thus, apart from issues around measuring and quantifying risk perception and/or behaviour change driven by information, a major modelling challenge revolves around model complexity. More precisely, how to achieve an optimal balance between model accuracy and tractability. In this *chapter*, starting from a pairwise model that accounts for the concurrent spread of an epidemic and information, modelling complexity and results are discussed by (1) evaluating the effectiveness of various information generating and transmitting mechanisms followed by (2) the deconstruction of the pairwise model to a simpler variant and by (3) discussing concrete modelling alternatives (i.e., pairwise and effective degree models for dynamic networks) and potential future modelling trends in the area of coupled models of human behaviour and disease transmission.

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1 Introduction

Classical epidemic models operate on the assumption of a "passive" population where neither individuals nor population can absorb and process information arising from a potential or an ongoing epidemic [1, 4]. This is a strong and unrealistic assumption since for most diseases (e.g., sexually transmitted infections (STIs), SARS, pandemic influenza, childhood diseases) the heightened risk of an outbreak or ongoing epidemic leads to a series of measures aimed at preventing or limiting the negative impact of an epidemic. These can be broadly divided into two classes: (1) information generation and dissemination and (2) concrete measures taken by individuals or groups to prevent infection or limit onward spread. While measures of the first type can range from centrally driven population-wide campaigns and dissemination of news via different mass-media to more local interactions in acquaintance circles, measures of the second type include concrete pre-emptive or reactive measures such as vaccination [2], limiting exposure via altering contact patterns [9], seeking early treatment or taking medication (e.g., antiviral drugs) [6].

In this context and probably against intuition, information is not always beneficial. For example, the risk associated with vaccination has been documented to lead to limited uptake to the extent where herd-immunity thresholds have been breached [2]. To capture such counterintuitive effects various game theoretical models have been developed to combine epidemic dynamics with risk perception and model different strategies of vaccine uptake or avoidance [18]. Such models first and foremost are determined by the type of disease, e.g., *SIS* (susceptible-infected-susceptible) or different versions of it for STIs [17] and *SIR* (susceptible-infected-recovered) for childhood disease and influenza, and these are then modified to account for information generation and transmission together with modelling the benefits or penalties of having the information and choosing to act on or ignore it. For example, for STIs, Chen [3] formulated an economic/game-theoretic epidemic model to capture the interplay between the quality of information and its availability, the prevalence of the infection and disease dynamics.

A more traditional, population dynamics type approach has been proposed by Funk et al. [7] where information about the disease generates awareness which in turn can lead to discounted infection rates. The model is based on an extended version of the *SIR* combined with results based on individual-based simulation. As a result of the added complexity imposed by the awareness, the S, I and R classes were further divided to reflect both disease and awareness status. They have found that for the compartmental ODE model the spread of awareness has no effect on the basic reproduction number R_0 but leads to a reduction in the number of infecteds. The consideration of the same model on theoretical network models has revealed that if the disease transmission is not too fast, the generation and transmission of awareness can stop the outbreak, i.e., $R_0 < 1$.

In this *chapter* a coupled model of information and disease transmission in the context of STIs [10, 17] is revisited and this model is used to discuss issues around the efficacy of various information generating and transmitting mechanisms and modelling complexity. The results and discussion from the analysis of the model

are followed by a deconstruction of the model into its simpler components by first relaxing assumptions about the population contact structure and then about the way in which information is generated and transmitted. This helps to pinpoint and discuss model assumptions along with identifying alternative modelling approaches which account for evolving or adaptive contact networks that link naturally to aspects around the concurrent spread of disease and information.

2 Model

The model presented here is based on that formulated by Hatzopoulos et al. [10] but with some new aspects on interpretation of results and calculation of R_0. This pairwise model captures both disease and information transmission where evolution equations are written down for the expected number of individuals of various types which in turn depend on the expected number of pairs. The dependency of singles on pairs and then of pairs on triples is curtailed by using a closure relation where triples are approximated in terms of singles and pairs [11]. This framework allows us to take the population contact structure explicitly into account and thus produce an accurate description of the problem where, as an added advantage, multiple routes of information transmission (e.g., local and global) can also be accounted for.

Following on from [10, 12], individuals can be divided into one of five different classes that specify the individuals' status with respect to disease and information. These are susceptible non-responsive (S_{nr}), susceptible responsive (S_r), infected non-responsive (I_{nr}), infected responsive (I_r) and in treatment (T). The term *responsiveness* denotes the willingness to act or respond to information and is key in trying to avoid infection or halting further spread [17]. The important components of the model relate to the *generation* and *transmission* of information as well as the *benefits of possessing and acting on* information. In the model, information or responsiveness is generated in three ways: (1) $I_{nr} \to I_r$ as a result of symptoms, (2) $I_x \to T$, where $x \in \{nr, r\}$, as a result of being diagnosed and moving to the treatment class and (3) $X_{nr} \to X_r$, where $X \in \{S, I\}$ as a result of global information transmission. While the first two are intuitive, the latter is used to model the effect of mass-media campaigns which act as a single-source of information with its strength and duration often linked to the prevalence of infection in the population. Information transmission is possible in two different ways: (1) local or individual to individual and (2) mean-field. While information dissemination locally captures circles of close friends or acquaintances, the mean-field type transmission accounts for a less clear-cut interaction at the population level, often centrally lead or orchestrated. Many of these mechanisms of information generation and transmission pathways can be easily linked to various ways in which information is disseminated in real life. The model also accounts for the depreciation or decay of responsiveness over time and this is achieved by allowing $X_r \to X_{nr}$-type transitions at rate d_X, where $X \in \{S, I\}$. The main benefits of being informed and responding to information amount to reduced susceptibility, reduced infectivity and/or faster recovery if infected. To keep the model as general as possible, all the above factors

Table 1 All transitions allowed by the coupled infection/information system, where $X,Y \in \{S,I\}$ with individuals in treatment acting as members of the responsive classes (i.e., $X_r \in \{S_r, I_r, T\}$). Individuals in the treatment class return to being susceptible non-responsive and responsive at rate pr and $r(1-p)$ with $0 \leq p \leq 1$, respectively. The reduced susceptibility, infectivity and faster recovery, as a result of acting on information, is captured by the discount factors $\sigma_s, \sigma_i \in (0,1]$ and $\sigma_r > 1$. To model the mean-field transmission of information it is assumed that per unit time an individual may momentarily come into contact with k_{MF} others not in their social network. Along such links information flows at a rate m_X. The function $G_X([I_{nr}],[I_r])$ maps the prevalence of infection to the unit interval and is subsequently multiplied by the constant rate δ_X. This form models the saturating effect of media on individual behavioural response

Transition	Rate	Contact	Type
$I_{nr} + S_{nr} \to 2I_{nr}$	τ	G_d	Infection
$I_{nr} + S_r \to I_{nr} + I_r$	$\sigma_s \tau$	G_d	Infection
$I_r + S_{nr} \to I_r + I_{nr}$	$\sigma_i \tau$	G_d	Infection
$I_r + S_r \to 2I_r$	$\sigma_s \sigma_i \tau$	G_d	Infection
$I_{nr} \to T$	γ_{nr}	Independent	Infection
$I_r \to T$	$\sigma_r \gamma_{nr}$	Independent	Infection
$T \to S_{nr}$	$r \cdot p$	Independent	Infection
$T \to S_r$	$r \cdot (1-p)$	Independent	Infection
$X_r + Y_{nr} \to X_r + Y_r$	α_X	G_i	Information transmission
$X_r + Y_{nr} \to X_r + Y_r$	$m_X k_{MF}$	Mean-field	Information transmission
$X_{nr} \to X_r$	$\delta_X G_X([I_{nr}],[I_r])$	Independent	Information transmission
$I_{nr} \to I_r$	ω	Independent	Information generation
$X_r \to X_{nr}$	d_X	Independent	Information generation

are accounted for, but their presence or absence will be determined by the precise modelling context and should be used accordingly. The full suite of transitions are given in Table 1.

3 Results

Using the pairwise model (for a sample, see group of equations given in Eq. (1)), the efficacy of different information generating and transmitting mechanisms in slowing or stopping disease spread is investigated. Results are followed by a close scrutiny of model complexity including a model deconstruction and discussion around alternative modelling directions in the area of modelling the concurrent spread of disease and information.

3.1 Pairwise Model: Impact and Efficacy of Different Information Generating and Transmitting Mechanisms

Pairwise ODE models [11] represent an improvement upon standard compartmental models as they allow us to capture the local nature of contacts. They also interpolate with success between simple and full simulation models allowing for some degree

of analytical tractability and transparency. Similarly to contact tracing models [5], for information transmission it is important to represent the network of contacts and be able to represent the formation of clusters of responsive individuals that are difficult to capture via simple compartmental models. The resulting pairwise model has 20 equations, 5 for singles and 15 for pairs (see Eq. (1) for a sample). The dimensionality of the system can be further reduced by taking into account that the population is closed and that all pairs add up to $\langle k \rangle N$, where $\langle k \rangle$ is the average node degree and N is the population size. The sample equations are:

$$
\begin{aligned}
[\dot{S_{nr}}] &= -\tau[S_{nr}I_{nr}] - \tau\sigma_i[S_{nr}I_r] + pr[T] - \lambda_C\alpha_s([S_{nr}S_r] + [S_{nr}I_r] + [S_{nr}T]) \\
&\quad -\lambda_{MF}m_sk_{MF}([S_r] + [I_r] + [T])[S_{nr}]/N - \lambda_G G_s([I_{nr}], [I_r])[S_{nr}] + d_s[S_r], \\
[\dot{S}_r] &= -\tau\sigma_s[S_rI_{nr}] - \tau\sigma_i\sigma_s[S_rI_r] + (1-p)r[T] + \lambda_C\alpha_s([S_{nr}S_r] + [S_{nr}I_r] + [S_{nr}T]) \\
&\quad +\lambda_{MF}m_sk_{MF}([S_r] + [I_r] + [T])[S_{nr}]/N + \lambda_G G_s([I_{nr}], [I_r])[S_{nr}] - d_s[S_r], \\
[\dot{I_{nr}}] &= +\tau[S_{nr}I_{nr}] + \tau\sigma_i[S_{nr}I_r] - \gamma[I_{nr}] - \lambda_C\alpha_i([I_{nr}S_r] + [I_{nr}I_r] + [I_{nr}T]) \\
&\quad -\lambda_{MF}m_ik_{MF}([S_r] + [I_r] + [T])[I_{nr}]/N - \lambda_G G_i([I_{nr}], [I_r])[I_{nr}] + d_i[I_r] - \omega[I_{nr}], \\
[\dot{I}_r] &= +\tau\sigma_s[S_rI_{nr}] + \tau\sigma_i\sigma_s[S_rI_r] - \gamma\sigma_r[I_r] + \lambda_C\alpha_i([I_{nr}S_r] + [I_{nr}I_r] + [I_{nr}T]) \\
&\quad +\lambda_{MF}m_ik_{MF}([S_r] + [I_r] + [T])[I_{nr}]/N + \lambda_G G_i([I_{nr}], [I_r])[I_{nr}] - d_i[I_r] + \omega[I_{nr}], \\
[\dot{T}] &= +\gamma[I_{nr}] + \gamma\sigma_r[I_r] - r[T], \qquad (1) \\
[\dot{S_{nr}I_{nr}}] &= +\tau[S_{nr}S_{nr}I_{nr}] + \tau\sigma_i[S_{nr}S_{nr}I_r] - \tau[I_{nr}S_{nr}I_{nr}] - \tau\sigma_i[I_rS_{nr}I_{nr}] - \tau[S_{nr}I_{nr}] \\
&\quad -\lambda_C\alpha_s([S_rS_{nr}I_{nr}] + [I_rS_{nr}I_{nr}] + [TS_{nr}I_{nr}]) \\
&\quad -\lambda_{MF}m_sk_{MF}([S_r] + [I_r] + [T])[S_{nr}I_{nr}]/N - \lambda_G G_s([I_{nr}], [I_r])[S_{nr}I_{nr}] \\
&\quad -\lambda_C\alpha_i([S_{nr}I_{nr}S_r] + [S_{nr}I_{nr}I_r] + [S_{nr}I_{nr}T]) \\
&\quad -\lambda_{MF}m_ik_{MF}([S_r] + [I_r] + [T])[S_{nr}I_{nr}]/N - \lambda_G G_i([I_{nr}], [I_r])[S_{nr}I_{nr}] \\
&\quad -\gamma[S_{nr}I_{nr}] + rp[TI_{nr}] + d_i[S_{nr}I_r] + d_s[S_rI_{nr}] - \omega[S_{nr}I_{nr}], \\
[\dot{S_{nr}I_r}] &= +\tau\sigma_s[S_{nr}S_rI_{nr}] + \tau\sigma_i\sigma_s[S_{nr}S_rI_r] - \tau[I_{nr}S_{nr}I_r] - \tau\sigma_i[I_rS_{nr}I_r] - \tau\sigma_i[S_{nr}I_r] \\
&\quad +\lambda_C\alpha_i([S_{nr}I_{nr}S_r] + [S_{nr}I_{nr}I_r] + [S_{nr}I_{nr}T]) \\
&\quad +\lambda_{MF}m_ik_{MF}([S_r] + [I_r] + [T])[S_{nr}I_{nr}]/N + \lambda_G G_i([I_{nr}], [I_r])[S_{nr}I_{nr}] \\
&\quad -\lambda_C\alpha_s([S_rS_{nr}I_r] + [I_rS_{nr}I_r] + [TS_{nr}I_r]) \\
&\quad -\lambda_{MF}m_sk_{MF}([S_r] + [I_r] + [T])[S_{nr}I_{nr}]/N - \lambda_G G_s([I_{nr}], [I_r])[S_{nr}I_{nr}] \\
&\quad -\gamma\sigma_r[S_{nr}I_r] - d_i[S_{nr}I_r] + d_s[S_rI_r] - \lambda_C\alpha_s[S_{nr}I_r] + pr[TI_r] + \omega[S_{nr}I_{nr}].
\end{aligned}
$$

To integrate the equations numerically, the standard closure proposed in [11] is used. This amounts to approximating all triples in terms of singles and pairs with the general closure relation given by

$$[ABC] = \frac{\langle k \rangle - 1}{\langle k \rangle} \frac{[AB][BC]}{[B]}. \tag{2}$$

This approximation closes the system and numerical integration can be performed. Parameter values are based on those used in [10] and, for simplicity, it is assumed that $\alpha_s = \alpha_i = \alpha$, $d_s = d_i = d$ and $\delta_s = \delta_i = \delta$. λs are binary and are used to switch on and off various information transmission routes. The system exhibits three qualitatively different behaviours: (1) neither disease nor responsiveness can spread, (2) only responsiveness spreads and a state of endemic-responsiveness is reached and (3) both responsiveness and infection are endemic.

The system accounts for disease transmission through a static network of contacts with information generated either by individuals in treatment or by those that are infected and likely to self-diagnose. The model accounts for three different routes of responsiveness transmission. The first overlaps completely with the disease transmission route, while the second and third account for mean-field and global transmission of information, respectively. The analysis compares the potential of different sources and pathways of information generation and transmission to reduce prevalence or stop infection. These desirable outcomes can be achieved due to fractions of the population moving to the responsive class. As a result, these informed individuals will experience decreases in their levels of susceptibility and infectivity and a faster recovery if infected.

The system is seeded with a small number of individuals of type I_{nr} and S_r and then it is numerically integrated to identify the smallest or critical rate that will lead to the desired prevalence level $I^{eq} = 0.01$. This is repeated for a range of τ values to determine the relative capacities of α, ω and δ to deliver a state of low infection prevalence. A value of $p = 0.9$ was used as this approaches a worse-case scenario limit whereby no information is generated by the individuals themselves through past experience. This setup allows us to examine the effects of α, ω and δ in relative isolation (peer-to-peer transmission at rate α relies on the presence of informed or responsive individuals via self-diagnosis or via treatment). According to Fig. 1a, contact-based transmission of information is by far the most potent pathway to generating a responsive population. Similarly to disease transmission, every receiver of information (I_{nr} or S_{nr}) immediately becomes a transmitter, in contrast to global transmission of information that acts in isolation and remains singular at all times. The mean-field type transmission of information, not shown in Fig. 1a, is equally effective and produces an outcome that is similar to the contact-based transmission case, especially if the network is densely connected. For smaller values of $\langle k \rangle$, and as expected, the mean-field transmission performs better than the purely contact-based but with small differences.

The transition to the responsive class due to media exposure is assumed to happen at a rate given by the function

$$G_s([I_{nr}], [I_r]) = G_i([I_{nr}], [I_r]) = \frac{\delta([I_{nr}] + [I_r])^n}{K + ([I_{nr}] + [I_r])^n},$$

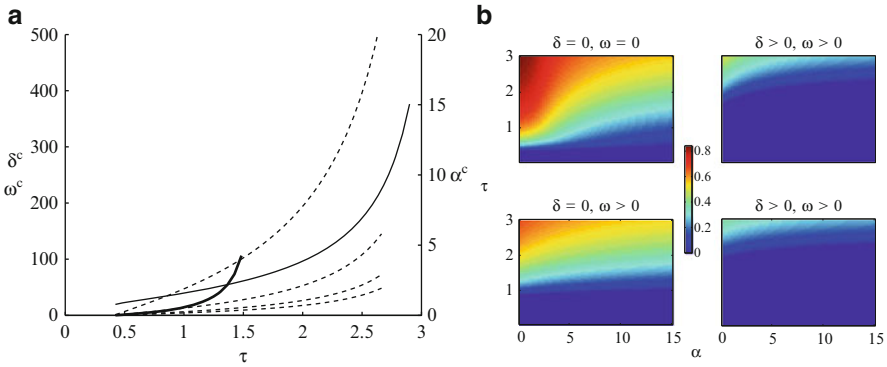

Fig. 1 (**a**) Critical information rates resulting in a prevalence of $I^{eq} = 0.01$ as a function of the per-contact infection transmission rate τ (computed via the pairwise model). For $\tau > 0.42$ and in the absence of information, the prevalence equilibrates at $I^{eq} > 0.01$. At and beyond this point different amounts of each information rate are needed to lower the prevalence to $I^{eq} = 0.01$. In this case, the effect of each transmission route is investigated in the absence of all others. *Solid and thick solid line* correspond to α^c and ω^c, respectively. The *four dashed lines* represent δ^c for different values of the population inertia parameter $K = [0, 5, 20, 100]$ increasing from *right* towards the *left*. The values for α^c are denoted on the *right y* axis and all the others on the *left y* axis. (**b**) The effect of combining different sources of information. On the *top left* panel the endemic infection prevalence is shown for a range of α and τ values. In the remaining panels, for each combination of α and τ, either global information or self-diagnosis or both are added with the same constant rate equal to 12. Other parameters are $p = 0.9$, $\sigma_s = \sigma_i = 0.5$, $\sigma_r = 2$, $\gamma_{nr} = 2$, $\gamma_r = \sigma_r \gamma_{nr}$, $d = \gamma_r$, $N = 10^4$, and $\langle k \rangle = 6$, from [10]. © Elsevier Science

where in this *chapter*, $n = 1$ at all times. The efficacy of global information (acting on I_{nr} or S_{nr}) strongly depends on the value of the K which controls the growth of $G(\cdot, \cdot)$, for low prevalence the function grows like $\frac{1}{K}(I_{nr} + I_r)^n$. The parameter K can be thought of as a measure of population's willingness in responding to information. Populations that resist behavioural change correlate with high values of K, and if it could be measured or inferred could act as an indicator for the quality of global information campaigns. For example, high values of K will simply translate to observing vanishingly small returns from global information campaigns. The critical rates for self-diagnosis are at best similar to those for global information, especially for diseases with low transmissibility. As is the case for global information, self-diagnosis lags behind the front of infection and will only produce benefits once infected individuals are present. This is made even worse given that ω can only act on I_{nr}.

Information generation depends heavily on the precise type of the disease. The self-diagnosis rate correlates directly with the disease being symptomatic. Diseases with mild symptoms or the slow generation of new sources of information transmission requires an efficient peer-to-peer communication and a population which is responsive and is ready to adapt. Finally, where the population's behavioural inertia

is high, self-diagnosis can be more effective than global information dissemination. This is illustrated by comparing the appropriate curves in Fig. 1a. The figure also shows that as τ increases it is less and less likely that information generation and/or transmission can prevent an epidemic. More precisely at large but finite values of τ, the rates of information generation and/or transmission needed to prevent the spread will tend to unfeasibly large values.

In reality information generation and transmission will not operate singly. Mass-media campaigns increase awareness which can bring forth behavioural change. Infected members of the population are likely to learn from experience and share their knowledge with their acquaintances. The model presented here is able to accommodate these elements as it is shown in Fig. 1b for various combinations of α, δ and ω. As indicated, the α and δ combination is the most effective, while the combination of all three is capable of preventing a significant proportion of epidemics, especially for large τ. Contact-based transmission of information is by far the most efficient as it generates new information transmitters. When epidemics are successfully halted, the responsive and non-responsive susceptible individuals form clusters that can resist infection invasions [10]. Such desirable endemic steady states, with no disease but with informed and/or aware individuals, provide an illustration of optimal dissemination of information that can prevent disease invasion and calculating the basic reproduction number at such an equilibrium can provide valuable insight into how disease, information and contact structure interact and determine the outcome of potential invasions. The basic reproduction number for such a setup, and with taking into account the heterogeneity in individuals' connectivity, can be written as

$$R_0 = \sum_{x,k} W_x^k (k-1) \sum_{y,l} P(S_y^l | I_x^k) P(I_x^k \to S_y^l), \tag{3}$$

where $W_x^k = kS_x^k / \langle k \rangle N$ is the probability that an initial index case chosen uniformly at random reaches an individual of type S_x^k with $x, y \in \{nr, r\}$ and $k, l \in \{k_{min}, \ldots, k_{max}\}$ with minimal an maximal nodal degree. $P(S_y^l | I_x^k)$ incapsulates the neighbourhood composition, e.g., the extent to which non-responsive or responsive individuals are surrounded by responsive individuals. The final component, $P(I_x^k \to S_y^l)$, simply denotes the probability of infection being passed across a link with infectious and susceptible individuals of different types and can be challenging to compute, see [10]. In this individual-based framework, R_0 involves the information generation and transmission components and provides a better representation when compared to simple ODE models and it can be used to explore the optimal arrangement that minimises the likelihood of an outbreak [8, 10].

3.2 Model Deconstruction

The pairwise model above can be deconstructed by relaxing the assumption about the mixing pattern in the population. Furthermore, applying it strictly under the assumption of asymptomatic disease [17] (i.e., $\omega = 0$), the model becomes [12]:

$$\dot{s_{nr}} = -\beta_{nr}(i_{nr}+i_r)s_{nr} - \alpha_s(s_r+i_r+\varphi)s_{nr} - g_s(i_{nr},i_r)s_{nr} + d_s s_r + pr\varphi, \quad (4)$$

$$\dot{s_r} = -\beta_r(i_{nr}+i_r)s_r + \alpha_s(s_r+i_r+\varphi)s_{nr} + g_s(i_{nr},i_r)s_{nr} - d_s s_r + (1-p)r\varphi, \quad (5)$$

$$\dot{i_{nr}} = \beta_{nr}(i_{nr}+i_r)s_{nr} - \alpha_i(s_r+i_r+\varphi)i_{nr} - g_i(i_{nr},i_r)i_{nr} - \gamma_{nr}i_{nr} + d_i i_r, \quad (6)$$

$$\dot{i_r} = \beta_r(i_{nr}+i_r)s_r + \alpha_i(s_r+i_r+\varphi)i_{nr} + g_i(i_{nr},i_r)i_{nr} - \gamma_r i_r - d_i i_r, \quad (7)$$

$$\dot{\varphi} = \gamma_{nr}i_{nr} + \gamma_r i_r - r\varphi, \quad (8)$$

where $g_x(\cdot,\cdot) = \delta_x(i_{nr}+i_r)/(k+(i_{nr}+i_r))$ with $x \in \{s,i\}$. A standard dynamical system analysis of the model above reveals two steady states ($(1,0,0,0,0)$ and $(1-s_0 = d_s/\alpha_s), s_0, 0, 0, 0)$ with two important threshold parameters ($R_0^r = \alpha_s/d_s$ for the responsiveness and $R_0^i = \beta_{nr}/\gamma_{nr}$ for the disease) and an analytical relation between the two determining the bifurcation picture of the system. In summary, the trivial disease-free steady state is locally stable if and only if $R_0^r < 1$ and $R_0^i < 1$ and the non-trivial disease-free steady state is locally stable if and only if $R_0^r > 1$ and

$$R_0^i - 1 < A(R_0^r - 1) \text{ with } A = \frac{(\gamma_r - \beta_r)(\alpha_i + \gamma_{nr}) + B(\gamma_{nr} - \beta_r)}{\gamma_{nr}(\alpha_i + \gamma_r + B)}, \quad B = d_i - \frac{\alpha_i}{R_0^r}. \quad (9)$$

This is illustrated in Fig. 2a and highlights that information at the right level can prevent an epidemic. However, it is important to note that in this simplified model, R_0^i does not depend on the information, as it was the case in [7]. This means that information cannot halt an epidemic at the onset but it can do so once information generation and transmission is quick started. In an *SIR* model this amounts to always experiencing a small epidemic whereas for an *SIS* model, the system can be driven back to full susceptibility and with a proportion of the population "infected" by awareness or responsiveness.

3.3 Alternative Modelling Approaches: Pairwise Models for Evolving Contact Structures

The principal aim of any pre-emptive or reactive interventions is to reduce the number of those affected by the disease. The reduction in onward spread can be achieved by either limiting or reducing the number of potentially infectious contacts, in network language amounting to cutting links, or keeping the connectivity but

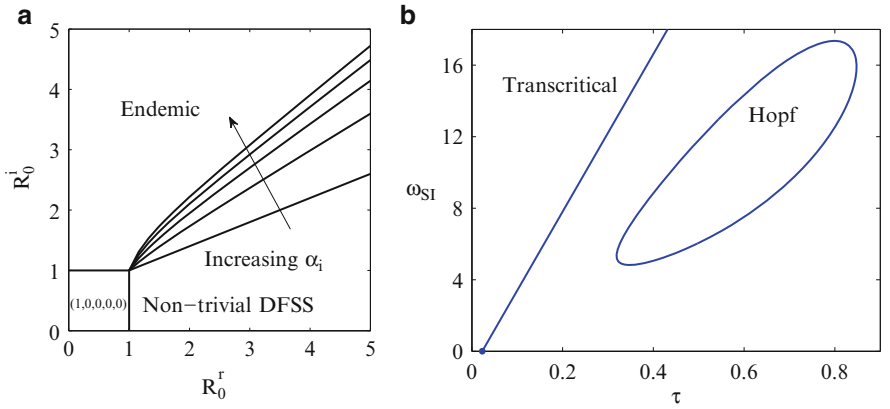

Fig. 2 (**a**) Illustration of the long-term behaviour of the system as a function of R_0^r and R_0^i for increasing values of $\alpha_i = 0.05\,j\,(j = 0,1,2,3,4)$ and $d_i = 1/(52$ weeks$)$ with other parameters being $\gamma_{nr} = 1/(26$ weeks$)$, $\gamma_r = 1/(13$ weeks$)$ and $\beta_r = \gamma_{nr}$. (**b**) The parameter space is divided into three regions: the disease-free is the only stable equilibrium (*above the transcritical curve*), one unstable (disease-free) and a stable endemic equilibria co-exist (*below the transcritical curve* and *outside the Hopf bifurcation island*) and, finally, a Hopf island with a stable limit cycle and unstable disease-free and endemic equilibria. Parameter values are as follows: $N = 100$, $\langle k\rangle = 10$, $\alpha_{SS} = 0.004$, $\alpha_{SI} = 0.005$, $\alpha_{II} = 0$, $\omega_{SS} = 0.005$, $\omega_{II} = 0$ and $\gamma = 1.0$

reducing the susceptibility and infectivity level as well as the typical time that an infectious individual spends in the population. While this last component cannot be modelled by the alteration of the network of contacts, the former aspects can be modelled by the explicit alteration of the connectivity pattern of the population. Evolving or adaptive networks have already been studied in terms of simple epidemic models where susceptible individuals break links to infected neighbours and reconnect to other susceptibles [9]. This model can be regarded as an implicit model of information generation and transmission where the action of individuals of certain type can lead to curtailing an epidemic. A generalisation of the model proposed by Gross et al. in terms of an *SIS*-based pairwise models can be written as:

$$[\dot{I}] = \tau[SI] - \gamma[I], \tag{10}$$

$$[\dot{SI}] = \gamma([II] - [SI]) + \tau([SSI] - [ISI] - [SI]) - \omega_{SI}[SI] + \alpha_{SI}([S][I] - [SI]), \tag{11}$$

$$[\dot{II}] = -2\gamma[II] + 2\tau([ISI] + [SI]) - \omega_{II}[II] + \alpha_{II}(([I] - 1)[I] - [II]), \tag{12}$$

$$[\dot{SS}] = 2\gamma[SI] - 2\tau[SSI] - \omega_{SS}[SS] + \alpha_{SS}([S]([S] - 1) - [SS]), \tag{13}$$

where, α_{AB} and ω_{AB} represent the rate at which AB-type links are created and cut $(A, B \in \{S, I\})$. This system is closed in the same way as the initial pairwise model (see Eq. (2)) and the system lends itself to a bifurcation type analysis in order to determine full system behaviour [13, 19]. The main outcome is illustrated in

Fig. 2b, where the cutting of $[SI]$-type links can halt the spread of the epidemic. While the precise mechanism of information generation and transmission is not explicit, this model is attractive in that it shows a qualitatively similar behaviour to result from models with explicit information components yet it keeps a good degree of transparency and analytical tractability. Moreover, for most diseases avoiding infection will involve a significant amount of contact reduction or limitation and hence a necessity of capturing evolving contact patterns. Previous models, explicitly including aspects of information transmission, have recognised the importance of also explicitly modelling contact and overlap between the disease and information transmitting contact [8, 10] but have not considered a changing network structure. Future research may shed light on whether the static network approach with information modelled explicitly or dynamic networks with or without explicit contact are more suitable and whether these should be used in combination or singly. As more data becomes available, model fitting techniques may lead to better understanding as to how link cutting and creation rates behave and whether these need to be considered as time dependent functions of prevalence, including delays. Dynamic network models of this type could be also refined to include aspects such as the propensity of informed individuals to seek early treatment and thus limiting further onward spread.

4 Discussion: Impact of Information and Modelling Outlook

In reference to the first pairwise model, Eq. (1), the numerical analysis suggests that contact-based transmission is always more efficient in lowering prevalence when compared to global information dissemination. Preliminary results also highlight that increasing individual specific heterogeneity in σ (while keeping the same mean) leads to lower prevalence as a large number of nodes, with small values of σ, are almost completely immune or unable to transmit infection. A similar observation holds for α, where a high proportion of individuals with weak potential to transmit the information will result in higher prevalence. The discrepancy between the impact of peer-to-peer and population-wide transmission of information on epidemic outcomes has important public health implications as illustrated in the United Kingdom's early AIDS epidemic, which was concentrated largely among men who have sex with men (MSM). Informal campaigns within the male homosexual community can be dated to early 1983. This was prior to dissemination in the gay press (1983–4) and much earlier then the wider government sponsored campaigns of 1986–7. It is estimated that HIV transmission peaked around 1983 among MSM [16], followed by a rapid decrease which limited the size of the HIV epidemic in the UK. The population-wide campaigns of 1986–7 were however associated with less dramatic changes in STI diagnosis.

On the modelling side further progress and model refinement can be made by looking at ODE-based models that have been developed for approximating epidemic transmission on static and dynamic networks. For example, the pairwise models

presented above do not take into account heterogeneity in the connectivity of individuals. This can be circumvented by using heterogenous pairwise models [5] where variables are determined by both disease status and number of links (e.g., $[S_k]$ - susceptible nodes with k contacts and $[S_k I_l]$ - pairs linking a susceptible with k contacts to and infected with l contacts). Obviously, this will increase the number of equations and including information explicitly may make the model difficult to analyse. In such cases, adaptive network models, where information is included implicitly, may be more desirable. A recently proposed novel approach that comes to meet this demand and also accounts for degree heterogeneity is the so-called effective-degree type model developed by Lindquist et al. [14] and extended further for dynamic networks by Marceau et al. [15] and Taylor et al. [20]. Here, a "smart" choice of variables, with equations formulated in terms of the expected number of S_{si} and I_{si} (susceptibles and infecteds with s susceptibles and i infectious neighbours, respectively), leads to further modelling flexibility and more accurate bookkeeping of nodes and the status of their contacts. However, this approach also relies on a closure and raises further questions about the performance of various approximate models when compared to true simulation. The large spectrum of modelling approaches coupled with the natural tendency to increase model accuracy can easily lead to overly complex models that are not transparent and difficult to analyse and thus we advocate a modelling approach that aims for a good balance between capturing key mechanisms and tractability.

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References

1. Anderson, R.M., May, R.M.: Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford (1991)
2. Buonomo, B., D'Onofrio, A., Lacitignola, D.: Math. Biosci. **216**, 9–16 (2008)
3. Chen, F.H.: Math. Biosci. **217**, 125–133 (2009)
4. Diekmann, O., Heesterbeek, J.A.P.: Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation. Wiley, Chichester (2000)
5. Eames, K.T.D., Keeling, M.J.: Proc. Natl. Acad. Sci. USA **99**, 13330–13335 (2002)
6. Ferguson, N.M., Cummings, D.A.T., Fraser, C., Cajka, J.C., Cooley, P.C., Burke, D.S.: Nature **442**, 228–452 (2006)
7. Funk, S., Gilad, E., Watkins, C., Jansen, V.A.A.: Proc. Natl. Acad. Sci. USA **106**, 6872–6877 (2009)
8. Funk, S., Gilad, E., Jansen, V.A.A.: J. Theor. Biol. **264**, 501–509 (2010)
9. Gross, T., Dommar D'Lima, C.J., Blasius, B.: Phys. Rev. Lett. **96**, 208701 (2006)
10. Hatzopoulos, V., Taylor, M., Simon, P.L., Kiss, I.Z.: Math. Biosci. **231**, 197–209 (2011)
11. Keeling, M.J.: Proc. R. Soc. Lond. B **266**, 859–867 (1999)
12. Kiss, I.Z., Cassell, J., Recker, M., Simon, P.L.: Math. Biosci. **225**, 1–10 (2010)
13. Kiss, I.Z., Berthouze, L., Taylor, T.J., Simon, P.L.: Proc. Roy. Soc. A **468**, 1332–1355 (2012)
14. Lindquist, J., Ma, J., van den Driessche, P., Willeboordse, F.H.J.: Math. Biol. **62**, 143–164 (2011)

15. Marceau, V., Noël, P.-A., Hébert-Dufresne, L., Allard, A., Dubé, L.J.: Phys. Rev. E **82**, 036116 (2010)
16. Nicoll, A., Hughes, G., Donnelly, M., Livingstone, S., De Angelis, D., Fenton, K., Evans, B., Nöel Gill, O., Catchpole, M.: Sex. Transm. Inf. **77**, 242–247 (2001)
17. Oh, M.K., Grimley, D.M., Merchant, J.S., Brown, P.R., Cecil, H.: Hook III, E.W.: J. Adoles. Health **31**, 40–47 (2002)
18. Reluga, T.C., Galvani, A.P.: Math. Biosci. **230**, 67–78 (2011)
19. Szabó, A., Simon P.L., Kiss, I.Z.: Differ. Equ. Appl. **4**, 277–296 (2012)
20. Taylor, M., Taylor, T.J., Kiss, I.Z.: Phys. Rev. E. **85** 016103 (2012)

Risk Perception, Heuristics and Epidemic Spread

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Abstract During an outbreak of an infectious disease, people often change their behaviour to reduce their risk of infection. In a given population, the levels of perceived risk of infection vary greatly among individuals. The difference in perception could be due to a number of different factors including varying levels of information regarding the pathogen, quality of local healthcare, availability of preventive measures, individual and group usage of heuristics in the decision-making process. First we discuss the rigorous assessment of the risk, then we describe how our brain assesses the risk through the use of heuristics that are still rooted in animal evolution. Then we discuss the impact and the role of mass media and social networks in modulating risk perception. Next, we show how mathematical modelling is challenged by multi-scale epidemiological problems where the risk perception level is coupled with all the other microscopic and macroscopic levels. Finally, we draw future scenarios of personal risk evaluation through self-monitoring devices and personal genomics. The aim of this chapter is to discuss the importance of risk perception related to the spreading of a disease and to present a variety of ideas that could be fruitfully explored through modelling.

1 The Relationship Between Epidemic Risk and Awareness

Current and future public health hazards do not depend only on the biological characteristics of the infectious organism and on our immune system capability of response but also on the responsible behaviour of individuals, particularly of those

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who are more likely to be infected. We find difficult to accurately evaluate infection risk because of the lack of data and multi-scale and multi-factorial conditions of infection events. We are able to estimate different health threats of different viral strains by comparing the binding energies of viral proteins with host membrane receptors, but it is still difficult to estimate all interaction combinatorics at the whole cell proteomics level. Recently animal models have provided important experimental data on influenza spreading. Lowen and co-authors [22] have found that the influenza virus can pass between guinea pigs by means of droplet spread and was transmitted from infected guinea pigs to healthy guinea pigs housed in the same cage, an adjacent cage, or a cage placed 91 cm away. Coughing, sneezing, talking, and breathing generate a cloud of airborne particles with diameters ranging from a few mm to less than 1 μm. Alford et al. [2] revealed that humans could contract influenza by inhaling an experimental small-particle aerosol containing low levels of influenza virus. We trust hospitals as safe places but they are known to originate the spread of infectious diseases in patients. Even isolation rooms equipped with advanced heating ventilation air conditioning (HVAC) systems may not be completely safe as shown in [4]. Here, 3D models of the room consider different, most typical, positions of the patients. Results indicate the best conditions for high induction air inlet diffuser and the scheme of pressures imposed in the room to provide the effective means of controlling flows containing virus droplets. The authors used finite element modelling software and CAD techniques to model the isolation room under different operating conditions (negative and positive pressure of the isolation room, airflow patterns associated with different cough conditions, switch on off of the HVAC). The authors found difficult to obtain technical details of surgery theatres, probably because results could change patients awareness and highlight structural deficiencies during economic crisis. The seasonal flu infection follows an age pattern: Brownstein [5] showed that influenza spread firstly in children aged 3–4 years old, then the infection involves their brothers and sisters who may have more hygienic behaviour, then their parents and with the start of the winter it spreads among the elderly who may be at greater risk. People affected by severe immune pathologies could have different infectious risks and different awareness. With age, both frailty and risk perception usually increase. A challenge task is to evaluate the probability of the emergence of new variety of pathogen strains. Although about 3,000 different viruses are nowadays known, next generation sequencing and metagenomic approaches have revealed the vast majority of the viruses on Earth is not yet characterised. Statistical bioinformatics models will be increasingly used to calculate the number of viral mutations between safety and pandemics with little population awareness due to scarce education about DNA sequences.

2 Putting Risk Evidences Together

Expensive and complex epidemiological data are gathered and being analysed in a rather simple way that runs the risk of missing the opportunity to uncover combinations of predictive and meaningful profiles among the data. The challenge

is to establish whether any causal conclusion suggested by the best fitting model is warranted by the data. Formal approaches to causal inference are needed in order to guide the researcher specifying the underlying causal assumptions, formulating the causal hypothesis in a non-ambiguous way, determining whether the data provide information to address that hypothesis. The complexly structured data, embracing molecular, subclinical and clinical, epidemiological information, social network require novel methodology to elucidate epidemics and health-related mechanisms. The multilevel data point at a huge space of causal models. The problem is not simply one of defining a suitable class of models and, within this class, to search for those models which provide the best fit but to combine the multilevel data within a study, with one type of data across studies, into multilevel data across studies. There is an increasing need to use all the available information, even with missing values, from different datasets (meta-analysis) and different dimensionality, which may be called super meta methodology.

An important approach in evidence synthesis is that of back-calculation, which is based on convolution equations; it uses reported numbers of diagnoses of a disease (say AIDS) in each calendar period, together with estimates of the distribution of time from infection to diagnosis of AIDS (the incubation period) to generate estimates of the underlying incidence of infections. Combined with information on survival, this approach allows to estimate current HIV prevalence. However, cheap diagnostic tools and medical treatments would change the actual incubation period (information ignorance). Another approach is the direct method where the general population is subdivided into mutually exclusive groups, indexed by g, at risk for HIV and information on the proportion of the population in each risk group, γ_g, is derived from routinely collected statistics or the census [12]. The task is then to estimate the number of prevalent diagnosed and undiagnosed infections in each risk group, as well as the risk group totals RG, which can be expressed as

$$RG = \sum_g N(\pi_g \gamma_g \delta_g + \pi_{gg}(1 - \delta_g)). \tag{1}$$

The direct method is not easy to implement in practice because it requires complete data from all the risk groups to compute confidence intervals for each group and the relationships between the various items of evidence. Interesting example of software is the Estimation and Projection Package [16] that fits a simple infectious transmission model to the prevalence data via sampling importance resampling and generates a cluster of epidemic curves for each urban/rural and subgroup-specific sub-epidemic. A novel promising approach is that of multi-parameter evidence synthesis which offers a coherent analytical framework designed to make rational and exhaustive use of the whole body of information available [1]. It constructs a formal specification of the relationships between data and parameters, which dictates how direct and indirect evidences on the parameters of interest can be integrated [15].

Recent advances in cognitive science have given insights into the human brain as a rational Bayesian machine. Risk perception of a particular disease is shaped by both past events experienced by the individual and available hints from living

environment at global and local scales. Given an incomplete picture Y_{obs} of the situation, the brain performs a filling-in process of the missing details Y_{miss} so it could come up with decisions of rational action. The inference is facilitated by assuming a single model with the relevant variables, specified by the set of parameters Θ with prior belief $p(\theta)$. The predictive distribution of missing details can be obtained by integrating out the parameter posterior space

$$p(Y_{miss}|Y_{obs}) = \int p(Y_{miss}|\Theta)p(\Theta|Y_{obs})d\Theta \tag{2}$$

where parameter posterior is in turn estimated from probable values of missing portion

$$p(\Theta|Y_{obs}) \propto p(\Theta) \int p(Y_{obs}, Y_{miss}|\Theta)dY_{miss} \tag{3}$$

An approximation of this iterated scheme [23] has been demonstrated to successfully uncover missing feature and relational data in the biological domain.

3 Perception as Human Quick Synthesis of Evidences

Since the individual decision-making process is affected by the risk perception, during evolution we have developed fast decision shortcuts, called heuristics, in order to increase our survival. Heuristics are efficient cognitive processes that ignore information and enable fast decisions. Because of their cognitive limitations, humans are often unable to perform rational calculations and instead rely on error-prone heuristics; moreover, even when people could optimise, that is, to compute the best decision, they often rely on heuristics to save efforts at the price of sacrificing some accuracy. These concepts are based on the principle of an accuracy-effort trade-off: the less information, computation or time one uses, the less accurate one's judgments will be. This trade-off is believed to be one of the few general laws of the mind. It is important to evaluate the heuristics in terms of its ecological rationality environment. How do people make decisions when optimisation is out of reach? Examples of the embedded heuristics toolbox we use at individual or social levels are the recognition heuristic, which states that if one of the two alternatives is recognised, one will infer that it has the higher value on the criterion (less-is-more effect is often detected); the $1/N$ equality heuristic, which allocates resources equally to each of N alternatives; and $tit\,for\,tat$, in which one cooperates first and then imitates her/his partner's last behaviour; other widely used heuristics are the imitation of the behaviour of majority and the imitation of the successful person. The last two heuristics are recognised as a driving force in bonding and group identification and therefore play an important role in our choices [11]. In 1950 Herbert Simon [27] first proposed that the people satisfice rather than maximise. Maximisation means optimisation, the process of finding the best solution for a problem, whereas satisficing (satisfying and sacrificing at the

same time) means finding a good enough solution. This corresponds to a well-known heuristics: in order to select a good alternative (e.g. a house or a spouse) from a series of options encountered sequentially, a person sets an aspiration level, chooses the first one that meets the aspiration and then terminates the search. The aspiration level can be fixed or adjusted following experience. For Simon, humans rely on heuristics not simply because of their cognitive limitation but also because of the task environment. We often trust a person we know well as non-infected while we may judge as potentially infected a person we do not know; sometimes these decision-making processes take less than one minute. Gigerenzer has shown that simple rules, that is, decision-making tree based on fast and frugal heuristics, behave nearly the same as more complex diagnostic procedures [32]. The self-diagnosis, which may correlate with the time you decide a medical visit is opportune, the choice of a doctor or of a therapy could be biased by the underlying presence of the recognition heuristics. There is a growing activity of mathematical modelling of the impact of heuristics in the theory of mind and in the ICT. Recent approaches are based on so-called ACTR (adaptive control of thought-rational) and establish analogies with an ecological model for strategy selection. In Parma during 1980s and 1990s Rizzolatti and colleagues demonstrated the existence of a mirror-matching system in the human brain [25]. It is nowadays accepted that the mirror neurons system mediates the automatic imitation and empathy; in some sense they provide basis for connecting individuals' emotions. The neurophysiology of mirror neurons could possibly suggest the origin of heuristics in the imitation and processing capabilities of mirror neurons and in the spread of risk perception levels by imitation. The ancient structure of the mirror neurons could provide some explanation for some ancestral fears and overestimated risk perception such as that for snakes. It is noteworthy that the link between heuristics and neurophysiology and the link between epidemics spreading and heuristics generate a connection between epidemics and the functioning of brain regions affected by fear and conscience. This connection is also affected by reading newspapers, twitter and blogs, watching television and Youtube.

4 Risk Perception Modulation by Mass Media and Social Media

Our risk perception is shaped by heuristics and more influenced by friends' recommendations than mass media channels such as newspapers and television. Nevertheless, mass media have a tremendous importance in influencing individual behaviour probably because of the concept of the wisdom of the crowds, that is, the many are smarter than the few. Mass media is influenced by commercial trends, politics and the journalistic practice, for example, an article could appear in the first page in large characters or towards the end of the newspaper in a minor section; moreover, there is a journalistic tendency to draw attention to certain features of

an issue while minimising attention to others. Social media is strongly influenced by our social constrains. Robin Dunbar and collaborators have found that social networks have a cognitive limit for emotional closeness of about 150 members (albeit with significant variance around this value); within a 150-people layer, there are those you know as persons. Beyond 150, we know people only as categories; interactions are defined by rules, not personal knowledge. Kin are given preference in the network where individuals from large families have fewer friends, and there are strong same-sex preferences. Kin networks are usually more dense than friend networks, suggesting that family links are less fragile than friends (reflecting the say that blood is not water) [8]. There is a widespread belief that social media have increased the amount and quality of information but also background rumours. Facebook, Twitter and other social websites have boosted the public awareness of disease outbreaks but also make it more difficult to separate facts from fiction. Many WHO experts have pointed out that social media are mixed blessing in epidemics. WHO officials reported that during the H1N1 swine flu that swept the world in 2009/2010, one of the Internet rumours was increasing your salt intake can help, consequently boosting a counteraction by WHO about the dangers of taking too much salt. Two important differences with respect to mass media are represented by specific information social networks for patients such as the website *PatientsLikeMe* and flu tracker phone or Internet-based networks which act as a quick alarm network and continuous coverage statistics on the evolution of an epidemic front. The website *Patients Like Me* acts as a quick self-diagnose based on symptomatic similarity and drug performance evaluation social network. The drawbacks could be mis-diagnoses and less personalised treatment (an individual takes the same drugs that have well performed for other patients disregarding his/her special conditions and past history of treatments). Although observational studies cannot meet the rigid standard of randomised clinical trials, they provide an opportunity to collect possibly useful data by capturing patients' conditions. There is more trust in people with similar conditions and the heuristics of imitating likewise people. A recent work reported that a person's overall web literacy predicts their behaviour to a significant extent. Especially for people with lower web literacy, the extent to which a web page's declared ideological perspective was consistent with their own was very important for whether a person decided to believe the information posted on that web page. In [31] the authors have proposed a susceptible (S)-infected (I)-hospitalised (H)-recovered (R) model where the media function is incorporated into the model using an exponentially decreasing function:

$$\frac{dS}{dt} = \Lambda - e^{-M(t)}\lambda S - \mu S + \delta R \tag{4}$$

where the rate of susceptibles depends on the recruited into the population Λ and on the media coverage over time $M(t)$ times the constant recruitment rate, λ; μ is the natural death rate and δ is the recovery rate. This model is able to highlight different levels of beneficial effects of media coverage. M(t) depends on both the number of cases and their rate. Their model is successful in fitting some relevant data but also opens the possibility for parameter estimation. Recent work by Durham

and Casman [9] has taken a step towards constructing a model for SARS that is based on time series of media coverage regarding the disease and on the proportion of the population wearing face masks during the outbreak. The approach of [9] demonstrates the possibility of identifying parameters of human behaviour using various data sources such as news, surveys or even search engine query data [13]. Models are at the level of the intensity of single source of data acquisition; we still need to approach the variety of data acquisition.

5 Heuristics and Undervaccination

Undervaccination is observed in both poor and wealthy communities [30]. In poor countries, intensive international programmes aiming at familiarising adult primary care providers (APCPs) with vaccine-preventable diseases and the importance of using vaccines are needed in order to improve vaccination rates. Recent work shows poor familiarisation of APCPs to inform hospitalised individuals about vaccinations [30]. Noteworthy, on Facebook (2011), there are more than 40,000 pages on vaccinations and more than 1200 groups; 95 % of them are negative towards vaccination; on Youtube 90 % of the 10,000 movies about vaccination are against. So the background noises for rumours have become much louder, making it so much harder to detect the really important segments. Typical reasons found in blogs are the following: *mom knows best; if vaccines caused autism, I would probably opt out of most vaccines, because most kids don't die of whooping cough or scarlet fever, but autism is forever; don't want my kids to get autism. So I will risk a deadly disease instead*. Clearly the decision is based on a heuristic approach and not on a careful reasoning which should have considered that for highly contagious viruses, like measles, about 95 % of the population need to be immunised to effectively prevent spread. In some sense the mother had not made a choice for her son only, but for everyone with whom he had come in contact. Is it reasonable that this mother's rights should include the right to have her child catch and transmit a potentially fatal infection? Peadiatricians must also take proactive precautions with the growing number of unvaccinated, potentially biohazardous children and immediately place them in an examination room away from office traffic flow. It is totally unfair to expose the rest of your patients who are trying their best to protect their children with recommended vaccines. Mathematical models have highlighted the different values of vaccination strategies and information (see for instance [19, 21, 24]). A model with pulse vaccination has shown that the media can trigger a vaccinating panic if the vaccine is imperfect and simplified messages may result in the vaccinated mixing with the infectives without regard to disease risk [31]. The perception of the individual responsibility in different context is an important factor that has not been incorporated in models.

6 Building Models of Risk Perception

A study on the psychological responses to the 2009 H1N1 virus, [14], reported significant reduction in the use of public transport, a high number of flight cancellations and a considerable amount of investment in preventative goods. Individuals undertaking such precautionary measures may succeed in reducing their susceptibility to the disease and thus potentially reduce the size of an epidemic outbreak. Despite the potentially considerable impact of behavioural changes in the population, the majority of mathematical models have only considered changes in human behaviour resulting from various public health interventions. The aim of such models is to study the effectiveness of interventions such as social distancing and the provision of treatment and prophylaxis in containing an emerging pandemic. [33] have also considered the compliance with suggested interventions, mentioning that the compliance of individuals may be closely related to various demographics and that levels of compliance may vary over the course of the disease outbreak. Even in the absence of institutionally enforced interventions, individuals may occasionally take the initiative and change their personal behaviour in response to their perceived risk of becoming infected. The risk perception framework was applied by [3] to study the effect of human behaviour on both homogeneous and directed scale-free networks [3]. In this framework, as a result of alertness to the disease, the probability of transmission of the disease due to contact between an infectious and a susceptible individual is multiplied by a factor of

$$A(s,k) = exp\left[-\left(H + J\frac{s}{k}\right)\right] \tag{5}$$

where s is the number of the individual's infected connections and k is the degree of the connectivity of the network. The parameter J represents the 'local' or personal perception and determines how strongly the individual reacts to observing disease symptoms in his close contacts. The global awareness parameter H determines the awareness that an individual has gained from publicly available information or due to access to treatment and preventative measures. The probability that an individual becomes infected following contact with at least one of its infectious neighbours is modelled as

$$\lambda\,(s,k) = 1 - [1 - A\,(s,k)\,\tau]^s\,. \tag{6}$$

[3] presented an additional approach to examining the effects of risk perception on a population. They showed that, for random networks and infectivity, there exists a critical value of the individual awareness J, above which it can prevent an epidemic outbreak.

7 Combining Community Structure and Risk Perception

Mean-field approach shows that, in the presence of several communities, a value of J higher than the critical value for the homogeneous case, is necessary to prevent a community from experiencing an epidemic. Since in a realistic situation the amount of precautions an individual can take are limited, a consequence of this result is that, in the presence of community interactions, even high awareness of the disease may be insufficient to prevent an epidemic. Different ethnic communities or communities in geographical regions (e.g., countryside versus city) may respond differently to an epidemic, so community models will provide a better fit to real situations [18, 19]. In [19] the authors developed an epidemic prediction tool that uses a combination of geographical, demographic and housing information. We foresee that similar tools will have automatic update of the relevant information. Following [18] we consider a network of N individuals described by five parameters: C is the number of communities; $n(X)$ is the size of community X; $p_i(X)$ is the probability of connection between nodes in community X; $p_e(X)$ is the probability of connection between nodes in community X and the nodes of any other community; and $H(X)$ the awareness of the disease in community X. We use ς to denote the set of all communities in the network. The first four parameters allow for variation in size and connectivity per community and are necessary for constructing a network of heterogeneous communities. The parameters $p_i(X)$ and $p_e(X)$ are chosen based on the required average internal and external connectivity per individual in each community. The $H(X)$ parameter is only necessary when the communities modeled also have varying levels of risk perception. A common approach for generating networks to test community detection algorithms is the use of the planted l-partition model [7, 10]. The algorithm divides a set of N nodes into l equally sized groups according to two probabilities: p_{in} is the probability of connection between nodes in the same group; p_{out} is the probability of connection between nodes belonging to separate groups. Links are generated between all pairs of nodes according to these probabilities and the result is an Erdos-Renyi-like (ER) random network of l communities, provided that $p_{in} > p_{out}$. This approach generates a network of communities of varying sizes. The average connectivity in the resulting network is homogeneous for individuals within the same community but varies across communities. The communities exhibit the small-world property. Across communities, the average shortest path L is likely to be larger than within communities, due to the lower density of edges between communities.

The investigation of the effects of boundary nodes (i.e. nodes within a community with at least one external connection) is a common procedure when examining community structure in networks [10]. In the case of non-overlapping communities, these nodes have a high betweenness centrality and represent the only means by which infection may travel between communities. In this model the probability of connection between two nodes, members of the communities X and V, respectively, is $p_e(X)p_e(V)$. The probability of a node in V not having a connection to any node in X is

$$[1 - p_e(V)p_e(X)]n(X). \tag{7}$$

Thus, the expected number of boundary nodes in V, considering all communities in ς, is given by

$$B_V = n(V)[1 - \prod_{X \in \varsigma, X \neq V} [1 - p_e(V)p_e(X)]^{n(X)}] \tag{8}$$

An isolated community is simply an ER random graph. Let us consider for simplicity the case of the arrival of the infection from outside the community and not its subsequent spread. The set of parameters we need to consider are thus the community size n (the size of the infected outside world is $N - n$), the probability of external connectivity p_e ($p_e = 1$ for the outside world) and the awareness of the community H. The expected number of infections entering a susceptible community is simply the number of boundary nodes which would become infected. The probability of an individual becomes infected following contact with at least one of its infectious neighbours is given by equation above.

If B is the number of boundary nodes of the community, then the expected number of infections, for an individual with s infectious out of k total contacts, is simply $\lambda(s,k)B$. If we do not consider the local awareness and the outside world is completely infected we can simplify $\lambda(s,k)$ to $1 - [1 - e^{-H}\tau]^{k^{out}}$ and we obtain

$$y_X(k,i) = \sum_{s=0}^{k} \binom{k}{s} \lambda(s, < k_X >) i^s (1-i)^{k-s} \tag{9}$$

where $y_X(k,i)$ is the prevalence of the disease and $< k_X > = < k_X^{in} > + < k_X^{out} >$. Note that the force of infection $y_X(k,i)$ considers the expected rate of infection over all possible neighbourhoods of any node in community X according to the current prevalence. Thus $y_X(k,i)$ serves to replace the uniform mixing assumption with an approximation of the mixing between infective and susceptible individuals occurring across different parts of the network. Next, we define the fraction of infected individuals both within and outside of community X. The prevalence of the disease within the community X is

$$i_X^{in} = \frac{I_X}{n(X)} \tag{10}$$

where i_X denotes the number of infected individuals in X. The expected number of infected external acquaintances to the boundary nodes of community X is given by

$$i_X^{out} = \frac{p_e(X)}{< k_X^{out} >} \sum_{Y \in \varsigma, Y \neq X} p_e(Y) I_Y \tag{11}$$

Using these definitions we can write expressions for the force of infection experienced by both boundary and non-boundary nodes. If S_X is the number of susceptible individuals of community X, the number of susceptible non-boundary

nodes and the force of infection they experience are, respectively,

$$\left(1-\frac{B_X}{n(X)}\right)S_X, \qquad y(<k_X^{in}>,i_X^{in}) \tag{12}$$

and the number of susceptible boundary nodes which can acquire infection from either outside or inside the community, and the force of infection they experience are, respectively,

$$\frac{B_x}{n(X)}S_X, \qquad y(<k_X^{in}>,i_X^{in})+y(<k_X^{out}>,i_X^{out})-y(<k_X^{in}>,i_X^{in})y(<k_X^{out}>,i_X^{out}) \tag{13}$$

Using the expressions defined above, the dynamics of community X can be described by the following ODEs:

$$\frac{dS_X}{dt}=-\left[S_X\left(y\left(<k_X^{in}>,i_X^{in}\right)+\frac{B_X}{n(X)}\left[y(<k_X^{out}>,i_X^{out}) -y(<k_X^{in}>,i_X^{in})y(<k_X^{out}>,i_X^{out})\right]\right)\right] \tag{14}$$

$$\frac{dI_X}{dt}=-S_X\left(y\left(<k_X^{in}>,i_X^{in}\right)+\frac{B_X}{n(X)}\left[y(<k_X^{out}>,i_X^{out}) -y(<k_X^{in}>,i_X^{in})y\left(<k_X^{out}>,i_X^{out}\right)\right]\right)-\alpha I_X \tag{15}$$

$$\frac{dR_X}{dt}=\alpha I_X \tag{16}$$

For a population of C communities, C sets of three equations need to be solved simultaneously to approximate the disease dynamics, as the equations all depend on i_X^{out} which is defined according to the prevalence across all communities. We can remove this dependency by setting $i_X^{out}=0$ for all communities, so that the external force of infection is $y(<k_X^{in}>)=0$, thus obtaining the dynamics of the disease if each community is isolated from the rest of the population.

This model has been implemented in an open software available from the authors that allow testing for different community structure, topologies of connections (variable boundaries), individual and community awareness J,H and modelling interventions. Using the mean-field approximation, [18] showed that in the presence of interaction between communities, values of J higher than the critical value are necessary to prevent a community from experiencing an epidemic. Since in a realistic situation the amount of precautions an individual can take are limited, a

consequence of this result is that, in the presence of community interactions, even high awareness of the disease may be insufficient to prevent an epidemic.

Applying a different transmission model to this framework is also possible. For example, if we wished to implement a susceptible-exposed-infected-recovered (SEIR) model we could easily do so by defining the mean period of time α for the exposed period, so that at every time step an individual in the exposed state becomes infected with probability $1/\alpha$. An important consideration might be to allow for the modelling of diseases with asymptomatic infectious cases, such as influenza. Asymptomatic individuals may still be infectious, although potentially less so than symptomatic cases.

At the microscale modelling, more efforts are needed to estimate better the effective reproduction number of seasonal versus pandemic disease and how the magnitude of this number is affected by both the presence of risky conditions because of health (e.g. the genetic structure) or behaviour of a community and the genetic diversity and the accumulation of mutations of the pathogen, particularly its antigenic evolution. At the macroscopic scale, the current economic crisis seems to produce relevant effects on the possibility of pandemic and seasonal diseases due to the toughened conditions for certain high-risk groups, including migrants, homeless persons, and prison populations that are particularly vulnerable to reductions in treatment access, quality of care due to drops in government spending [28]. These groups show stress with increased high-risk behaviour, consumption of alcohol, tobacco, substance abuse and worse nutrition. Clearly a better description of the information acquisition dynamics and of heuristics involved in the decision making process for various communities would lead to better prediction.

The combining analysis of micro- and macroscales of an epidemic could provide an accurate estimate of the effective reproduction number of the disease. The aim of mitigation strategies is to reduce the effective reproduction number of the disease to a value close to or less than the epidemic threshold and thus prevent the disease from causing a large epidemic outbreak.

Recently Lio et al. [20] have combined formal languages and hybrid modelling to model the use of different therapies between therapies following the spread of an epidemic. Important efforts are focused on developing multi-scale approaches of epidemics: from the intracellular signalling and the communication between cells which form the levels of the immune response, to the tissue and organs levels that form the level of the structural response variation induced by the disease and are at the core of therapies application, to the population levels where parameters are related to social contacts, economy, psychology, for instance the cost of the therapies and vaccination. Note that all scales of description are dependent on each other. Furthermore, usage of personal technology tools will increase the individual and community differences of awareness.

8 Future Risk and Awareness Management Through Self Monitoring Devices and Personal Genomics

There is growing interest in using technological devices to continuously monitor one's own health. In the past these tools were used by people trying to lose weight or improve their fitness. Athletes and their coaches commonly make detailed notes on nutrition, training sessions, sleep and other variables. New technologies (e.g. wristbands for heart rate, sleep patterns, skin conductance) make it simpler than ever to gather and analyse personal data. Sensors have shrunk and become cheaper. In USA and Europe, quantified self conferences are showing people new ways to deal with medical problems or improve their quality of life with technology. For instance together with various signals such as heart rate, posture, motion and temperature, co-ordination, reaction times, memory and emotions could be monitored. Personal genomics will provide an estimate of the personal risk in an epidemics. Ultra-high-throughput sequencing strategies have now been used to sequence more than 10,000 full, individual human genomes. One of the clinical implication is the possibility to obtain an almost complete map of the antigenic coverage of each of us against existing and predicted (on genomic basis) epitopes of pathogens. The availability of personal genome sequences and antigenic response data will require the development of models that will incorporate such information. It is noteworthy that the price of sequencing is dropping quickly. This suggests that samples could be collected from mining sewage systems and spots like toilets in pubs, trains, airports or emergency rooms to monitor public health concerns , for example, flu outbreaks that can then be sent off for sequencing, allowing us to build an early alarm map over time of the arrival of pathogens. We can imagine this map to be consulted using a phone in the same way we now watch the weather forecasting map. The combination of personal genomics would provide useful information on the personal threat posed by the arising pathogen strain.

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References

1. Ades, A.E. Sutton, A.J.: J. R. Stat. Soc. Ser. A Stat. Soc. **169**, 5 (2006)
2. Alford, R.H., Kasel, J.A., Gerone, P.J., Knight, V.: Proc. Soc. Exp. Biol. Med. **122**, 800 (1966)
3. Bagnoli, F., Liò, P., Sguanci, L.: Phys. Rev. E. Stat. Nonlin. Soft. Matter Phys. **76**, 061904 (2007)
4. Balocco, C., Lio, P.: Energ. Buildings **43**, 246 (2011)
5. Brownstein, S.J., Kleinman, K.P., Mandl K.D.: Am. J. Epi. **162**, 686 (2005)
6. Coelho, F.C., Codeo, C.T.: PLoS Comput. Biol. **5**(7), e1000425 (2009)
7. Condon, A., Karp, R.M.: Random Struct. Algor. **18**, 116 (2001)
8. Dunbar, R.I., Shultz, S.: Science **317**, 1344 (2007)
9. Durham, D.P. Casman, E.A.: J. Roy. Soc., Interface **9**, 562 (2012)

10. Fortunato, S.: Phy. Rep. **486**, 75 (2010)
11. Gigerenzer, G., Hertwig, R., Pachur, T.: Heuristics: The Foundations of Adaptive Behavior, 1st edn. Oxford University Press, USA (2011)
12. Giesecke, J., Johnson, A., Hawkins, A., Noone, A. Nicoll, A.J.: Roy. Statist. Soc. Ser. A **157**, 89 (1994)
13. Ginsberg, J., Mohebbi, M.H., Patel, R., Brammer, L., Smolinski, L., Brilliant, L.: Nature **457**, 1012 (2009)
14. Goodwin, R., Haque, S., Neto, F. Myers, L.B.: BMC Infect. Dis. **9**, 166 (2009)
15. Goubar, A., Ades, A.E., De Angelis, D., McGarrigle, C.A., Mercer, C.H., Tookey, P.A., Fenton, K., Gill, O.N.: J. Roy. Statist. Soc. Ser. A **171**(3), 541 (2008)
16. Ghys, P.D., Brown, T., Grassly, N.C., Garnett, G., Stanecki, K.A., Stover, J. Walker, N.: Brit. Med. J. **80**, i5 (2004)
17. Grenfell, B.T., Pybus, O.G., Gog, J.R., Wood, J.L., Daly, J.M., Mumford, J.A., Holmes, E.C.: Science **303**, 327 (2004)
18. Kitchovitch, S., Liò, P.: PLoS ONE **6**(7), e22220. doi:10.1371/ (2011)
19. Leung, I.X.Y., Gibbs, G., Bagnoli, F., Sorathiya, A., Liò P. Contact Network Modeling of Flu Epidemics. In: Umeo, H., Morishita, S., Nishinari, K., Komatsuzaki, T., Bandini, S. (eds.) Cellular Automata, Proceedings vol. 5191, pp. 354–361 (2008)
20. Liò, P., Merell, E., Paoletti, N.: Disease processes as hybrid dynamical systems. Proceedings of the First International Workshop on Hybrid Systems and Biology. Newcasle upon Tyne, UK, September 3, (2012)
21. Li, Y., Cui, J.: Commun. Nonlinear Sc. Numer. Simulat. **14**, 2353 (2009)
22. Lowen A.C., Mubareka S., Tumpey T.M., Garca-Sastre A., Palese P.: PNAS **103**, 26 (2006)
23. Nguyen, V.A., Koukolíková-Nicola, Z., Bagnoli, F., Lió, P.: Bayesian Inference on Hidden Knowledge in High-Throughput Molecular Biology Data. PRICAI 2008: Trends in Artificial Intelligence, pp. 829–38 (2008)
24. dOnofrio, A., Manfredi, P., Salinelli, E.: Theor. Pop. Biol. **71**, 301 (2007)
25. Rizzolatti, G., Craighero L.: Annu. Rev. Neurosci. **27**, 169 (2004)
26. Rosenquist, J.N., Murabito, J., Fowler, J.H., Christakis, N.A.: Ann. Intern. Med. **152**, 426 (2010)
27. Simon, H.A.: Models of Bounded Rationality. Economic Analysis and Public Policy, vol. 1, pp. 235. MIT Press, Cambridge (1955)
28. Suhrcke, M., Stuckler, D., Suk, J.E., Desai, M., Senek, M., McKee, M., Tsolova, S., Basu, S., Abubakar, I., Hunter, P., Rechel, B., Semenza, J.C.: PLoS One. **6**, e20724 (2011)
29. Sjoberg, L.: Risk Anal. **20**(11), 40 (2000)
30. Tan, T.Q., Bhattacharya, L., Gerbie, M.V.: J. Reprod. Med. **56**, 301 (2011)
31. Tchuenche, J.M., Dube, N., Bhunu, C.P., Smith, R.J., Bauch, C.T.: BMC Public Health **11** (Suppl 1), S5 (2011)
32. Wegwarth O., Gaissmaier W., Gigerenzer, G.: Med. Educ. **43**, 721 (2009)
33. Wu, J.T., Riley, S., Fraser, C., Leung, G.M.: Plos Med. **3**(9), e3614057 (2006)

The Mechanism and Phenomena of Adaptive Human Behavior During an Epidemic and the Role of Information

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Abstract Disease transmission can be described phenomenologically at the population level or mechanistically as the aggregate result of individual behaviors. To explain why epidemics evolve as they do in response to information, a mechanistic approach is required. However, taking a mechanistic approach reveals that information can be parsed in terms of forecasting models or the approach to forming expectations, timeliness or quality of information, and information processing and how the information is used to make trade-offs. We develop a mechanistic model that uses microeconomic theory to describe adaptive or strategic human behavior. We show that phenomenological forecasting models and forecasting models based on classical epidemiological theory guide human behavior towards similar biological results, but different social well-being results. Moreover, we find that assumptions about information processing method, i.e., the utility function of individuals, may have a substantial influence on an epidemic.

1 Introduction

The persistent use of Kermack and McKendrick's (1929) [33] compartmental modeling framework for epidemics attests to the usefulness and parsimony of their framework for describing epidemics. A key contribution of the framework is that it treats the total population as heterogeneous, dividing the population into health classes. From the mixing levels of these health classes the epidemiological

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dynamics emerge. Hence, from the perspective of epidemiological trends, the Kermack and McKendrick framework can be seen as a mechanistic description of the epidemic. But, what is mechanistic at one scale is phenomenological at another. The Kermack and McKendrick framework and most modern applications (many following [3]) is purely phenomenological with respect to the mixing levels; so much so that it is unclear where human behavior fits into the Kermack and McKendrick compartmental framework. Most attempts at including human behavior do so by extending compartmental classes via analyst-defined static rules [23].[1] Such extensions are a double-edged sword in the quest to better understand why epidemics evolve as they do, and how public policy can or should intervene, because these extensions do not qualitatively change the nature of the basic model [26]. The advantage of modeling human behavior as an extension of compartments is that many of the known properties of epidemiological models persist [26] and concepts like the basic reproductive number can be generated in a straightforward manner [31]. The disadvantage of extending compartmental models to address adaptive human behavior is that the models remain chiefly phenomenological at the level of behavior, making it inappropriate to extend them beyond the range of observed data to novel situations or to investigate counterfactual policy scenarios – two key goals of applied science. The purpose of this chapter is to present an alternative approach to mechanistically modeling human behavior that builds on the insights of the compartmental model by leveraging insights from microeconomic models of human behavioral responses to dynamic and partially endogenous risks [46]. We do this while working from the standard susceptible-infected-recovered compartmental model. Developing behavioral choices at the phenomenological level allows us to provide a relatively mechanistic description of disease dynamics. We use this mechanistic description to more clearly define what is meant by information and model the role of information, and perhaps epidemiology itself, in shaping the nature of an epidemic

2 The Model

2.1 A Mechanistic Model of an Epidemic

To open a place for explicitly modeling adaptive human behavior in the compartmental epidemiological model [3,33] for a communicable disease that imposes costs on individuals while infected, but does not cause mortality, we factor the contact rate and the infectiveness parameter [6, 7, 38], writing the model as[2]

[1] Agent-based [36], network [45], and distributed parameters [49] can be seen as generalization to the compartmental modeling framework.

[2] Our notation and model development follows [20]. The framework is easily adapted to handle disease-induced mortality, but this requires tracking changes in the total population thereby adding

$$\dot{S} = -\frac{C(\cdot)\beta SI}{N} \tag{1}$$

$$\dot{I} = \frac{C(\cdot)\beta SI}{N} - \nu I \tag{2}$$

$$\dot{Z} = \nu I \tag{3}$$

The population that is incurring an epidemic is divided into health compartments. We restrict our analysis to the three basic time-varying epidemiological compartments: susceptible, S, infected and infectious, I (for the purpose of this chapter we use these terms interchangeably), and recovered with immunity, Z, in a fixed population, N. $C(\cdot)I/N$ is the rate that susceptible individuals contact infectious individuals. Parameter β represents the likelihood that contact with an infectious individual yields infection, i.e., the conditional infectiveness of a pathogen. The rate of recovery and acquired immunity is ν, and we assume no loss of immunity. The model is constructed so that N is fixed and scaled to 1 so that the state variables are fractions of the population, and individuals within a particular compartment are homogeneous. The outbreak is temporary, so we focus on dynamics as opposed to steady states (see [22] for a similar treatment).

Factoring the $C(\cdot)$ function provides a 'place' in the compartmental model for human behavior. Fixing $C(\cdot) = c$ as parameter, which is the implicit assumption when the terms $C(\cdot)\beta = \widetilde{\beta}(t) = c\ \forall t$, gives the standard mass-action model [6]. To the extent that this describes behavior, it does not provide mechanism. Time-varying or nonlinear descriptions of $\widetilde{\beta}(t)$, [9, 34] seldom describe a mechanism, but often use behavior to motivate nonlinear functional forms. Information change has motivated many of these papers, and general mathematical insights have been gleamed [17, 18]. These approaches can be seen as working from phenomena towards mechanism.

An alternative line of inquiry begins with behavioral mechanisms, based on the goal-seeking behavior of individuals (e.g., utility maximizing). Economic theory suggests that individuals will engage in adaptive or strategic behavior in response to a disease if disease creates benefits or costs broadly defined. These behaviors include adoption of treatment and vaccine [7, 21, 25, 42], changes in risky sexual behavior [5, 35], migration behavior [39], and general risk reduction through decreasing contact opportunities [11, 20]. Behavior in these models is not simply adaptive or reactionary to past events, but strategic-adaptive to expected future events. A key component of models with strategic behavior is that heterogeneity is endogenous [5, 20]. Endogenous heterogeneity means that the fraction of the population facing a set of incentives changes as the epidemic progresses, but that the epidemic

an additional state variable. It is also possible to include population turnover (see supplemental material in [20]). However, our primary goal is to consider adaptive behavior during an epidemic such as flu and such epidemics are often managed as if they will eventually die out (see [21] for a similar treatment).

progression is driven in part by response to incentives created by the epidemic itself. This endogenous heterogeneity makes predetermining behavioral compartments impossible. Indeed, the basic model structure itself introduces heterogeneity among health classes [33], and there is reason to believe that individuals in different health classes would face different incentives and behave differently. Game theoretic disease models are emerging and implicitly addressing some of these issues [24,43], but these game theoretic models often focus on Nash equilibria as opposed to dynamics and trade-offs for policy.

Prior to developing a mechanistic model of strategic behavior it is useful to specify the contact function, $C(\cdot)$, to allow individuals in different health classes to behave differently. The specification should have the property that it nests the mass-action specification if all individuals behave identically. Index individuals by health type, $Y = \{s,i,z\}$, to be the set of possible health types (corresponding to S, I, and Z). Next, define contacts between m-type and n-type individuals, with $m,n \in Y$, as

$$C^{mn}(\cdot) = \frac{C^m C^n}{SC^s + IC^i + ZC^z} \tag{4}$$

C^m is the expected number of contacts made by a type-m individual. When $m = s$ and $n = i$, $C^{mn}(\cdot) = C^{si}$ corresponds to $C(\cdot)$ in Eqs. (1) and (2). We emphasize that C^m is a *choice* made by a type m individual. C^m could be chosen directly or by engaging in certain activities (e.g., taking public transportation). Equation (4) implies conditional proportional mixing. Mixing is proportional but also conditional on the behaviors and the distribution of individuals of different health types. If all types choose the same number of contacts $C^h = c \ \forall h \in Y$ and $\forall t$, irrespective of health class, then $C^m(\cdot) = c$, satisfying our nesting criteria.

Equation (4) generalizes the model from Eqs. (1)–(3) to allow different behaviors by health class. Now we turn our attention to developing a mechanistic model for behaviors of the three health classes. We model a representative agent who is goal seeking. Following [20] and other economic models of infection (e.g., [21, 22]), we model goal-seeking behavior using economic consumer theory [48]. We assume that individuals have a single period utility function that depends on their current health state, $h \in Y$, and current-period contacts with others. Specifically, a type-h individual's instantaneous utility is $u(h,C^h)$. Single-period utility is assumed to be a concave and single-peaked function in contacts and infection reduces single-period utility, so that $u(i,c) < u(s,c)$, and $u(i,c) < u(z,c)$. We may also expect that $u(z,c) \leq u(s,c)$, suggesting the possibility of lasting fixed cost effects from infection. This departs somewhat from the majority of the economic literature which often models utility as a function of health expenditures and health class [10, 25, 42]. One could view forgone contacts as a special case of health expenditures, but our specification has the advantage of more directly connecting to epidemiological theory.[3]

[3]Conversely, the specification has the disadvantage of not modeling time allocation directly since contacts are not actual goods that are consumed. Bridging this divide is an active area of research.

If agents act in their own best interests and ignore the impacts of their behaviors on the well-being of others, then each individual type behaves as if he solves a dynamic problem formalized by the Bellman equation

$$V(h) = max_{C^h} \left\{ u(h, C^h) + \delta \sum_{Y} P^{h,j}(C^h : S, I, Z, C^{-h}, \bar{C}^h)(V(j) - V(h)) \right\} \quad (5)$$

where δ is the discount factor. $P^{h,j}$ is the probability of transition from state $h \in Y$ to state $j \in Y$ conditional on choice C^h for a given time step. The probability $P^{h,j}$ in the current period may be derived from Eqs. (1)–(3) (see [20] for details). The probability $P^{h,j}$ depends on the current state of the system and the behaviors of individuals in the other health classes, C^{-h}, where $-h$ indexes all but the h health state, and the behavior of individual's own health class is $\bar{C}^h$, which the individual takes as given, but which *ex post* is identical to the individual's choice. We focus on the case when $P^{h,j} = 0$ for $h \neq j$, except for the basic epidemiological transitions of $P^{s,i}$ and $P^{i,z}$ were $P^{i,z}(C^i) = \bar{P}^{i,z}\ \forall C^h$. For example,

$$P^{s,i}(C^s; S, I, Z, C^{-s}, \bar{C}^s) = 1 - exp\left(-\frac{\beta I C^s C^i}{S\bar{C}^s + IC^i + ZC^z} \right).$$

This structure implies that the recovery rate is invariant to behaviors in the population, it is not possible to go from s to z, or z to s, and $P^{z,z} = 1$.

The solution to problem (5) depends on the individual's current state and expectations about the future. Consider the problem for type-z individuals. Type-z's first-order condition is $u_{C^z}(z, C^z) = 0$ because there is no dynamic effect of type-z's decision. The concave and single-peaked nature of $u(h, C^z)$ implies that C^z is constant, finite and positive value. The assumption that $P^{i,z}(C^i) = \bar{P}^{i,z}\ \forall C^h$ implies that type-i individuals have a similar result, $u_{C^i}(i, C^i) = 0$, implying that C^i is a constant, finite and positive value. Recovered and infected individuals do not behave strategically with respect to the epidemic. Susceptible individuals make forward-looking decisions, which are modeled by satisfying[4]

$$u_{C^s}(s, C^s) - \delta P^{si}_{C^s}(\cdot)(V(s) - V(i)) = 0 \quad (6)$$

Equation (6) implies

$$V(i) = V(s) - \frac{u_{C^s}(s, C^s)}{\delta P^{si}_{C^s}(\cdot)} \quad (7)$$

[4]The partial derivative in Eq. (6) is only taken with respect to C^s. However, C^s is substituted for $\bar{C}^s$ after the derivative is taken prior to solving Eq. (6) for the optimal C^s. This ensures that all individuals in the same class behave the same but do not consider the homogeneity of behavior when making behavioral choices.

As the state of the epidemic changes, the marginal contribution of an individual's behavior to the probability of infection, $P^{si}_{C^s}(\cdot)$, changes. If the $V(i)$ is constant, which is the case if infection does not affect behavior [20], then as the state of the epidemic changes, so must the optimal marginal utility from contacts, the present value of being in the susceptible state, $V(s)$, or both. The only way to change realized marginal utility of a contact is to change behavior. Behavior changes as the state of the epidemic changes, and Eqs. (5)–(7) provide a mechanism, at the scale of the disease dynamics, to model this behavioral change. Furthermore, $V(s)$ is also partially dependent on behavior. A goal-seeking susceptible individual will change his behavior as the general state of the epidemic changes.

2.2 Information and Expectations

Nonlinear incidence is often motivated by behavioral change in response to information [17, 18], and information quality has been shown to affect behavior [12]. But, the idea of information is vague. Information can be knowledge of the current state of the world or information may be forecasts about the future state of the world. Information may also be confounded with information processing [40]. How information is processed may be just as relevant as the package of data. In our mechanistic model information is processed via the form and parameterization of the utility function and Bellman equation. The utility function indicates relative preferences for health compared to an unspecified numeraire good. To develop simulations below, we adopt the same form of utility function as in [20]

$$u^h_t(h, C^h) = (b^h C^h_t - C^{h^2}_t)^\gamma - a^i.$$

The functional form implies that infection reduces the marginal utility of a contact through reductions in b and imposes a lump sum cost through a. Other functional forms are possible, e.g., [10]. We wish to compare three potential interpretations of the idea of information affecting an epidemic by providing incentives for changes in behavior. The first mode by which information may affect epidemiological dynamics is through effects on expectations. Expectations play a prominent role in Eq. (5), via the summation over Y. It is possible to convert Eq. (1) into a probability of being infected in a single time step [20], but it is much more difficult to choose a single model as to how expectations should be formed over the entire planning horizon. Adaptive expectations models are based on the idea of learning and updating [37]. An agent forms a set of expectations, solves his dynamic optimization problem and carries out the solution for a relative short period of time (e.g., one time step), collects new information, forms new expectations and resolves the entire dynamic optimization problem and uses the new policy function. Multiple authors have used adaptive expectations models to model information in economic-epidemiological models like the one developed here [5, 20]. However, the

expectations modeled in these models are somewhat naive. Traditionally, adaptive expectation asserts that the agent takes the current measurement as fixed when forecasting out expectations. We use this approach as a baseline and refer to this as classical adaptive expectations.

In addition to the classical adaptive expectations model, we develop two forms of scientific adaptive expectations models.[5] To form scientific expectations models we fit phenomenological models to the data generated within the simulation of the epidemiological-economic model, a model defined by Eqs. (1)–(6). This notion of adaptive expectations models has been shown in some cases to lead to similar behavior as rational expectations, fully accounting for future strategic behavior [37].[6] The first phenomenological model is based on theory and the estimation of the basic reproduction number, R_0. There are multiple ways to estimate R_0 [15]. For illustrative purposes, and given the simplicity of our model, we adopt an approach based on the intrinsic growth rate of the infected population in the classical SIR model, r, measured from the initial epidemic phase. Even though the approach is simple, it is commonly used in applied epidemiology [14, 41]. We take the initial epidemic phase as the period over which cumulative incidence increases at an increasing rate. Assuming homogeneous mixing (an assumption violated in our data-generating model) and that the mean generation time of the pathogen is exponentially distributed, R_0 can be approximated as

$$R_0 = 1 + rq \tag{8}$$

where q is the expected time until recovery (calculated as $1/P^{i,z}$, where $P^{i,z} = 1 - e^{-v}$). The intrinsic growth rate, r, can be calculated assuming an initial exponential epidemic growth phase, where

$$y = Ae^{rt+\varepsilon} \tag{9}$$

and where y is the curve of cumulative incidence at time t, A is a constant, and ε is a mean zero error term [14]. The value of r is estimated by linear regression following a log transformation of Eq. (9). The forecast resulting from this model is then provided as the forecast for the state variables out to the planning horizon. We refer to this as the R_0-based forecast.

The second phenomenological model simulates a time series analysis. We use the two-day running average to fit a third-order polynomial to the time series of prevalence. The next T elements in the series following the polynomial are used as forecasts for the expectations about S and I populations. We refer to this as the simulated time series forecast.

A few comments about these forecasting models are in order. First, we do not include any stochastic shocks in our simulations. The data generating mechanisms

[5] Such an approach has a history in economics, and is not always differentiated from classical adaptive expectations [13, 37].

[6] We do not consider rational expectations because the necessary market assumptions to impose as if rational behavior do not exist.

Table 1 Parameter values used in the simulations

Parameter	Interpretation	Value
$b^h, h \neq i$	Twice utility maximizing contacts, with no disease	10
b^i	Twice utility maximizing contacts, with disease	6.667
γ	Exponent in utility function	0.25
α	Utility loss due to disease in utility function	1.826
τ	Length of planning horizon	12
β	Disease transmission rate per infected contact	0.0925
ν	Recovery rate	0.1823

$b^i = 10$ in the non adaptive SIR model

for our estimated models are deterministic at the system level. Second, all residual error, ε, comes from misspecification because the phenomenological models ignore changing behavioral dynamics. We believe this approach is informative because to our knowledge models that jointly estimate behavioral response and disease dynamics have not yet been developed. Indeed, Geoffard and Philipson [26] point out that the development of such models is likely to be a nontrivial problem. In addition to alternative expectations models, we vary the rate of at which new information becomes available so that information is less timely but not inherently corrupted. We also explore alternative parameterizations of the utility function. We simulate each model on a daily time step using parameters from [20] repeated here in Table 1, and use a planning horizon of 12 days, twice the expected recovery time.

Simulations were completed in Mathematica 8.0 (Wolfram Research).

3 Results

3.1 The Role of Expectations

Disease dynamics at the system level are remarkably unaffected by the forecasting model used. Indeed, the results from the classical adaptive expectations forecast and the simulated time series are nearly identical. This is true regardless of the metric used (Table 2 and Figs. 1 and 2).

At first, this result is surprising, but [5] considers a model of HIV with classical adaptive and rational (when the agent full considers the effect of behavior on the future disease dynamics) expectations and finds little difference in the course of an HIV epidemic between classical adaptive and rational expectations. Our scientific expectations models may be thought of as intermediate cases. Furthermore, [37] suggest that forecasting approaches similar to our description of scientific expectations may approximate rational expectations. What is striking is the difference between the static behavioral models (dotted curve, Fig. 1) and any model with adaptive or strategic behavior. Fenichel et al. [20] point out that is possible to fit models that assume static behavior to data generating mechanisms with adaptive

Table 2 Summary statistics by expectations model

Model	Cumulative cases	Peak prevalence	Peak time	Minimum contacts	Cumulative utility (N)	Cumulative utility (S)
Classical	0.6391	0.08799	47	3.65	259.8	163.9
App R_0	0.6830	0.09110	52	2.63	258.0	158.2
Time series	0.6445	0.09085	47	3.79	259.9	162.8
Delayed classical	0.6422	0.09683	48	3.76	260.0	161.8
Delayed App R_0	0.6666	0.08136	53	2.63	258.3	162.0
Delayed time series	0.6409	0.09476	47	3.73	260.0	162.5

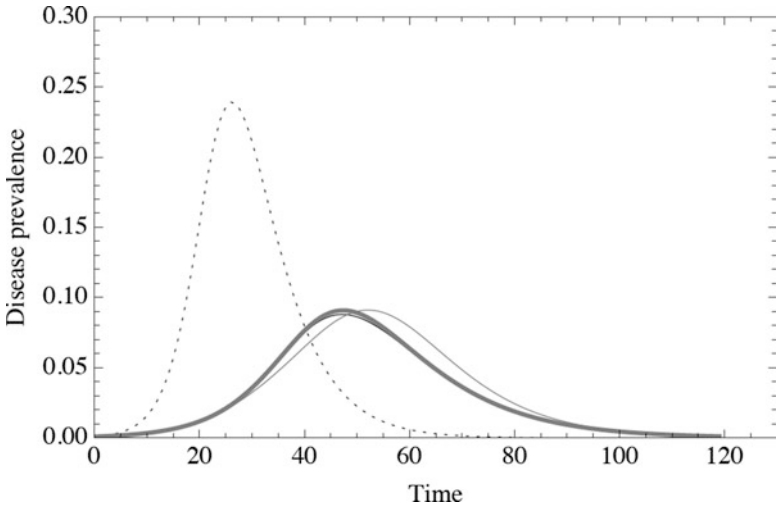

Fig. 1 The *dotted curve* represents an epidemic curve with constant behavior. The *three solid curves* are epidemic curves for the same biological and economic parameters, but with different expectations models. The *black curve* corresponds to classical adaptive expectations, the *thin gray curve* (to the *right*) corresponds to expectations based on estimates using R_0 theory, and *thick gray curve* that largely overlaps the *black curve* is based on a simulated time series analysis to forecast expectations

behavior, but that the parameters that result do not have the usual biological interpretations. Given Fig. 1, this concern seems robust to how expectations are formed, at least for some cases. Among the three forecasting models, simulations that include the R_0-based forecasting model deviate from simulations where the other forecasting models are used. When agents are provided the R_0-based forecast, the model yields similar epidemiological metrics. Agents are also made worse off in terms of utility (Table 2) and engage in much greater averting behavior (Fig. 2). If panic is defined as a strong irrational behavior that has little effect on the overall dynamics, then R_0-based forecasts could be described as inducing panic. Under R_0-based forecasting, the realized cumulative infection and peak prevalence is greater, but the epidemic is slowed by the strong initial response of susceptible individuals.

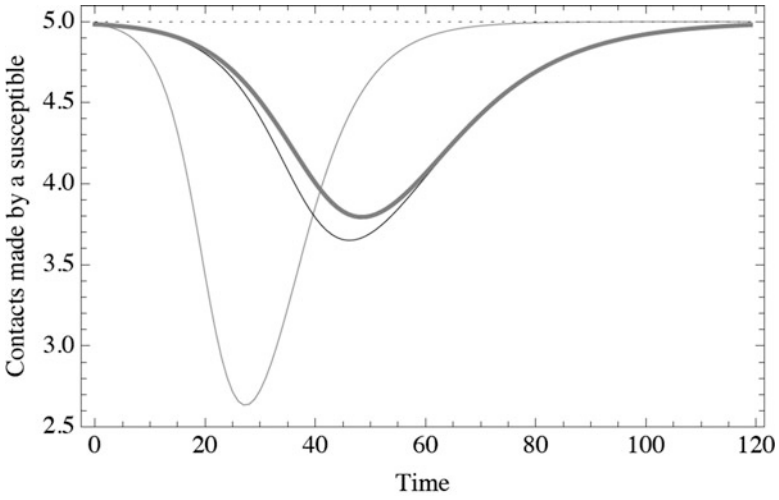

Fig. 2 The *dotted curve* represents constant behavior. The *three solid curves* are behavioral responses to the expectations about the epidemic for the same biological and economic parameters, but with different expectations models. The *black curve* corresponds to classical adaptive expectations, the *thin gray curve* (to the *left*) corresponds to expectations based on estimates using R_0 theory, and *thick gray curve* that largely overlaps the *black curve* is based on a simulated time series analysis to forecast expectations

3.2 The Timeliness of Data

Relative insensitivity of results to the forecasting model suggests that perhaps the quality or timeliness of information is more important than the actual forecasting model. In the previous section we assumed all information was available for forecasts. To investigate the importance of the timeliness of information we delay the availability of information by one week (Fig. 3). In addition to informing the role of information and adaptive human behavior during an epidemic, these results suggest the importance of considered data feasibility in the approach to forecasting disease risks for the public to respond to.

Information delay has the expected effect of increasing peak prevalence if classical adaptive expectations or simulated time series forecasting is used to form expectations. In both cases averting behavior lags slightly relative to more timely information and results in greater peak prevalence. However, the higher peak prevalence yields a stronger behavioral response as the epidemic wanes and ultimately results in fewer cumulative cases, though the marginal proportion of the population ultimately avoiding the infection do to information delay is small (Table 2). Delaying information has a counterintuitive effect if R_0-based forecasts are used. Delaying information reduces cumulative cases and peak prevalence relative to timely information. The reason is that because information is delayed susceptible individuals believe that there is less chance of being infected as

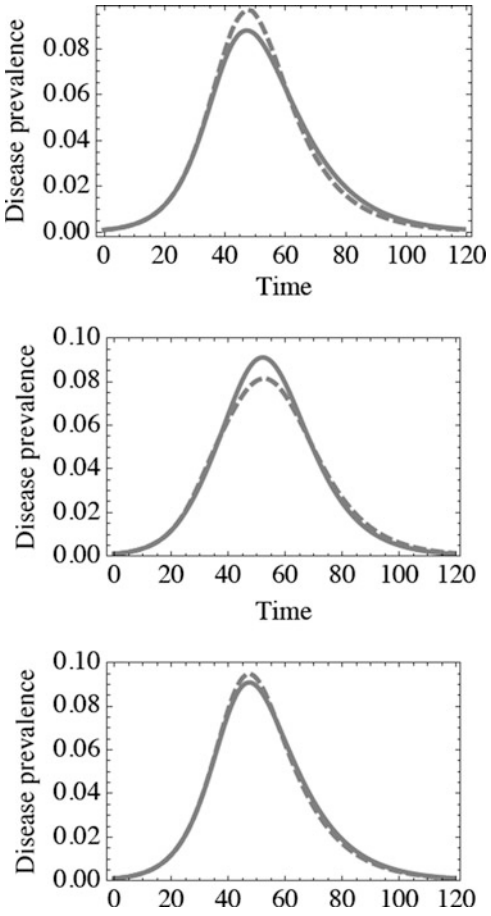

Fig. 3 The relative effect of information delay *(dashed curve)* compared to no information delay *(solid)* on the epidemic curve conditional on the forecasting model: classical adaptive expectations *(upper panel)*, R_0-based forecasts *(central panel)*, and simulated time series *(lower panel)*

prevalence increases. This tempers the panic response induced by the R_0-based forecast. In our simulations, this offsetting effect is sufficiently large so that a time-delayed R_0-based forecast yields the lowest peak prevalence of models that we investigated (Table 2). We caution that which effect dominants in real systems is an empirical question, but this result suggests that R_0-based forecasting is missing something important. The net effect of information delay on utility is positive when then entire population is considered. It is odd that less information could make people better-off. This suggests that all of these phenomenological models miss something important. But the delay has little effect on the cumulative utility earned by the overall population conditional on the simulated time series analysis. However, delaying information makes susceptible individuals worse off, except in the case of R_0-based forecasts Consistent with counterintuitive effects on disease dynamics, delaying information slightly increases the utility payoff if R_0-based forecasts are used, which seems to violate the Le Chatelier principle. Perhaps this

occurs because when there is strategic or adaptive behavior R_0 lacks a mechanistic interpretation, but provides a poor case for a phenomenological model. The utility payoff from delayed R_0-based forecasts is still less than timely versions of the other two forecasting systems.

3.3 Preferences and Tradeoffs

The interpretation of information, or what exactly the information means, is important. To adaptive or strategic individuals, forecasts about the future state of public health must be assimilated into an index (utility) that guides behavior. This behavior results from making trade-offs. Therefore, understanding the construction of the utility index is likely important for parsing the biological and behavioral effects associated with a pathogen. This separation of biological and behavioral effects is particularly important when public health planners make decisions about non-pharmaceutical interventions such as social distancing policies [50], and pharmaceutical interventions such as providing drugs to speed recovery. The table reported in Fig. 4 shows the sensitivity of epidemic statistics to the parameters in our model. Only two statistics, peak prevalence and susceptible utility, are generally sensitive (greater than unit elastic in absolute value) to parameters in our model.[7]

Health policy makers need to make a normative decision about which epidemic statistics to use to guide policy decisions. A goal of low peak prevalence or cumulative cases does not necessarily suggest the same forecasting model or the same interventions to effectively change the parameters in our model. Moreover, how the public learns about disease and forms expectation may matter for targeting intervention. It is not clear that focusing on biological metrics associate with the epidemic is in the best interest of society as a whole. Keogh-Brown et al. [32] and Smith et al. [47] focus on economic impact or shocks to consumption.[8] In our model lower levels of minimal contacts could be considered as a proxy for decreased economic activity. If the goal of policy makers is to avoid economic disruption, then R_0-based forecasting could be rather disruptive and yield little value to society in terms of other goals. Most economists advocate a welfare-based approach [10, 42]. In the context of our model, this means looking at cumulative utility over the epidemic. One draws rather different conclusions about the benefits of intervening to change a parameter value if one focuses on the entire population or just the susceptible population. If the focus is on the entire population, then all

[7]Minimum contacts are also greater than unit elastic in absolute value to the transmission parameter β for two of the forecasting models.

[8]These authors point out that consumption smoothing associated with borrowing and savings over an epidemic shock implies that in the long run epidemics may have little effect on the level of economic activity in developed countries. The results of an epidemic in developing countries may be more sever [10], and there may long-run lasting effects on human capital from infection [1, 2].

parameter	Expectations Model	Minimum contacts	Peak Prevalence	Cumulative Cases	Cumulative Utility (*N*)	Cumulative Utility (*S*)
$b^h\ h \neq i$	Classical	9.4	1.2	0.4	4.9	4.4
	AppR0	0.8	6.2	1.5	4.7	3.1
	MA	9.5	1.3	0.4	4.8	4.5
b^i	Classical	-9.7	22.9	7.7	-0.3	-11.4
	AppR0	-3.3	13.7	6.5	-0.2	-11.3
	MA	-8.4	24.9	7.8	-0.3	-11.8
γ	Classical	3.2	1.9	1.0	8.4	7.7
	AppR0	6.2	1.4	0.3	8.4	8.0
	MA	2.4	1.4	0.8	8.4	7.8
β	Classical	-10.5	24.4	8.0	3.3	-11.8
	AppR0	-11.5	23.9	8.7	3.5	-13.6
	MA	-9.1	26.7	8.2	-0.3	-12.3
v	Classical	8.6	-26.0	-10.8	3.3	10.4
	AppR0	7.6	-26.1	-11.3	0.7	11.7
	MA	7.1	-26.8	-10.9	0.6	10.7

Fig. 4 Sensitivity analysis (percent change) to a 10% increase parameters conditional on a forecasting model. *Shaded cells* represent responses that are greater in absolute value than unit arc elastic

interventions are less than unit elastic so a 10% change in the parameter elicits less than a 10% change in the utility payoff in absolute value. Furthermore, if the focus is on population level cumulative utility, then the most sensitive parameters are related to behavior (i.e., utility parameters, b^s, b^z, and γ) not biology. But, if the focus is just on the utility accrued by the susceptible population, then the model is also sensitive to traditional epidemiological parameters and is generally greater than unit elastic.

4 Discussion

Over the last century, policy makers have increasingly looked to science to shape policy to improve public well-being. Great strides have been made in the area of public health. Phenomenological descriptions are essential for picking patterns from the noise of data and describing past events. If events are common enough and the luxury of designed experimentation exists, then mechanistic theory may not be needed to inform policies. However, in the case of the emergence of novel infectious diseases, it is unlikely that sufficient data will exist for policy design. Moreover, in the twenty-first century science is about explaining why we observe the phenomena that we do. This calls for a mechanistic approach, but mechanism is

a question of hierarchical organization. With respect to epidemiological dynamics we have developed a mechanistic model that is based on the behavioral response of people to disease risk. Phenomenological models still have an important role in forecasting. For example time series analysis often does better at predicting events in the near future than complicated mechanistic models do. Worst of all would be to use mechanistically derived models that miss important mechanisms, e.g., strategic human behavior, for short-term forecasting. This seems to be one use of models based on R_0. Basic reproductive number theory and R_0 are prolific in epidemiology [3, 15, 19, 29, 30, 44] and much has been done to generalize R_0-based approaches [4, 28, 31]. As a descriptive approach of a dynamical system, it is difficult to argue with the long record or persistent use, and this approach is useful for some questions. However, models do not exist for the sake of the model; models help us answer questions. It is important to consider how science and models are used. One use of science and models is to forecast the future so people can make informed decision much like a weather forecast. We have shown that at least in some dimensions, R_0-based models may perform relatively poorly.

Perhaps, the enthusiasm for R_0 should be tempered (see [16] for an example of this enthusiasm)? While the R_0 concept is useful in some situations, it is likely less useful for making policy with respect to or providing informing to the public so that individuals can adapt behavior during ongoing disease outbreaks. This is because it provides a relatively poor phenomenological model but also misses critical mechanistic components. Increasingly, health officials have expressed interest in behavior-based policy responses to infectious diseases [27, 50] and evidence suggests that people alter behavior when faced with infection risk [8]. Standard susceptible-infected-recovered models do not easily incorporate individual behavioral responses or policies directed at shaping individual's behaviors. Geoffard and Philipson [26] state that estimators for compartmental models are not consistent or unbiased if people adapt behavior.

In this chapter we have shown that using R_0-based models to forecast epidemics to a population that uses this information to adjust behavior may produce counterintuitive and perhaps undesirable results relative to simply providing the current state of the system or a simple phenomenological time series estimate. This suggests a potential problem with the application of basic reproductive number theory to important questions related to including individual behavior into epidemic models.

It is possible to build behavior into the compartmental framework that has served epidemiology well for almost 100 years, but it cannot be done at the phenomenological level of the dynamics of the disease. The approach taken in this chapter offers one mechanistic approach to incorporating behavior into epidemiological models. An advantage of this approach is that it has allowed us to parse the idea of information into three parts. Doing so reveals the need to better understand the phenomenon of individuals making trade-offs. Empirical advances in behavioral epidemiology of infectious disease will require recovering parameters of the utility functions that guide behavioral decisions. Effectively, this means estimating the demand for contacts as a function of the current state of the epidemic.

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References

1. Almond, D.: J. Polit. Econ. **114**, 672–712 (2006)
2. Almond, D., Mazumder, B.: Am. Econ. Rev. **95**, 258–262 (2005)
3. Anderson, R.M., May, R.M.: Nature **280**, 361-367 (1979)
4. Aparicio, J.P., Pascual, M.: Proceedings of the Royal Society, London B. Vol. 274, pp. 505–512 (2007)
5. Auld, M.C.: J. Health Econ. **22**, 361-377 (2003)
6. Begon, M., Bennett, M., Bowers, R.G., French, N.P., Hazel, S.M., Turner, J.: Epidemiol. Infect. **129**, 147–153 (2002)
7. Boulier, B.L., Satta, T.S., Goldfarb, R.S.: The B.E. J. Econ. Anal. Policy **7** (2007)
8. Caley, P., Philips, D.J., Mccracken, K.: J. Roy. Soc. Interface **5**, 631–639 (2007)
9. Capasso, V., Serio, G.: Math. Biosci. **42**, 43–61 (1978)
10. Chakraborty, S., Papageorgiou, C., Sebastian, F.P.: J. Monetary Econ. **57**, 859–872 (2010)
11. Chen, F., Jiang, M., Rabidoux, S., Tobinson, S.: J. Theor. Biol. **278**, 107–119 (2011)
12. Chen, F.H.: Math. Biosci. **217**, 125–133 (2009)
13. Chow, G.C.: The Rev. Econ. Stat. **71**, 376–384 (1989)
14. Chowell, G., Bertozzi, S.M., Colchero, M.A., Alpuche-Aranda, C., Hernandez, M., Miller, M.A.: The New Engl. J. Med. **361**, 674–679 (2009)
15. Chowell, G., Brauer, F.: The basic reproduction number of infectious diseases: Computation and estimation using compartmental epidemic models. In: Chowell, G., Hyman, J.M., Bettencourt, L.M.A., Castillo-Chavez, C. (eds.) Mathematical and Statistical Estimation Approaches in Epidemiology. Springer, New York (2009)
16. Cohen, J.E., Enserink, M.: Science **324**, 572–573 (2009)
17. Cui, J., Sun, Y., Zhu, H.: J. Dyn. Diff. Equat. **20**, 31–53 (2008)
18. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **256**, 473-478 (2009)
19. Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J.: J. Math. Biol. **28**, 365–382 (1990)
20. Fenichel, E.P., Castillo-Chaves, C., Ceddia, M.G., Chowell, G., Gonzalez Parra, P.A., Hickling, G.J., Holloway, G., Horan, R., Morin, B., Perrings, C., Springborn, M., Velazquez, L., Villalobos, C.: Proceedings of the National Academy of Sciences. Vol. 108, pp. 6306–6311 (2011)
21. Francis, P.J.: Dynamic epidemiology and the market for vaccinations. J. Public Econ. **63**, 383–406 (1997)
22. Francis, P.J.: J. Econ. Dyn. Control **28**, 2037–2054 (2004)
23. Funk, S., Salathe, M., Jansen, V.A.A.: J. Roy. Soc. Interface **7**, 1247–1256 (2010)
24. Galvani, A.P., Reluga, T.C., Chapman, G.B.: Proceedings of the National Academy of Sciences. Vol. 104, pp. 5692–5697 (2007)
25. Geoffard, P.Y., Philipson, T.: Int. Econ. Rev. **37**, 603–624 (1996)
26. Geoffard, P., Philipson, T.: Biometrika **82**, 101–111 (1995)
27. Glass, R.J., Glass, L.M., Beyeler, W.E., Min, H.J.: Emerg. Infect. Dis. **12**, 1671–1681 (2006)
28. Heesterbeek, J.A.P., Roberts, M.G.: Math. Biosci. **206**, 3–10 (2007)
29. Heffernan, J.M., Smith, R.J., Wahl, L.M.: J. Roy. Soc. Interface **2**, 281–293 (2005)
30. Hethcote, H.W.: SIAM Rev. **42**, 599–653 (2000)
31. Keeling, M.J., Grenfell, B.T.: J. Theor. Biol. **203**, 51–61 (2000)

32. Keogh-Brown, M.R., Wren-Lewis, S., Edmunds, W.J., Beutels, P., Smith, R.D.: Health Econ. **19**, 1345–1360 (2010)
33. Kermack, W.O., McKendrick, A.G.: Proceedings of the Royal Society, London Series A. Vol. 115, pp. 700–721 (1929)
34. Korobeinikov, A., Maini, P.K.: Math. Med. Biol. **22**, 113–128 (2005)
35. Kremer, M.: The Q. J. Econ. **111**, 549–573 (1996)
36. Longini, I.M., Halloran, M.E., Nizam, A., Yang, Y.: Am. J. Epidemiol. **169**, 623–633 (2004)
37. Marcet, A., Sargent, T.J.: Am. Econ. Rev. **78**, 168–172 (1988)
38. Mccallum, H.I., Barlow, N., Hone, J.: TRENDS Ecol. Evol. **16**, 295–300 (2001)
39. Mesnard, A., Seabright, P.: J. Public Econ. **93**, 931–938 (2009)
40. Mitchell, M.: Complexity: A Guided Tour. Oxford University Press, New York (2009)
41. Nishiura, H., Castillo-Chaves, C., Safan, M., Chowell, G.: Eurosurveillance **14**, 1–4 (2009)
42. Philipson, T.: Econ. Epidemiol. Infect. Dis. **1**, 1761–1799 (2000)
43. Reluga, T.C.: PLoS Comput. Biol. **6**, e1000793 (2010)
44. Roberts, M.G.: J. Roy. Soc. Interface. **4**, 949–961 (2007)
45. Shaw, L., Schwartz, I.B.: Enhanced vaccine control of epidemics in adaptive networks. Phys. Rev. E **81**, 046120 (2010)
46. Shogren, J.F., Crocker, T.D.: J. Environ. Econ. Manag. **37**, 44–51 (1999)
47. Smith, R.D., Keogh-Brown, M.R., Barnett, T., Tait, J.: BMJ **339**, b4571 (2009)
48. Varian, H.R.: Microeconomic Analysis 3rd. W.W. Norton and Company, New York (1992)
49. Veliov, V.M.: J. Math. Biol. **51**, 123–143 (2005)
50. World Health Organization. Emerg. Infect. Dis. **12**, 88–94 (2006)

Part III
Modeling Vaccinating Behaviour

The Economic Approach to Modeling Self-protective Behavior in Epidemiology

Frederick Chen

Abstract The economic approach to studying the transmission of infectious diseases provides an analytical framework for making predictions about how people will respond to an epidemic. Furthermore, this framework can be used for normative analysis to determine how various policies and control strategies can affect the well-being of the population under consideration. By examining explicitly people's incentives to alter their behavior in response to an infectious disease, the economic approach often yields counterintuitive results with significant policy implications.

1 Introduction

How quickly as well as how widely an infectious disease spreads depend in large part on the behavior of individuals. The severity of flu epidemics is a function of the number of people who are vaccinated. The prevalence of a sexually transmitted disease is determined by, among other factors, the number of sexual partners people have and the type of sex acts that people engage in. How often people go out to public places such as restaurants, how much people utilize public transportation, or how frequently people socialize with others all can impact the rate at which infectious agents are transmitted.

Conversely, the presence of an infectious disease can affect people's behavior. As has been shown by numerous studies, the HIV/AIDS pandemic led many individuals to alter their sexual behavior in order to reduce the risk of infection [1, 11]. In response to the SARS outbreak in 2003, many people in the affected regions avoided public gatherings and using public transportation [17]. Therefore, to accurately

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forecast the course of an epidemic and the effects of various control measures requires: (1) an understanding of how disease spread depends on human behavior; and (2) the incentive people have for altering their behavior during an epidemic.

While mathematical models are vital—in fact, indispensable—for predicting the population level impact of infectious diseases, their value and accuracy depend on how well people's behavior is captured and specified in them. For instance, overestimating or underestimating how many people would choose to get vaccinated during an epidemic in modeling work could have significant policy implications if mathematical models are relied on for evaluating different potential control measures. Moreover, mathematical modeling alone cannot tell us how people would behave during an epidemic, since an analysis of what causes behavior change ultimately belongs in the realm of the social and behavioral sciences.

The optimization foundation of utility theory from the field of economics provides an ideal framework to study the determinants of people's behavior in the presence of an infectious disease. In utility theory, people's preferences are taken as given and it is assumed that people try to achieve the best outcome—best from their own perspective—subject to the constraints that they face. By focusing on people's incentives to act in different ways, utility maximization theory allows us to look at how people's behavior is affected by their decision environments and how various policies can alter the way people behave. In addition, since utility theory is based on people's preferences, it allows us to quantify in a rigorous way a population's well-being and lets us evaluate different outcomes or policies based on the population's welfare.

It should be noted that, in the context of infectious disease transmission, people's decision environments are inherently dynamic in nature and affected by the choices and actions of other people. How likely one is to get infected depends not only on the choices one makes, but also on the behavior of other people. For example, the probability that an individual will get the flu should be decreasing in the fraction of people in the population that get vaccinated. This means that people's decision problems in this context are interdependent: everyone's optimal choice of actions is dependent on the choices that everyone else makes. Another central notion in economics, that of an equilibrium, is useful for predicting how people would act in these situations and what outcome would obtain in the population. Put simply, an equilibrium is characterized by the condition that people's actions maximize their own utility given the behavior of other people, where other people's behavior is also the result of utility maximization. Therefore, in an equilibrium, no one wants to change his or her behavior given what everyone else is doing.

There has been growing interest in recent years to apply the tools and concepts from economics and game theory to study the spread of infectious diseases [e.g., 2,3, 10,13–15,18–20]. This chapter provides an overview of the economic approach that models individuals as forward-looking agents seeking to maximize their utility over their lifetime. The focus will be on risk-reduction actions that individuals can take to lower the probability of acquiring an infection. Examples of such risk-reducing actions include vaccination, more frequent handwashing or wearing of mask in the case of flu, or the use of condoms when looking at STDs.

2 The Framework

Time is discrete, and the population consists of a large number of agents, each of whom can be in one of the following (mutually exclusive) health states in any time period: susceptible, infected, and vaccinated. Assume for convenience that once infected, an agent remains infected for life, i.e., there is no cure or recovery for the disease in question. It should be noted that, although only susceptible-infected (SI) models are considered here, the economic approach to modeling infectious disease transmission can be applied to any other settings; moreover, many of the qualitative results discussed here do not depend on the assumption that being infected is an absorbing state.

In any period, a noninfected agent receives the utility or payoff $u_h > 0$, while the payoff to an infected agent is $u_i \in (0, u_h)$. To protect against the risk of infection, noninfected agents can at any point in time choose a self-protective action that reduces their probability of infection *just in that time period* (e.g., handwashing, wearing of condoms, etc.). In addition, susceptible agents can in any period choose to get vaccinated, where the vaccine confers lifelong immunity. Both the self-protective action and vaccination are costly in the sense that choosing either one reduces the utility of an agent: the cost in utility of the self-protective action is $c_s > 0$, and the cost of getting vaccinated is $c_v > 0$.

Let P_t denote the fraction of the population that is infected at time t, i.e., P_t is the time t prevalence. It is assumed here that there is random mixing in the population (see [6] for the model with preferred mixing as defined in [16]): in any period t, the probability that a susceptible agent will get infected in that period is βP_t, where $\beta \in (0,1]$ is the transmission probability, if the agent does not take any action to reduce the risk of getting infected; and the probability of infection is $\beta(1-\varepsilon_s)P_t$ if the agent chooses the self-protective action in that period, where $\varepsilon_s \in (0,1]$ is the efficacy of the self-protective action. An agent that is vaccinated has probability $\beta(1-\varepsilon_v)P_t$ of acquiring an infection in time t, where $\varepsilon_v \in (0,1]$ denotes the efficacy of the vaccine, without taking the self-protective action; and the probability of infection is $\beta(1-\varepsilon_v)(1-\varepsilon_s)P_t$ with the self-protective action. Let $\beta_s \equiv \beta(1-\varepsilon_s)$, $\beta_v \equiv \beta(1-\varepsilon_v)$, and $\beta_{vs} \equiv \beta(1-\varepsilon_v)(1-\varepsilon_s)$.

For ease of exposition, it will be assumed that the (expected) length of an agent's lifetime is independent of the agent's health status. In particular, an agent, regardless of health state, has probability $\delta \in (0,1]$ of dying at the end of any period. Given that the size of the population is large by assumption, this implies that the fraction δ of all agents will die at the end of every period. There is no payoff from death. New susceptible agents enter the population at the beginning of each time period. For convenience, assume that in every period the number of new agents equals the number of deaths so that the population size is a constant.

All agents are forward-looking expected utility maximizers: they seek to maximize their expected lifetime utility by choosing what actions to take in every period that they are not infected. Agents discount future payoffs using the discount factor $\alpha \in [0,1]$. The dynamic optimization problem of agents can be formulated using

standard dynamic programming arguments [21]. Suppose the prevalence of the disease over time is given by $\{P_0, P_1, \ldots, P_t, \ldots\}$. Let $U_v(P_t)$ denote the maximum expected lifetime utility of a vaccinated agent starting at time t, i.e., $U_v(P_t)$ is—in expectation—a vaccinated agent's maximum sum of (discounted) utility over the rest of the agent's lifetime starting in time t. Similarly, let $U_h(P_t)$ denote the maximum expected lifetime utility of a susceptible agent from time t onwards, i.e., $U_h(P_t)$ is the maximum expected value of a susceptible agent's sum of (discounted) utility over the rest of the agent's lifetime starting in time t. Note that, given the assumption that agents' length of life is geometrically distributed, neither $U_v(P_t)$ nor $U_h(P_t)$ depends on an agent's age. Given $\{P_t\}_{t=0}^{\infty}$, the value functions U_v and U_h, respectively, satisfy the Bellman equations:

$$U_v(P_t) = \max \begin{cases} u_h - c_s + \gamma \left[\beta_{vs} P_t \left(\frac{u_i}{1-\gamma} \right) + (1 - \beta_{vs} P_t) U_v(P_{t+1}) \right] \\ u_h + \gamma \left[\beta_v P_t \left(\frac{u_i}{1-\gamma} \right) + (1 - \beta_v P_t) U_v(P_{t+1}) \right] \end{cases} \tag{1}$$

and

$$U_h(P_t) = \max \begin{cases} U_v(P_t) - c_v \\ u_h - c_s + \gamma \left[\beta_s P_t \left(\frac{u_i}{1-\gamma} \right) + (1 - \beta_s P_t) U_h(P_{t+1}) \right] \\ u_h + \gamma \left[\beta P_t \left(\frac{u_i}{1-\gamma} \right) + (1 - \beta P_t) U_h(P_{t+1}) \right] \end{cases}, \tag{2}$$

where $\gamma \equiv (1-\delta)\alpha$ and $\frac{u_i}{1-\gamma} \left(= \sum_{k=0}^{\infty} \gamma^k u_i \right)$ is the expected lifetime utility of an infected agent. For convenience, define $W_v(P) \equiv U_v(P) - \frac{u_i}{1-\gamma}$, $W_h(P) \equiv U_h(P) - \frac{u_i}{1-\gamma}$, and $w \equiv u_h - u_i$. Eqs. (1) and (2), respectively, can then be simplified to

$$W_v(P_t) = \max \begin{cases} w - c_s + \gamma(1 - \beta_{vs} P_t) W_v(P_{t+1}) \\ w + \gamma(1 - \beta_v P_t) W_v(P_{t+1}) \end{cases} \tag{3}$$

and

$$W_h(P_t) = \max \begin{cases} W_v(P_t) - c_v \\ w - c_s + \gamma(1 - \beta_s P_t) W_h(P_{t+1}) \\ w + \gamma(1 - \beta P_t) W_h(P_{t+1}) \end{cases}. \tag{4}$$

Using the contraction mapping theorem, it can be shown that there exist uniquely continuous functions W_v and W_h that satisfy (3) and (4).

Let S_t and V_t, respectively, denote the proportion of susceptible and vaccinated agents at time t. Assuming for simplicity that the population is homogeneous in terms of preferences, i.e., all agents have the same preference parameters u_h, u_i, c_s, c_v, and α, the disease transmission dynamics can be described as follows (see [7] for the model specification when agents are heterogeneous with respect to preference structure):

$$S_{t+1} = (1-\delta) S_t \left[\sigma_{n,t} (1 - \beta_s P_t) + \rho_{n,t} (1 - \beta P_t) \right] + \delta, \tag{5}$$

$$P_{t+1} = (1-\delta)P_t\left[1+\sigma_{n,t}\beta_s S_t+\rho_{n,t}\beta S_t+\sigma_{v,t}\beta_{vs}S_t \right.$$
$$\left. +\rho_{v,t}\beta_v S_t+r_t\beta_v V_t+(1-r_t)\beta_{vs}V_t\right], \tag{6}$$

$$V_{t+1} = 1 - S_{t+1} - P_{t+1}. \tag{7}$$

Below are the definitions of the notations used:

- r_t: The proportion of vaccinated agents in period t who choose not to self-protect in that period
- $\sigma_{v,t}$: The proportion of susceptible agents in period t who choose to self-protect and be vaccinated in that period
- $\sigma_{n,t}$: The proportion of susceptible agents in period t who choose to self-protect and not to be vaccinated in that period
- $\rho_{v,t}$: The proportion of susceptible agents in period t who choose to be vaccinated but not self-protect in that period
- $\rho_{n,t}$: The proportion of susceptible agents in period t who choose not to self-protect and not to be vaccinated in that period

Note that r_t, $\sigma_{v,t}$, $\sigma_{n,t}$, $\rho_{v,t}$, and $\rho_{n,t}$ are derived from agents' optimization problems (3) and (4) as follows:

$$r_t \begin{cases} =1 & \text{if } c_s > \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1}) \\ \in[0,1] & \text{if } c_s = \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1}); \\ =0 & \text{if } c_s < \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1}) \end{cases} \tag{8}$$

- If $W_v(P_t) - c_v > \Omega(P_t)$, where

$$\Omega(P_t) \equiv \max\left\{w - c_s + \gamma(1-\beta_s P_t)W_h(P_{t+1}),\, w+\gamma(1-\beta P_t)W_h(P_{t+1})\right\},$$

then $\sigma_{v,t}+\rho_{v,t}=1$, where

$$\rho_{v,t} \begin{cases} =1 & \text{if } c_s > \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1}) \\ \in[0,1] & \text{if } c_s = \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1}); \\ =0 & \text{if } c_s < \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1}) \end{cases} \tag{9}$$

- If $W_v(P_t) - c_v < \Omega(P_t)$, then $\sigma_{n,t}+\rho_{n,t}=1$, where

$$\rho_{n,t} \begin{cases} =1 & \text{if } c_s > \gamma(\beta-\beta_s)P_tW_h(P_{t+1}) \\ \in[0,1] & \text{if } c_s = \gamma(\beta-\beta_s)P_tW_h(P_{t+1}); \\ =0 & \text{if } c_s < \gamma(\beta-\beta_s)P_tW_h(P_{t+1}) \end{cases} \tag{10}$$

- If $W_v(P_t) - c_v = \Omega(P_t)$, then $\sigma_{n,t}+\rho_{n,t}\in[0,1]$ and $\sigma_{v,t}+\rho_{v,t}\in[0,1]$, where

$$\rho_{n,t} \begin{cases} \geq 0 \text{ if } c_s \geq \gamma(\beta-\beta_s)P_tW_h(P_{t+1}) \\ =0 \text{ if } c_s < \gamma(\beta-\beta_s)P_tW_h(P_{t+1}) \end{cases} \tag{11}$$

and

$$\rho_{v,t}\begin{cases}\geq 0 \text{ if } c_s \geq \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1})\\ =0 \text{ if } c_s < \gamma(\beta_v-\beta_{vs})P_tW_v(P_{t+1})\end{cases}. \tag{12}$$

Condition (8) tells us that all vaccinated agents would choose the self-protective action in period t if the value of self-protection ($w-c_s+\gamma(1-\beta_{vs}P_t)W_v(P_{t+1})$ in Eq. (3)) exceeds the value of not doing so ($w+\gamma(1-\beta_vP_t)W_v(P_{t+1})$ in Eq. (3)); no vaccinated agent would self-protect in period t if the value of self-protection is below the value of not self-protecting; and if the two values are the same, the proportion of vaccinated agents who self-protect in time t can be any number between 0 and 1.

Similar interpretations apply to conditions (9)–(12). When $W_v(P_t)-c_v>\Omega(P_t)$, the value of vaccinating in period t is greater than the value of not vaccinating; therefore, the proportions $\sigma_{v,t}$ and $\rho_{v,t}$ must sum to 1, i.e., the proportion of susceptible agents that choose to vaccinate must be 1. Whether susceptible agents would choose to self-protect in period t in addition to being vaccinated depends on c_s: if the value of also self-protecting (which is given by $w-c_s+\gamma(1-\beta_{vs}P_t)W_v(P_{t+1})$) is higher than the value of not self-protecting ($w+\gamma(1-\beta_vP_t)W_v(P_{t+1})$), then all susceptible agents would self-protect and be vaccinated; if the value of self-protection given vaccination is lower than the value of no self-protection given vaccination, then the agents would all choose to be vaccinated without also taking the self-protective action; and $\sigma_{v,t}$ (or $\rho_{v,t}$) can be anywhere in $[0,1]$ when the value of self-protection given vaccination equals the value of no self-protection given vaccination.

On the other hand, when $W_v(P_t)-c_v<\Omega(P_t)$, it is better not to be vaccinated. Whether susceptible agents would choose to self-protect then depends on the comparison between the value of no vaccination and no self-protection ($w+\gamma(1-\beta P_t)W_h(P_{t+1})$ in Eq. (4)) and the value of self-protection without also being vaccinated ($w-c_s+\gamma(1-\beta_sP_t)W_h(P_{t+1})$ in Eq. (4)).

In the case where $W_v(P_t)-c_v=\Omega(P_t)$, the value of vaccination in period t is the same as the value of not vaccinating so that the proportion of susceptible agents who choose to be vaccinated can be anywhere between 0 and 1. Whether susceptible agents would choose the self-protective action in time t is determined by comparing the value of self-protection to the value of no self-protection: for agents who choose to be vaccinated, the comparison is between $w+\gamma(1-\beta_vP_t)W_v(P_{t+1})$ and $w-c_s+\gamma(1-\beta_{vs}P_t)W_v(P_{t+1})$; for agents who choose not to be vaccinated, the comparison is between $w+\gamma(1-\beta P_t)W_h(P_{t+1})$ and $w-c_s+\gamma(1-\beta_sP_t)W_h(P_{t+1})$.

A **rational expectations equilibrium** (**REE**) of the model is given by

$$\{S_t,P_t,V_t,r_t,\sigma_{v,t},\sigma_{n,t},\rho_{v,t},\rho_{n,t}\}_t$$

such that Eqs. (3)–(12) are satisfied. Since agents' behavior in any period is a function of current and future prevalence and since prevalence at any point in time depends on how agents behave, the equilibrium concept of a REE requires that agents' behavior and the prevalence of disease be consistent with one another. In a **steady state equilibrium**, $S_t=S$, $P_t=P$, $V_t=V$, $r_t=r$, $\sigma_{v,t}=\sigma_v$, $\sigma_{n,t}=\sigma_n$,

$\rho_{v,t} = \rho_v$, and $\rho_{n,t} = \rho_n$ for all t. Say that a steady state equilibrium is **endemic** if $P > 0$. It can be shown that an endemic equilibrium exists if $(1-\delta)\beta/\delta > 1$ (see [7]). Otherwise, the disease-free equilibrium in which $P = 0$ is the only steady state equilibrium. The value $(1-\delta)\beta/\delta$ is the reproductive number R_0. In a steady state, the aggregate payoff or, using the language of economics, the social welfare of the population in every period is given by

$$Pu_i + V\left(u_h - (1-r)c_s\right) + S\left(u_h - (\sigma_v + \sigma_n)c_s - (\sigma_v + \rho_v)c_v\right).$$

3 Some Results

Assume henceforth that $(1-\delta)\beta/\delta > 1$ so that an endemic equilibrium exists.

3.1 The Model with Only Self-protective Action

Consider for now a setting in which vaccination is not an option for agents (or, equivalently, the cost of vaccination is prohibitively high so that no one ever chooses to get vaccinated); therefore, the only decision that a susceptible agent needs to make in any period is whether to engage in the self-protective act or not. In a steady state, Eq. (4) tells us that the difference in expected lifetime utility between taking the self-protective action and not doing so is

$$\frac{w - c_s}{1 - \gamma(1 - \beta_s P)} - \frac{w}{1 - \gamma(1 - \beta P)} = \frac{w\gamma P(\beta - \beta_s) - c_s(1 - \gamma(1 - \beta P))}{(1 - \gamma(1 - \beta_s P))(1 - \gamma(1 - \beta P))}.$$

Hence, susceptible agents' decision boils down to a comparison of the benefit of self-protection, $\frac{w\gamma P(\beta - \beta_s)}{1-\gamma(1-\beta P)}$, with the cost of the self-protective action, c_s. Since the benefit of self-protection is monotonically increasing in the steady state prevalence P, it can be shown that, in this case, an endemic equilibrium must be unique (it is shown in [5] that, with $\varepsilon_s = 1$, the endemic equilibrium is globally stable).

To see how the endemic equilibrium of the model is affected by changes in agents' decision environments, we can look at the impact of changing the values of the model parameters. For convenience, assume henceforth that $\varepsilon_s = 1$. With regard to the effect of changing the cost of the self-protective action, it is not surprising that the steady state equilibrium prevalence is nondecreasing in c_s. This obtains since an increase in c_s reduces agents' incentive to take the self-protective action and lowers the proportion of susceptible agents that engage in self-protection in equilibrium. Similarly, an increase in u_i, which can result if there is an improvement in the treatment of infected agents or if infected agents have better access to treatment, lowers the benefit of taking the self-protective action in a steady state and causes the equilibrium prevalence to rise (weakly).

In contrast, the effect of changes in the transmission probability on the steady state prevalence is non-monotonic. Specifically, in increase in the transmission probability β can in fact lead to a lower equilibrium prevalence, since susceptible agents are more likely to engage in self-protection when the transmission probability is high. Somewhat counterintuitively, the population as a whole can be better off with a higher value of β. To understand why, note that when the transmission probability increases, there can be two opposing effects on the steady state social welfare. On the one hand, the population can be better off because the prevalence may decrease. On the other hand, a higher transmission probability increases the equilibrium proportion of susceptible agents who choose to self-protect, and this—all else being fixed—decreases the population welfare since self-protection is a costly activity. The overall effect of a higher transmission probability thus depends on which effect is greater. The following numerical example shows that the population welfare in an endemic equilibrium can increase when the transmission probability rises.

Example 1. Suppose $\delta = 1/20$, $\alpha = 95/100$, $c_s = 7$, $u_h = 10$, and $u_i = 1$. When $\beta = 1/2$, the endemic equilibrium prevalence is 0.756; in every period, the fraction of susceptible agents who choose to self-protect is 0.568, and the population welfare is 2.22. When $\beta = 3/5$, the endemic equilibrium prevalence is 0.630; in every period, the fraction of susceptible agents who choose to self-protect is 0.763, and the population welfare is 2.35.

This result has obvious policy implications. For instance, it suggests that implementing a mass vaccination campaign during an epidemic, where the vaccine is imperfect but lowers the transmission probability of the disease, can lead to a worse outcome for the population as a whole. Not only would such a program be costly to the population when considering the resources needed to develop, produce, and distribute the vaccines, it would not generate any benefit to society if the aggregate payoff of the population decreases subsequently.

Similar caveats apply to policies that encourage infected agents to reduce contact with people or take other actions to lower the likelihood of spreading their disease such as the wearing of mask in the case of flu. They are also relevant when considering improvements in the treatment of infected individuals that may result in their having lower infectivity (e.g., HAART for HIV/AIDS). If susceptible individuals expect a disease to become less infectious—whether as a result of policy intervention or medical innovation—they would rationally be less likely to take precautionary actions; and this change in behavior can worsen an epidemic and result in lower well-being for the population.

3.2 The Model with Only Vaccination

Although getting vaccinated is a form of action one can take to reduce the likelihood of infection, its analysis differs in considerable ways from that of the self-protective

action considered above. The difference arises because vaccines offer protection over several time periods, while the self-protective action in the model is effective only during the period in which it is taken. This distinction affects the cost-benefit calculations of agents, and thus can yield dissimilar results.

To examine the effects of vaccination more closely, assume that a vaccine is available but that the self-protective action is not an option (or, equivalently, c_s is prohibitively high). Unlike the model with only the self-protective action and no vaccine, an endemic equilibrium need not be unique when agents can get vaccinated. Specifically, there is only one endemic equilibrium when vaccine efficacy is sufficiently high; otherwise, multiple endemic equilibria can coexist (see [7] or [9] for numerical examples). In a model in which all susceptible agents are identical with respect to their preference parameters and cost of vaccination, there can be at most three endemic equilibria, which differ in vaccine coverage and steady state prevalence. Note that unless the vaccine is sufficiently efficacious, there can be an endemic equilibrium in which all susceptible agents choose to be vaccinated.

Multiple endemic equilibria can coexist since, counterintuitively, the benefit of vaccination need not be monotonically increasing in prevalence in a steady state (see [9] for an illustration). In fact, when ε_v is not sufficiently high, the benefit of vaccination is decreasing in prevalence when prevalence is high. This means that there can be an equilibrium with a relatively low level of prevalence in which a high number of susceptible agents choose to be vaccinated, and an equilibrium with high prevalence in which susceptible agents rationally choose not to be vaccinated due to the lower benefit of vaccination. On the other hand, if vaccine efficacy is above some threshold level, then the benefit of vaccination in a steady state is strictly increasing in prevalence. In this case, it can be shown that an endemic equilibrium must be unique [7]. Note that this is a major distinction between vaccination and the self-protective action: as pointed out earlier, the benefit of taking the self-protective action is increasing in the steady state prevalence regardless of the value of ε_s, but the benefit of vaccination may not be monotonic in prevalence depending on the value of ε_v.

Because there can be multiple endemic equilibria, the steady state prevalence—as well as the equilibrium behavior of agents—in the model may not behave monotonically or even continuously with respect to changes in parameter values. To see this, consider the effect of a change in the cost of vaccination c_v. When vaccine efficacy is sufficiently high so that there is a unique endemic equilibrium, the steady state prevalence is nondecreasing in c_v as the incentive to vaccinate is lower when the cost to do so rises. However, if multiple endemic equilibria coexist, then how the equilibrium behavior of agents and the steady state prevalence are impacted by increasing c_v depends on which equilibrium is selected before and after the change in the vaccination cost. Therefore, it is possible for the population to jump from the high vaccine coverage equilibrium (with a relatively low prevalence) to the no-vaccination equilibrium (in which prevalence is high), or vice versa, when the cost of vaccination is increased. Changing c_v can also affect the number of endemic equilibria. Specifically, if, for some given value of c_v, more than one endemic equilibrium exist, the multiplicity can always be eliminated by making c_v

sufficiently large so that no agent ever chooses to get vaccinated. This observation implies that small changes in c_v around the value where the multiplicity disappears can bring about an abrupt, discontinuous change in steady state behavior and prevalence. For an example, suppose c_v is such that multiple endemic equilibria coexist and that the population is initially in the high vaccine coverage equilibrium. Assuming that c_v is very close to the threshold value above which no one would ever choose to get vaccinated, a tiny increase in the cost of vaccination would push the population to the no-vaccination equilibrium, resulting in a much higher steady state prevalence.

Not surprisingly, increasing the value of u_i reduces the benefit of vaccination. As with changes in the value of c_v, when multiple endemic equilibria coexist, it is possible for the population to jump discontinuously from the high vaccine coverage equilibrium to the no-vaccination equilibrium with higher steady state prevalence when u_i rises. This implies, for instance, that making treatment more affordable or accessible can drastically increase the number of infected individuals. It is important to note, however, that a rise in steady state prevalence does not necessarily mean a lower aggregate payoff for the population. To see this, consider the following example.

Example 2. Suppose $\delta = 1/10, \alpha = 1, c_v = 13/10, \varepsilon_v = \frac{1}{2}, \beta = \frac{3}{5}$, and $u_h = 2$. When $u_i = 1$, there is an endemic equilibrium in which all susceptible agents choose to be vaccinated. In this equilibrium, the prevalence is 0.63, and the social welfare in each period is 1.24. When $u_i = \frac{11}{10}$, the no-vaccination equilibrium with prevalence 0.81 is the unique endemic equilibrium, and the social welfare in every period is 1.27.

When the vaccine is imperfect, the benefit of vaccination is not necessarily increasing in the transmission probability β, holding all else fixed. In other words, as β increases—as the disease becomes more infectious—it is possible for the benefit of vaccination to decrease instead. This means, in particular, that the equilibrium number of agents who choose to get vaccinated can fall when β rises.

Example 3. Suppose $\delta = 1/20, \alpha = 18/19, c_v = 124/100, \varepsilon_v = \frac{1}{2}$, and $u_h - u_i = 1$. When $\beta = 3/5$, there is an endemic equilibrium in which all susceptible agents choose to get vaccinated. However, when $\beta = 7/10$, there is a unique endemic equilibrium in which no one gets vaccinated.

Assuming multiple endemic equilibria coexist, which one the population will reach may not be pinned down by the initial conditions. As shown in [9], fixing the initial prevalence P_0 and assuming that there are no vaccinated agents at time 0, there can exist multiple REEs which differ significantly in their limiting behavior. For the same value of P_0, there can be a REE in which the population converges to the high vaccine coverage equilibrium, **another** REE in which the population converges to the no-vaccination equilibrium, **as well as** REEs in which the prevalence oscillates over time and never reaches a steady state value.

These results regarding the model with voluntary vaccinations have important policy implications. Because there can be multiple equilibria when vaccine efficacy is not sufficiently high, it can be difficult to predict beforehand the effects of

various public health policies to combat epidemics. In particular, as discussed in [9], when multiple equilibria coexist, agents' beliefs and expectations regarding how the epidemic will play out in the future can determine which equilibrium will obtain. This is the case since agent's expectations affect their actions, which in turn influence the behavior of prevalence over time. Thus, the model suggests that, in formulating control strategies, there are situations in which policy-makers need to also consider what kind of messages and information to convey to the public, since these can affect people's forecasts and expectations and thereby impact the course of an epidemic.

3.3 The Model with Both Self-protective Action and Vaccination

The model with both the self-protective action and vaccination lets us examine how agents select among multiple risk-reduction options that can differ in efficacy and cost. In particular, it allows us to analyze how people respond in terms of their risk behavior to the increased availability of a vaccine and the subsequent effects on the population as a whole. As with the model in which vaccination is the only risk-reducing strategy available, multiple endemic equilibria can coexist when vaccine efficacy is low.

Assuming that vaccination is initially not an option, making an imperfect vaccine accessible to the population at cost c_v can lead to a perverse outcome in which the steady state prevalence increases [7]. This occurs due to behavioral disinhibition: with the availability of the vaccine, agents have less incentive to take the self-protective action; and if ε_s, the efficacy of the self-protective action, is sufficiently high, this behavioral response can result in higher prevalence. Similarly, when a vaccine is already available in a population, behavioral disinhibition can cause the prevalence to rise when the cost of vaccination decreases (which can result, e.g., from a government subsidy for vaccination). Note that this perverse effect of introducing a vaccine cannot occur in a model in which the self-protective action is not available as an option. In such a setting, making a vaccine available cannot lead to a higher equilibrium prevalence.

It is well-known from the literature on voluntary vaccinations that, in general, the equilibrium amount of vaccination in a population is lower than the socially optimal amount [4, 12]. However, this result assumes that vaccination is the only risk-reduction option available to individuals. An important topic that can be pursued in future research in this area is to consider how the equilibrium level of vaccination compares to the socially optimal level when people can engage in multiple forms of risk-reducing behavior.

4 Conclusion

The economic approach to studying the transmission of infectious diseases provides an analytical framework for making predictions about how people will respond to an epidemic. Furthermore, this framework can be used for normative analysis to determine how various policies and control strategies can affect the well-being of the population under consideration. By examining explicitly people's incentives to alter their behavior in response to an infectious disease, the economic approach often yields counterintuitive results with significant policy implications. It is important to note that, from an economic perspective, reducing prevalence may not always be socially desirable. This follows since we need to take into account society's cost of reducing prevalence and weigh that against the welfare cost of infection. If the cost to society as a whole of a policy that decreases the number of infections by a certain amount exceeds the resulting gain to society, then such a policy would lower social welfare if implemented.

The model presented here is highly stylized and omits many aspects of people's decision-making process, how people interact with others, or the disease transmission process. Nevertheless, this simplified model is useful for identifying the relevant trade-offs people have to make during an epidemic and how these are affected by changes in their decision environment. This understanding can thus serve as key building blocks for the analysis of more complex economic models of disease transmission.

An important extension of the existing literature in economic epidemiology is to consider the effect of imperfect information. The model discussed here assumes that people always know with certainty their infection status. Naturally, such an assumption would not be appropriate when studying diseases that have an asymptomatic phase during which one can infect others without showing any signs of illness. Furthermore, agents in the model are assumed to know the prevalence in every period, which need not obtain even if everyone always has perfect information regarding their own health status. As has been shown in [8], varying the amount of information that agents have about how widespread a disease is can affect their behavior and hence disease incidence. Given that economists have already developed a rich set of analytical tools to study decision-making with imperfect information, future research in the economic modeling of epidemics can examine how people's behavior is affected by uncertainty regarding one's own health status or the health status of others in the population. This would give us a better idea as to how disease transmission will be affected as people modify their behavior during an epidemic outbreak and what policy or mix of policies to implement to optimally manage the situation.

References

1. Ahituv, A., Hotz, V., Philipson, T.: J. Hum. Resour. **31**, 869 (1996)
2. Althouse, B.M., Bergstrom, T.C., Bergstrom C.T.: P. Natl. Acad. Sci. USA **107**, 1696 (2010)
3. Bauch, C., Earn, P.: Natl. Acad. Sci. USA **101**, 13391 (2004)
4. Brito, D.L., Sheshinski, E., Intriligator, M.D.: J. Public Econ. **45**, 69 (1991)
5. Chen, F.: Theor. Popul. Biol. **66**, 307 (2004)
6. Chen, F.: Math. Biosci. **199**, 141 (2006)
7. Chen, F.: J. Math. Biol. **53**, 253 (2006)
8. Chen, F.: Math. Biosci. **217**, 125 (2009)
9. Chen, F., Cottrell, A.: J. Biol. Dyn. **3**, 357 (2009)
10. Chen, F., Jiang, M., Rabidoux, S., Robinson, S.: J. Theor. Biol. **278**, 107 (2011)
11. Feinleib, J., Michael, R.: Prev. Med. **27**, 400 (1998)
12. Fine, P.E.M., Clarkson, J.A.: Am. J. Epidemiol. **124**, 1012 (1986)
13. Francis, P.J.: J. Econ. Dyn. Control. **28**, 2037 (2004)
14. Gersovitz, M.: Annu. Rev. Resour. Econ. **3**, 277 (2011)
15. Gersovitz, M., Hammer, J.S.: World Bank Res. Obser. **18**, 129 (2003)
16. Jacquez, J., Simon, C., Koopman, J., Sattenspiel, L., Perry, T.: Math. Biosci. **92**, 119 (1988)
17. Lau, J.T.F., Yang, X., Tsui. H., Kim, J.H.: J. Epidemiol. Commun. Health **57**, 864 (2003)
18. Liu, J., Kochin, B.F., Tekle, Y.I., Galvani, A.P.: J. R. Soc. Interface **9**, 68 (2012)
19. Philipson, T.: Economic epidemiology and infectious diseases. Handbook of Health Econ, vol. 1, pp. 1761. Elsevier, Amsterdam (2000)
20. Reluga, T.: PLoS Comput. Biol. **6**, e1000793 (2010)
21. Stokey, N., Lucas, R. (with Prescott, E.): Recursive Methods in Economic Dynamics. Harvard Univ. Press, Cambridge (1989)

Mathematical Epidemiology and Welfare Economics

Mark Gersovitz

Abstract Economics provides theories of private behavior and government policy that can be integrated with mathematical epidemiology, as illustrated in a susceptible-infected-susceptible model of infection. Confronting infections, people decide on prevention and therapy with regard to consequences for themselves but not for others, the economic concept of an externality. Public policy can optimally offset the externality by subsidizing prevention and therapy at equal rates (or less practically, taxing infection). Absent such interventions, seemingly beneficial changes such as a decreased cost of infection can perversely lower welfare by worsening the externality, the economic concept of immiserization. Other issues discussed include uniqueness and stability of the optimal steady state and its response to parameter changes.

1 Introduction

This chapter discusses choices that affect people's health, choices about prevention and therapy made by individuals and governments in an environment of infectious diseases. Choice requires options. The range of options and their consequences provide the constraints on choice. Choice also presupposes objectives, the goals that individuals and governments pursue. This chapter discusses both constraints and objectives and how the decisions of individuals and governments to maximize their objectives subject to their constraints produce behavioral outcomes and the dynamics of infectious diseases. To fix ideas, this chapter illustrates these general principles with a model of transmission of a susceptible-infected-susceptible (SIS)

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disease, drawing on [6].[1] Throughout, the discussion is abstract and is therefore an exercise in pure theory that is not yet ready to guide actual policy toward any particular disease.

Any approach to infectious diseases recognizes that a person who becomes infected and stays that way poses risks of infection to others. Presumably in many if not most such instances a person who poses such risks does not take into account in deciding about prevention and therapy the benefits to other people if that person is uninfected. Any such subsequent infections of other people, however, impose costs on them and their own attempts to avoid such infections also imposes costs on them. In modeling infectious diseases, one focus of economics is understanding the discrepancy between the costs and benefits as seen by self-interested individuals who make choices about prevention and therapy and the totality of these costs and benefits as seen by society as a whole. This discrepancy is termed an externality, for the costs and benefits that are external to the person making the decisions. Differences in the optimal choices as seen by individuals and by governments about prevention and therapy then provide the rationale for public policy to align private and social choices.

Certainly, epidemiologists are well aware that infectious diseases pose problems because the infection of an individual may have consequences for others. They use terms such as mass or community effects or herd immunity for phenomena that economists would term externalities. What primarily distinguishes these notions from the externality is that the economic concept of an externality is anchored in an explicit comparison between the incentives faced by rational individuals acting alone and by the policy maker acting for society as a whole. Furthermore, in acting for society as a whole, the policy maker's valuation of an individual's well-being does not differ from that individual's own valuation. Where the policy maker differs from individuals is in recognizing that individuals' actions taken together have consequences for people's well-being as a whole. This notion is made more precise in the succeeding sections in which the objective of the social planner and the representative private decision maker are congruent but their constraints differ.

Like any models, therefore, the one presented here has its assumptions, some of which may be unfamiliar, even uncongenial, to noneconomists. First of all, the decision makers both private and public are rational in that they maximize an objective subject to constraints. Second, because the problem is a dynamic one, individuals and policy makers have to form expectations about the future most especially about future values of the infection rate which determines the probability of infection. To avoid compounding the identification of any externalities with problems of myopia, decision makers are assumed to foresee perfectly the dynamics of the infection as summarized in the proportion of the population that is infected (a special case of rational expectations because the model is not inherently stochastic). Furthermore, to the extent that disease persists, it affects the well-being

[1]This chapter is not a survey of contributions by economists to the study of infectious diseases and does not undertake any literature review. Paper [3] provides such a survey and should be seen as a complement to this chapter.

of people into the indefinite future. Decisions taken today affect the future course of the disease and therefore affect the welfare of people in the future, including the welfare of people born after the decisions were made. The decision makers are therefore assumed to have objectives formulated in a way that provides a consistent accounting for present and future well-being so that decisions are made taking into account their future consequences. Finally, the model is simplified so that people do not care whether they have access to insurance against the costs of the disease or not, again to focus on externalities rather than problems in insurance markets. I sketch some alternative ways to formulate the model so that people do care about access to insurance, a topic for future research.

The next section lays out the accounting for people by disease status and the dynamics that move people from one status to another, the constraints on optimization. The following section introduces the objective of decision makers taking into account the costs of prevention, therapy, lost work time, pain, and suffering. As is conventional in modeling externalities, this chapter next discusses the problem of a hypothetical social planner who can directly control all preventive and therapeutic actions. Maximization of the objective function subject to the constraints provides the optimal solution to the social planner's problem and some of its properties. The next section looks at decisions by individuals, their deviations from the social planner's choices, and hence the existence of externalities and the role for public interventions to achieve the social planner's optimum.

2 The Dynamics of Infection and the Constraints on Choice

In the SIS model of infections transmitted from person to person, the total number of people (N) is the sum of the number who are susceptible (S) or infected and infectious (I):

$$N = S + I. \tag{1}$$

The proportions of these groups in the population are denoted by s ($= S/N$) and i ($= I/N$) so that $s + i = 1$. The birth rate of the population is ε. For simplicity no deaths occur at all. An assumption that people die at the same rate regardless of whether they are infected or not would just introduce an extra parameter of no interest to the questions of this chapter. Specifying a death rate that depends on infection status is contrary to the assumption of an SIS infection; [6] discuss a model in which infection raises the probability of death. The net change in the population is therefore

$$\dot{N} = \varepsilon N. \tag{2}$$

The number of susceptibles changes over time according to

$$\dot{S} = \varepsilon N - \alpha S i + \beta I. \tag{3}$$

Given Eq. (2), the first term of the right-hand side embodies the assumption that all newborns are susceptible. The second term reduces the number of susceptibles by those people who become infected. Under the assumption of random (or homogeneous) mixing, the probability per contact of a susceptible person's meeting an infected (and infectious) person is the proportion of infected people in the population, $i = I/N$. The product, Si, is the number of susceptibles who do so. The factor α is a composite term incorporating both the rate of contact and the inherent infectiousness of an infected (or susceptibility of a susceptible). The third term, βI, is the addition to the susceptible pool resulting from the recovery of infecteds at rate β. Eqs. (1)–(3) can be solved for the change in the proportion of susceptibles:

$$\dot{s} = -\alpha s(1-s) + (\beta + \varepsilon)(1-s). \tag{4}$$

So long as the symbols α and β represent constant parameters, this equation is a classic model in mathematical epidemiology. In traditional epidemiological modeling, α and β are invariant (or exogenous) within any model. In particular, they do not vary with the prevalence the infection, i, or equivalently in an SIS model, the variable s. A simple representation of behavior in such a model is to assume that in some places or times, α and β take specific values but that in other places or times, they take different values. For instance, there may be immutable customs that differ among communities and affect the ease of becoming infected and of recovering with corresponding consequences for α and β. But an economist would not think of these differences as constituting a behavioral model of the transmission dynamics of an infectious disease. In such circumstances there would not be any choices that individuals could make and consequently none that could or should be affected by government policy.

Behavior enters the model if people make choices about preventive effort and therapeutic effort that affect α and β. Most importantly, these choices respond to the state of the infection (summarized by s in an SIS model), because the risk of infection is proportional to the infection prevalence, $i = 1 - s$, and this risk shifts the costs and benefits of prevention and therapy. A summary representation of these notions would be to make α and β functions of s, so that Eq. (4) would be modified to:

$$\dot{s} = -\alpha(s)s[1-s] + [\beta(s) + \varepsilon][1-s]. \tag{5}$$

Philipson [9] termed this type of dependence of α and β on s the prevalence elasticity of behavior, and he emphasized it as the touchstone of an economic approach to epidemiology.

Certainly, there are properties of Eq. (5) that are worth exploring. Such properties include whether the steady-state value of s is unique, whether it is stable, and the conditions under which these properties obtain. Some of these issues are discussed in [4]. But if Eq. (5) is the starting point for an investigation, little can be said about the functional forms of $\alpha(s)$ and $\beta(s)$, how they differ according to whether individuals are making all the decisions or governments are also intervening, and therefore the social desirability of the choices made by individuals and the role for public interventions.

Thus it is desirable to move back from Eq. (5) and rebuild it from the underlying components of the problem, the objectives, and constraints faced by maximizing decision makers and their consequent choices. The first step is to recognize that α and β do not depend directly on the prevalence of the infection, $i = 1 - s$, but rather on the inputs of preventive effort and therapeutic effort which are in turn choices.

Either input may be targeted in the sense that only a proportion of the population generates costs associated with the input. Let θ^j, $j = a, b$ be the proportions of the population that generate either preventive or therapeutic costs associated with an infectious disease. The θ^j are termed targeting functions; in general, they depend on s. The most natural formulation would be for prevention to be targeted at the susceptible ($\theta^a = s$) and for therapies to be targeted at the infected ($\theta^b = 1 - s$). Other formulations may, however, be plausible depending on the ability to identify and reach different groups and what makes sense in terms of the disease and the balance of costs and benefits. The type of targeting may be a choice variable, but in this chapter it is a technical given. For example, in the case of a respiratory infection such as a cold or influenza, θ^a could plausibly take values of 1, s, $1 - s$, and $s(1 - s)$. In the first case, everyone wears a mask, in the second only the uninfected do so, in the third only the infected do so (as in Japan), and in the fourth only in matchings involving an uninfected and an infected person do people wear masks. For therapeutic interventions, the simplest case is targeting exclusively at the infected so that $\theta^b = (1 - s)$. If it is difficult to diagnose the disease, cheap to treat, and treatment does not have important side effects, then mass treatment may be adopted with $\theta^b = 1$. Such targeting has been tried for sexually transmitted diseases.

In all these targeting schemes for prevention and for therapy, it is the level of these health inputs per targeted person that affect the parameters of the model directly, with prevention lowering α and therapy raising β. The number of units of preventive effort is denoted by a and the number of units of therapeutic effort is denoted by b so that $\alpha(a)$ and $\beta(b)$. Thus a and b determine, respectively, the rate of new infections and the rate of transition back to being susceptible. The preventive and therapeutic interventions exhibit positive but diminishing marginal products, i.e., $\alpha' < 0$, $\alpha'' > 0$, $\beta' > 0$, and $\beta'' < 0$. For many if not all diseases there is scope for undertaking additional preventive and therapeutic interventions although they are marginally less and less productive.

All types of targeting considered in this chapter will produce a dynamic equation of the form

$$\dot{s} = -\alpha(a)s[1 - s] + [\beta(b) + \varepsilon][1 - s]. \tag{6}$$

Other types of targeting would not. For instance, if only some of the susceptibles are targeted by prevention, then there would be two groups of susceptibles and their dynamics would have to be tracked separately and the model would no longer have only one state variable. But for the types of targeting considered in this chapter, Eq. (6) is operative and the problem is then to show how a and b depend on s.

3 The Well-Being of Individuals and the Consequences of Infectious Diseases

In evaluating situations, economics usually starts with the utility function, a relationship between consumption and well-being. It provides both a component of predictive theories based on the hypothesis that individuals maximize utility and a method of evaluating any situation from a social perspective based in individuals' own evaluation of that situation. When the situation is one involving health, a general formulation of the utility function would make it depend on health status as well as consumption. This approach differs from that of cost-effectiveness analysis which explicitly sidesteps the question of the utility of health; paper [5] discuss criticisms of cost-effectiveness.

A person who is susceptible (and therefore healthy) and who consumes commodities other than those involved in health of quantity c_s has utility function $\Psi^s(c_s)$, $(\Psi^s)' > 0$, and $(\Psi^s)'' < 0$, with these derivative conditions representing the assumption that marginal utility of consumption is positive but diminishing. A person who is infected and therefore ill consumes other commodities of quantity c_i and has utility $\Psi^i(c_i)$ with the same derivative properties. The costs of being infected, therefore, affect the utility of individuals in two ways. First, there are monetary costs. People may have less to spend on the consumption of other commodities if they become infected because they spend on therapy and because their ability to earn income is impaired. They may also be continuing to spend on prevention. At the same time, they may be receiving insurance payments and paying insurance premiums. If people are uninfected (and susceptible), they may be spending on prevention and paying insurance premiums. Second, people who are infected experience pain, suffering, and other physical impairments which affect their level of well-being. Formally, these latter consequences of illness are represented by the fact that the functions $\Psi^k(c_k)$ $k = i, s$ are superscripted and are therefore potentially completely different functions of the argument. About all that can be said is $\Psi^i(c) < \Psi^s(c)$, the utility of being infected is less than the utility of being susceptible if the amount of consumption is identical. Importantly, there is no presumption about the relative magnitudes of the marginal utilities of consumption, the $(\Psi^k)'$, if consumption is identical, i.e., $\left(\Psi^i(c)\right)'$ and $(\Psi^s(c))'$ bear no necessary relation to each other.

A specialization of these utility functions is: $\Psi^i(c_i) = \Psi(c_i) - h$ and $\Psi^s(c_s) = \Psi(c_s)$, $h > 0$ in which case the marginal utilities of consumption are the same if the value of consumption is the same and only the term h represents the utility loss from pain, suffering, and other physical impairments. Nonetheless, there are potentially important effects of the dependence of utility on health status even in this restricted specification.

A yet further simplification is to assume that all the effects of illness can be represented by money and can therefore be subtracted from available income (or have lowered income beforehand in the case of lost work opportunities). In this case, utility depends only on consumption and the utility function is the same regardless of disease status, $\Psi(c)$. There is potentially a long list of these monetary costs.

Suppose prevention costs p_a per unit and each targeted person receives a units. There are $\theta^a N$ such people so that the total cost of prevention is $p_a a\theta^a N$. Similarly, if therapy costs p_b per unit, the total cost of therapy is $p_b b\theta^b N$. These costs may be direct monetary costs, such as the cost of a drug, or they may also involve time in which case monetary estimates could be made and they could be included in the relevant p_j, $j = a, b$.

Some of the costs of actually being infected and ill are also monetary in a straightforward way. For instance, people may be unable to work and thereby lose income. It is more difficult to attach a monetary value to the costs of illness in terms of pain, suffering, and disability. The simplest cases to consider are ones in which it is possible to do so. If so, everyone who is ill experiences a monetary cost of p_I that includes the costs of missed work, pain, suffering, and disability and the total costs of being infected and ill are then $p_I(1-s)N$. Costs of therapy as discussed above are in addition.

If all these consequences of the existence of the disease can be measured in monetary terms then once one knows who pays, one can calculate the consequences for each individual's well-being. For instance, assume that everyone has income of V_0 available for consumption if there were no disease at all. Furthermore, assume that targeting is such that susceptibles undertake and pay for prevention ($\theta^a = s$) and the infecteds undertake and pay for therapy ($\theta^b = 1-s$) as well as experience the costs of being ill valued at p_I. In particular, there is no health insurance or sharing of these burdens. In this case the consumption of commodities other than health of a susceptible person (c_s) is

$$c_s = V_0 - p_a a, \tag{7}$$

and the consumption of an infected person (c_i) is

$$c_i = V_0 - p_I - p_b b. \tag{8}$$

So long as the marginal utility of consumption is declining, there is a motivation for insurance. People would like to receive an assured level of consumption through insuring it rather than have a level of consumption that fluctuates with their health status. Insurance markets are, however, problematic and therefore complicate the analysis. The simplest assumption is therefore that the utility function, Ψ, is proportional to the level of consumption, c, so that motivations for insurance do not arise. In this case, utility maximization is identical to the minimization of the total costs of the infectious disease, the approach adopted in this chapter following [6] as well as other earlier analyses of the optimal control of infectious diseases. Part of the agenda for future research is to introduce more complicated versions of the utility functions into the analysis with the ultimate goal of providing an understanding of both externalities and insurance.

The next section shows how the social planner, an idealized decision maker for all people in the society, can use this notion of utility to specify objectives to maximize subject to the constraints of the infection process outlined in the preceding section. The important principle is that the social planner's valuation of any situation in terms

of the prevalence of infection and the availability of resources for consumption of commodities other than health is an aggregation of the valuations of the members of the society. The difference between the decisions of the idealized social planner and of individuals is not how the social planner values each person's well-being relative to how that person values his own well-being but rather in how the social planner accounts for externalities.

4 The Social Planner's Problem

The objective of government policy is to maximize people's well-being over the indefinite future, not just in the current period. Some method is therefore needed to aggregate people's well-being as represented by their utility in each and every period. In the case of cost minimization, the present discounted value of consumption is the obvious criterion because it takes account of the time value of money. Costs incurred at different times can be expressed in the common unit of present discounted value by using the interest rate. If the interest or discount rate is constant, the present discounted value of social welfare is

$$W = \int_0^\infty \{c_s S + c_i I\} e^{-rt} dt = \int_0^\infty \left\{V_0 N - [p_I i N + p_a a \theta^a N + p_b b \theta^b N]\right\} e^{-rt} dt \quad (9)$$

in which r is the discount rate.

Equation (9) therefore provides the objective function and Eqs. (2) and (6) provide the dynamic equations that constrain the optimization problem. The current-value Hamiltonian, H, is

$$H = N\left\{V_0 - \left[p_I(1-s) + p_a a\theta^a + p_b b\theta^b\right]\right\} + (\lambda_s N)[(1-s)(\varepsilon+\beta) - \alpha s(1-s)] + \lambda_N[N\varepsilon], \quad (10)$$

in which $(\lambda_s N)$ and λ_N are the current-value multipliers. Because $\lambda_s N$ is the multiplier on the change in s, it has the interpretation of the value of a unit increase in s on social welfare, W. The variable λ_s therefore has the interpretation of the value of an increase in s on the welfare of the average member of society, or alternatively as the value of an increase in one susceptible person on social welfare. Because W is measured in monetary units, e.g., dollars, λ_s is measured in monetary units and is like a price, but because it is not actually a price in a market, economists term it a shadow price. In Eq. (10) and what follows, the arguments a and b of α and β and their derivatives are suppressed for compactness when there should be no ambiguity.

The first derivatives of H with respect to the controls, a and b, set equal to zero imply

$$p_a \theta^a = -\lambda_s \alpha' \, s(1-s), \quad (11)$$

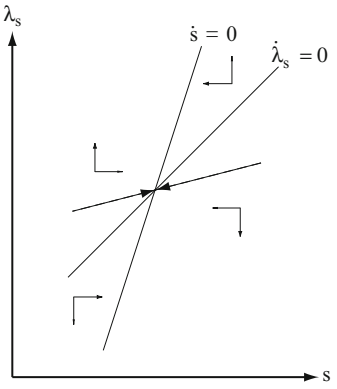

Fig. 1 The phase diagram of an SIS disease: a stable case

and

$$p_b\theta^b = \lambda_s\beta'(1-s), \tag{12}$$

Equation (11) equates the marginal cost of an increase in the preventive intervention as determined by the product of its price and targeting function to the marginal benefit of the increase in the proportion of the population that is uninfected achieved by the increase in preventive effort as valued using the shadow price of s, λ_s. Equation (12) similarly equates the marginal cost of an increase in therapeutic intervention as determined by the product of its price and targeting function to the marginal benefit of the increase in the proportion of the population that is uninfected achieved by the increase in therapeutic effort. All marginal costs and benefits are expressed in terms of the welfare of the average member of the economy measured in monetary units.

Under the assumptions on the θ^j and on α' and β', the λ_s must be positive if Eqs. (11)–(12) are to hold. In addition, the dynamic equation for the multiplier implies:

$$\dot{\lambda_s} = r\lambda_s - (p_I - p_a a\theta_s^a - p_b b\theta_s^b) + (\alpha(1-2s)+\beta)\lambda_s. \tag{13}$$

Note that Eqs. (6) and (11)–(13) form a system of equations without the need for Eq. (2) or consideration of the variable N. Thus the steady state (states if there are more than one) of the system can be found by setting Eqs. (6) and (13) to zero and using Eqs. (11)–(12) to substitute (implicitly) for the variables a and b. Similarly, some qualitative properties of the dynamics of the system can be inferred from the phase diagram plotted in s-λ_s space, Fig. 1.

To simplify what follows, assume that $\theta^b = 1-s$, so that targeting of therapeutic interventions is restricted to the infected and therefore $\theta_s^b = -1$. Total differentiation of Eqs. (11)–(12) implies

$$a_\lambda \equiv \frac{\partial a}{\partial \lambda_s} = -\frac{\alpha'}{\lambda_s \alpha''} > 0, \tag{14}$$

$$a_s \equiv \frac{\partial a}{\partial s} = \frac{\alpha'}{\theta^a}\left[\frac{\theta^a_s s(1-s) - \theta^a(1-2s)}{\alpha'' s(1-s)}\right] \lessgtr 0, \tag{15}$$

$$b_\lambda \equiv \frac{\partial b}{\partial \lambda_s} = -\frac{\beta'}{\lambda_s \beta''} > 0, \tag{16}$$

and

$$b_s \equiv \frac{\partial b}{\partial s} = 0. \tag{17}$$

These expressions simplify the following discussion. They all have straightforward interpretations, except perhaps the indeterminate sign of the expression in Eq. (15) for the partial effect of s on a. This ambiguity arises because s influences both the marginal cost of an increase in a, via its role in the targeting function, and the marginal benefit of an increase in a, via the effect of s on the dynamics of the infectious diseases. The variable a_s: (1) has the same sign as $(1-2s)$ if $\theta^a = 1$; (2) is negative if $\theta^a = s$; (3) is positive if $\theta^a = (1-s)$; and (4) is zero if $\theta^a = s(1-s)$.

So far the discussion has proceeded on the presumption that Eqs. (6) and (11)–(13) determine a path to a unique optimal steady state, but this need not be so. There may be bifurcations in the phase diagram in $s - \lambda_s$ space so that a Skiba point exists that divides the state space into different regions from which the system converges to different optimal steady states [8]. Paper [7] provides an analysis of this phenomenon in a model that is similar to the one in this chapter and paper [4] provides some further discussion of the model in this chapter. There do not seem to be general conditions that ensure uniqueness in terms of the underlying structure of the problem. In what follows, I assume that there is a unique path to a unique optimal steady state. By implicit differentiation, the slope of the locus in the s-λ_s plane that is obtained from setting Eq. (6) to zero is

$$\left[\frac{\partial \lambda_s}{\partial s}\right]_{\dot{s}=0} = \frac{\alpha + \alpha' s a_s}{\beta' b_\lambda - \alpha' s a_\lambda} = \frac{?}{+}, \tag{18}$$

and the slope of the locus from setting Eq. (13) to zero is:

$$\left[\frac{\partial \lambda_s}{\partial s}\right]_{\dot{\lambda}_s=0} = \frac{-(p_a a_s \theta^a_s + p_a a \theta^a_{ss} - 2\alpha\lambda_s + (1-2s)\alpha' a_s \lambda_s)}{[r - \alpha s + \beta + (1-s)(\alpha + \alpha' s a_s)]} = \frac{+}{?}. \tag{19}$$

The signs of both slopes are ambiguous, partially for the same reason that the sign of a_s is ambiguous. Further progress requires the separate consideration of the different cases of θ^a.

In two cases, $\theta^a = s$ and $\theta^a = s(1-s)$, both slopes are positive when the equations of motion are linearized about the steady state so long as a variant of the conventional condition that the interest rate exceeds the population growth rate holds, $r > \varepsilon$, so that the society will not have infinite present discounted value and it makes sense to maximize the integral in Eq. (9). If the slope of the $\dot{\lambda}_s = 0$ locus is

flatter than that of the $\dot{s} = 0$ locus in s-λ_s space, there is a unique stable path to the steady state because the characteristic equation of the linearized dynamic system has one positive and one negative real root (see Fig. 1). On this path, the variables s and λ_s move together toward the steady state, and b and β move with them so that therapeutic effort increases as the proportion of susceptibles is increasing as it approaches the equilibrium from below (or the reverse if from above). Preventive effort, a, and α move as determined by the relation between a and b as given by Eqs. (11)–(12), decreasing with the proportion of susceptibles if $\theta^a = s$ and varying with it if $\theta^a = s(1-s)$. If the slope of the $\dot{\lambda}_s = 0$ locus is steeper than that of the $\dot{s} = 0$ locus in s-λ_s space, however, there is no stable path to the steady state. This chapter, however, does not discuss these divergent cases and is restricted to situations in which the structure of the model is such that policy takes the system to a unique optimal steady state in which the disease is endemic ($0 < s^* < 1$).

The two remaining cases, $\theta^a = 1$ and $\theta^a = 1 - s$, are slightly more complicated. When the model is linearized about the steady state both slopes may be positive, as in the preceding two cases and the foregoing analysis obtains. It may be that the slope of the $\dot{\lambda}_s = 0$ locus is positive and that of the $\dot{s} = 0$ locus is negative or both slopes may be negative, but the $\dot{\lambda}_s = 0$ locus is more negatively sloped. Both these cases are unstable and are not considered on the assumption that there is a unique stable steady state.[2]

The economic parameters of the model are the three prices, p_I, p_a, and p_b, and the interest rate, r. Changes in these parameters affect choices about prevention and therapy and the outcomes of welfare and the infection rate, i. Welfare rather than the infection rate is really what is important; it is, after all, what is being maximized.

For any change in the price parameters $x = p_I, p_a, p_b$, the effect on W is given by the dynamic envelope theorem (see [1], Chap. 9 and 14):

$$\frac{dW}{dx} = \int_0^\infty e^{-rt} \frac{\partial H}{\partial x} dt, \tag{20}$$

in which H is given by Eq. (10). By inspection of Eq. (10), it is immediately apparent that the effects of increases in all three prices is to lower welfare as would be expected.

Although secondary to the effects on welfare, the effects of the parameters on the steady-state infection rate, $i = 1 - s$, may also be of interest. The parameters p_I and r enter Eq. (13) for $\dot{\lambda}_s$ but not Eq. (6) for $\dot{s}$, nor do they enter Eqs. (11)–(12). They therefore shift the $\dot{\lambda}_s = 0$ locus but not the $\dot{s} = 0$ locus.

Consider the effect of an increase in p_I on s^*, the steady-state number of susceptibles in the stable case of Fig. 1. The $\dot{\lambda}_s = 0$ locus shifts up and s^* rises;

[2]Paper [6] mistakenly stated (pp. 13–14 and Fig. 1c) that there could be a stable case with both isoclines negatively sloped and with the s-isocline more negatively sloped. This case would be stable were it possible, but it is impossible under the restrictions of the model as can be proved by careful collection of algebraic terms.

use of therapy increases but the change in prevention depends on targeting. The reverse change, a decrease in p_I, naturally produces the reverse change in s^* and the equilibrium infection rate, $i^* = 1 - s^*$, rises. The use of therapy declines, and in epidemiological terminology, there is disinhibition of therapy which may extend to prevention as well depending on targeting. On balance, disinhibition is so strong that the social planner adjusts the package of prevention and therapy in a way that leads to an increase in infection. But the well-being of members of society increases consequent on the decrease in p_I regardless as has already been established in the discussion of Eq. (20). The change in well-being and not that in the infection rate is what is ultimately important and avoiding disinhibition is not relevant to what the social planner should do. Indeed, if the social planner were arbitrarily ordered to keep the levels of a and b at the values that were optimal before the fall in p_I, welfare would not rise as much because it is suboptimal not to adjust a and b given the shift in costs relative to benefits.

The effect on s^* of an increase in r is opposite to that of p_I. The costs of prevention or therapy are borne immediately while their benefits are received over time. Because an increase in r leads to a diminished weight of the future in decisions, an increase in r leads to an increase in the optimal steady-state proportion of the population that is infected.

The effects of the other two parameters are more complicated, however, because both loci shift. The impact effect (s and λ_s fixed) of an increase in the price of either preventive or therapeutic interventions is to decrease the amount used via Eqs. (11)–(12) and therefore either a and α or b and β are affected in both equations.

In the case of an increase in p_b, both the $\dot{s} = 0$ and the $\dot{\lambda}_s = 0$ loci shift up. The shift in the $\dot{s} = 0$ locus tends to lower s^* while the shift in the $\dot{\lambda}_s = 0$ locus tends to raise s^* and consequently the net outcome is ambiguous even when the algebraic magnitudes of these shifts are taken into account. The rationale for this ambiguity is as follows: The price of a therapeutic intervention, p_b, enters the dynamic equation for the co-state variable in the same way as the cost of being infected, p_I. One of the effects of an increase in p_b is therefore to raise s, just as an increase in p_I does; in effect an increase in the cost of being cured is like an increase in the cost of being infected because every infection induces expenditures on therapeutic inputs. But there is also the fact that it is more expensive to be cured so that it may be desirable to spend less on b and be cured less quickly. That the first effect can dominate is easily seen from the special case when b is fixed at some positive value (perhaps for technological reasons) so that therapeutic effort is not adjusted in response to its price increase. The preventive intervention can still respond, however, as it would to a change in p_I and the steady state proportion of the uninfected, s^*, is thereby increased.

In the case of an increase in p_a, the $\dot{s} = 0$ locus also always shifts up regardless of targeting. When the system is linearized about the steady state, the $\dot{\lambda}_s = 0$ locus shifts according to the sign of

$$\frac{-a\theta_s^a - \theta^a a_s}{r - \varepsilon + (1-s)(\alpha + \alpha' a_s s)},$$

rising with an increase in p_a if this expression is positive and falling if it is negative. The denominator is unambiguously positive regardless of θ^a so long as the steady state is stable. The sign of the numerator is ambiguous in all four cases; if $\theta^a = 1$ or $\theta^a = s(1-s)$, this numerator has the sign of $(2s-1)$. Once again, these ambiguities stem from the role of s in affecting both the costs and benefits of an increase in a (see the discussion of a_s). Consequently, little can be said about the effect of p_a on s^*.

5 Decentralization

To this point the discussion has concerned the problem of the social planner who directly controls the values of a and b in a model without people who make decisions that affect their own health. The next step is to consider private decisions and their implications for government policy. If people do not take into account the effect on the infection of the general population caused by their ability to infect others if they become infected, they generate an externality.

In the model, governments can subsidize preventive and therapeutic activities, the privately chosen values of a and b. In reality, for some diseases, there will be some inputs that are marketed and some inputs that do not go through markets, like time and effort by the person at risk for infection or already infected. Some of these activities may even be entirely unobservable by third parties because they involve private and intimate behavior. Thus the government can subsidize condoms but not the act of safer sex. Some public health programs such as directly observed therapy short course (DOTS) in the case of tuberculosis and other diseases are attempts by the public health authorities to monitor and encourage patient compliance at least partially for its benefits external to the patient. The expenditure on such programs is, of course, a type of subsidy. In the case of any specific infectious disease and its control, these issues need detailed attention. In general, when a and b involve non-marketed and unobservable actions the subsidy/tax interventions may be infeasible or may have to be targeted only on the marketed components of preventive and therapeutic activities with limitations on their effectiveness.

The simplest way to illustrate the externality and its implications for policy is to assume that private decisions are made by a group of people termed a household, a construct that serves as the representative decision-making agent. This construct provides a logically consistent and analytically tractable model to contrast with the model of the social planner: First, the household's objective function is fully congruent with the social planner's. Furthermore, the household understands and anticipates the dynamics of the infection and therefore how the variable i will evolve and is fully forward-looking with regard to its future status as well as its current one. In its current decisions, the household takes account of the dynamics of the infection, its implications for the future risk of infection, and its implications for all the household's descendants. For instance, if the future probability of infection is high it affects the current incentive of the household to make therapeutic expenditures. It is therefore the case that the rationale for government interventions does not

depend either on myopia or on a discrepancy between the social planner's and the representative agent's valuation of outcomes. Instead, the assumptions isolate the pure externality motivation for government intervention. To the extent that there are deviations from the preceding assumptions on the behavior of the household, there may be other important reasons for government interventions but they are not the subject of this chapter.

As is conventional in the public-economics treatment of externalities, the only distinction between the social planner and the representative agent is that the household is assumed to be small relative to the population as a whole, in this case so that the proportion of the household in any disease status does not affect the proportion of the population as a whole that is in that status. In particular, this household takes as given the proportion of the population that is infected at any time, $i = 1 - s$, which equals the probability, π, that any random contact is with an infected person. The household neglects its effects on the aggregate infection rate because such an effect is too small for the household to take into the account as it affects the well-being of its own household members and because the selfish household does not care about its effects on all the other households even though these effects taken together are not negligible. Second, the household is assumed to be sufficiently large that it can fulfill the role of a representative agent and therefore that the proportion of the household in each disease status is identical to the corresponding population proportion. Finally, it is this household that takes decisions about the interventions, a and b. Because the instantaneous utility function is linear, there is no sense in which the household is performing any implicit insurance function for its members. A perhaps more realistic but only perhaps (because people do indeed live in households) and less tractable approach would build the society from private decision makers each of whom is in one or another disease status at any one time and taking decisions about either prevention or therapy, with regard to their possible future status as well as their current one.

The dynamic equations of this version of the model are the same as for the social planner except that in Eq. (6) the term $\alpha s(1-s)$ is replaced by $\alpha s\pi$ to denote the exogeneity from the household's viewpoint of the proportion, π, of the population (in contrast to the proportion, i, of the household) that is infected.

A further change has to be made to the objective function to reflect the possibility of government interventions. If there is an externality, the government may find it optimal to subsidize or tax preventive and/or therapeutic inputs. To allow for these possibilities, the representative household faces prices of $q_j = (1+t_j)p_j$, $j = a,b$. As is standard in public economics, so that any interventions are revenue neutral in a way that does not have any incentive effects beyond the t_j, the household receives a lump-sum payment (possibly negative) per household member of T that it takes as exogenous to its own choices about prevention and therapy but that in fact equals $t_a p_a a^h \theta^a + t_b p_b b^h \theta^b$. A superscript indicates that the variables are evaluated at the household's values rather than the social planner's. If this lump-sum offset were not part of the package, the household's welfare would be affected by its experiencing a net loss or gain of income as the government intervenes with taxes or subsidies

to offset the externality. The decentralization results that follow would not obtain as can be seen by following the steps of the proofs without the assumption of revenue neutrality.

With these modifications, the household's current-value Hamiltonian is:

$$\begin{aligned} H^h = N^h \left\{ V_0^h - [p_I i^h + q_a a^h \theta^a + q_b b^h \theta^b] + T \right\} \\ + (\lambda_s^h N^h)[(1 - s^h)(\varepsilon + \beta) - \alpha s^h \pi] \\ + \lambda_N^h [\varepsilon N^h]. \end{aligned} \tag{21}$$

All functions of variables (θ, α, and β) are evaluated at the household values of their arguments while ε is a constant common to both the social planner's and the household's models.

Once again, assume that only the infected are targeted by therapies, so that $\theta^b = (1 - s^h)$. Differentiation of Eq. (21) with respect to a and b implies:

$$q_a \theta^a = -\lambda_s^h \alpha' s^h (1 - s) \tag{22}$$

and

$$q_b \theta^b = \lambda_s^h \beta' (1 - s^h), \tag{23}$$

and the co-state equation is:

$$\dot{\lambda}_s^h = r\lambda_s^h - [p_I - q_a a^h \theta_s^a - q_b b^h \theta_s^b] + [\alpha(1 - s) + \beta]\lambda_s^h. \tag{24}$$

Because the group is representative of society, s must equal s^h. Once this substitution is made, the only differences between Eqs. (11)–(13), the planner's problem, and Eqs. (22)–(24), the private problem, are the q_j and the $(1 - s)$ term at the end of Eq. (24) rather than the $(1 - 2s)$ term at the end of Eq. (13). This latter difference reflects precisely the fact that the household takes the general rate of infection as exogenous in making its decisions and this difference determines whether the government's optimal intervention is a tax or a subsidy as is shown below. Note that the s-isocline takes the same form for the problem of Eq. (21) as for the problem of Eq. (10) and therefore has the same position in Fig. 1. The λ-isocline has been altered from Eq. (13) to Eq. (24) and is lower in Fig. 1 than in the social planner's problem if there is no government intervention ($t_a = t_b = T = 0$). Consequently the steady state value of s is lower with households rather than the social planner making decisions, indicative of the diminished incentive to undertake prevention and therapy faced by households when acting without government interventions.

At this point, there are two natural goals to the investigation:

First is to establish what the government can do to induce private households to undertake choices that have been shown to be optimal for the social planner (in the preceding section). In particular, the goal is to find the taxes (or subsidies depending

on whether they are negative or positive) that induce this behavior, termed the decentralization problem. If the social planner's choices can be decentralized then the analysis of the effects of parameter changes on well-being and the infection rate is identical to that of the social planner and, in particular, disinhibition, if any, is a side effect of the optimal choices and is not relevant in guiding what should be done.

Second is to establish some of the consequences if the government does not intervene at all. For instance, there is the question of how welfare responds to changes in the parameters if the government does not intervene. In particular, can a change such as a decrease in the cost of infection, p_I, that improves welfare when the social planner is taking decisions instead lower welfare when decisions are made by households in the absence of government intervention to implement (decentralize) the social planner's solution? If it does so, it is because the direct effect of the parameter change (corresponding to what would happen in the social planner's problem) is overwhelmed by a worsening of the externality, the discrepancy between the social and private decisions. Immiserization is the economist's term for this type of outcome.

Turning to the first goal, the main result is that, in principle, the government can induce private decision makers to make decisions that coincide with the planner's problem by instituting equiproportionate changes in p_a and p_b. Comparison of Eqs. (11)–(12) with Eqs. (22)–(23) shows that a property of successful decentralization of the social planner's problem is $t_a = t_b = t$. In other words, the government compensates for any differences between λ_s and λ_s^h in Eqs. (11)–(12) and (22)–(23). It does so with a lump-sum offset, T, so that any revenues or expenditures from the price interventions also appear in the household's budget. Because the intervention is only to λ_s^h and because of the way λ_s^h enters Eqs. (22)–(23), a and b activities are affected to the same degree. At the steady state, the intervention is a subsidy (negative tax) at rate t^*:

$$t^* = -\frac{\lambda_s^* \alpha s^*}{p_I + \lambda_s^* \alpha s^*} < 0, \tag{25}$$

in which λ_s^* and s^* are the values from the planner's steady state [6]. Furthermore, for any non-steady-state s, the government must intervene with a subsidy [6]. This finding that the intervention is a subsidy coincides with the intuition that private decisions ignore the benefits to society as a whole from taking preventive and therapeutic measures. Subsidization is at equal rates because it is equally beneficial in preventing further infection to get a person out of the infected pool as to have prevented the person from getting into it in the first place. These benefits are equally overlooked by the private decision makers. Note that this policy could also be implemented by taxing the condition of being infected (raising p_I) to raise λ_s^h to coincide with λ_s.

The second goal is to consider what happens if the government does not intervene to implement the social planner's solution, i.e., $t_a = t_b = T = 0$. Clearly, the first observation is that because the choices from the solution to the problem of Eq. (21) under these conditions are not the same as the solution from the problem of Eq. (10), the level of well-being under private decision making is lower than when the

social planner takes decisions. The social planner maximizes well-being; the private decision maker (household) ignores something that has to be taken into account to maximize well-being, namely that $\pi = (1 - s)$.

Furthermore, starting from a steady state, the effect of a change in a parameter, x, on welfare, W, is more complicated when the household takes decisions and the optimal subsidies have not been put in place. The equation determining the outcome is

$$\frac{dW}{dx} = \int_0^\infty e^{-rt} \left[\frac{\partial H}{\partial x} + \frac{\partial H}{\partial \pi} \frac{d\pi}{dx} \right] dt = \int_0^\infty e^{-rt} \left[\frac{\partial H}{\partial x} + \lambda_s N \alpha s \frac{ds}{dx} \right] dt. \qquad (26)$$

This result is an extension of the dynamic envelope theorem to account for the fact that the household ignores its effect on s through its effect on π (the derivation is the same as in [1], Chaps. 9 and 14). The term $\partial H/\partial x$ has the same sign regardless of whether it derives from the social planner's or the household's problem, although the values at which it is evaluated differ between the two situations. Because the model has only one state variable, the state moves monotonically from one steady state to another so the sign of ds/dx is the same along the path as the sign of the difference between steady states.

As an illustration of what can happen if the social planner's solution is not implemented consider the effect of a decrease in p_I. This change increases H as it did in the social planner's problem. However, such a change also lowers s, through disinhibition as households slacken off on prevention and therapy taken together. Thus Eq. (26) raises the possibility that the net effect on welfare could be negative if disinhibition is extreme enough not just to lower s but to lower it so much that the first term of the right-hand side of Eq. (26) is dominated by the second term. At this point, I do not have an example that leads to immiserization based on a special case, but substitution for the terms in Eq. (26) makes it plausible that one exists. The reason immiserization may occur is that households make choices that are sub-optimal because they disregard their effect on others' welfare. A decrease in the cost of infection could worsen this discrepancy between the social planner's and the private solution and on balance lower welfare even though the direct effect of the decrease in the cost of infection is to increase welfare. The outcome is then immiserization, a perverse transformation of a seemingly beneficial change into an actual lowering of welfare. This outcome is, of course, only possible if the social planner's solution is not decentralized through taxes or subsidies. If the social planner's solution is implemented, a decrease in p_I does decrease s, but it cannot decrease welfare because the consequence for welfare is given by Eq. (20) for the social planner. One could say that the social planner is disinhibited or that households facing the optimal tax/subsidy package implementing the social planner's solution are optimally disinhibited, but they are not immiserized. This observation underlines the position that the goal of policy is the maximization of well-being inclusive of all costs and not the minimization of infection.

6 Conclusions

This chapter has tried to build a bridge between epidemiology and economics, as regards both terminology and substance. In this chapter, the epidemiological model is one in which infection spreads from person to person and people recover from the disease without becoming immune. Paper [6] presents results for models of infection from person to person that result in death or immunity as well as infections involving vectors. Gersovitz [2] presents a model of externalities and vaccinations that leads to explicit formulae for optimal subsidies in terms only of the underlying parameters of the models without need to calculate multipliers as in Eq. (25).

An important direction for further research in economic epidemiology is to make the models more realistic by capturing more aspects of infections and their transmission. A key part of such progress would seem to be a more explicit modeling of behavior by private decision makers and possibly the strategic interaction of people who know at least some of the people who are putting them at risk such as their sexual partners in the case of sexually transmitted infections or their family members in the case of tuberculosis. Another way to enrich the understanding from these models is to deal with motivations for public policy in addition to the externality. Questions of equity arise when people are in different situations especially because they have different incomes. If people are risk averse cost minimization is not an appropriate goal and it is necessary to substitute utility maximization with an explicit treatment of insurance markets and their attendant problems. The first step is to implement a version of utility maximization rather than cost minimization as sketched in Sect. 2.

References

1. Caputo, M.R.: Foundations of Dynamic Economic Analysis. Cambridge University Press, Cambridge (2005)
2. Gersovitz, M.: Births, recoveries, vaccinations and externalities. In: Arnott, R., Greenwald, B., Kanbur, R., Nalebuff, B. (eds.) Economics for an Imperfect World: Essays in Honor of Joseph E. Stiglitz. MIT Press, Cambridge (2003)
3. Gersovitz, M.: Annu. Rev. Resour. Econ. **3**, 277–296 (2011)
4. Gersovitz, M.: Infection Control and Uniqueness in a Model of Susceptible-Infected-Susceptible (SIS) Diseases, mimeo, Johns Hopkins University(2012)
5. Gersovitz, M., Hammer, J.S.: The World Bank Res. Obser. **18**, 129–57 (2003)
6. Gersovitz, M., Hammer, J.S.: The Econ. J. **114**, 1–27 (2004)
7. Goldman, S. M., Lightwood, J.: Top. Econ. Anal. Policy **2**, 1–22 (2002)
8. Grass, D., Caulkins, J.P., Feichtinger, G., Tragler, G., Behrens, D.A.: Optimal Control of Nonlinear Processes: With Applications in Drugs, Corruption and Terror. Springer, Berlin (2008)
9. Philipson, T.: Economic epidemiology and infectious diseases. In: Cuyler, A.J., Newhouse, J.P. (eds.) Handbook of Health Economics. North Holland, Amsterdam (2000)

Modeling Influenza Vaccination Behavior via Inductive Reasoning Games

Raffaele Vardavas and Christopher Steven Marcum

Abstract Past experiences with seasonal influenza and immunization may affect individual decisions about whether to obtain vaccinations. Individuals continually adapt to recent influenza-related experiences, using inductive thought to reevaluate their options to obtain vaccinations. We explore this concept by constructing an individual-level model of adaptive decision-making. We couple this model with a population-level model of influenza that includes vaccination dynamics. The coupled models allow us to explore how individual-level decisions may change influenza epidemiology and, conversely, how influenza epidemiology might change individual-level decisions. By including the effects of adaptive decision-making within an epidemic model, we show that the behavioral dynamics of vaccination uptake could lead to severe influenza epidemics even without the presence of a pandemic strain. We further show that these severe epidemics might be prevented if vaccination programs provided commitment-based incentives or if mass media released epidemiological information that individuals can use to evaluate the prudence of vaccination. Finally we discuss and present some preliminary results of the model when social networks offer preferential paths for transmission.

1 Introduction

The impact of the spread of an infectious disease through a population can be strongly influenced by people's decision-making. Perceptions of the risk of disease versus that of immunization are driving factors in the decision to be vaccinated and,

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consequently, the overall population-level vaccination coverage (i.e., the proportion of the population that gets vaccinated). Individuals who choose to be vaccinated protect themselves and others they come in contact with, which hinders the further spread of the disease. When a significant proportion of the population is immunized, the disease can no longer spread, leading to the protection of the whole population and to what is known as *herd immunity* [1]. Arguably, people may be consciously or sub-consciously aware of the concept of herd immunity, and this awareness could affect their vaccination behavior. If individuals act in their own self-interest, they might rely on the protection of others being immunized, rather than obtaining vaccinations themselves, resulting in what is known as a *free-rider* problem [2].

There has been growing interest in constructing mathematical models of epidemics, in which individuals' vaccination decisions are influenced both by personal risk perceptions and by perceptions of whether others are being vaccinated [3]. The first approaches consider a homogenous population of rational self-interested individuals who, by logical deductive reasoning, make vaccination-related decisions. Based on a game theoretic approach, individuals maximize their utility and reach a Nash equilibrium by choosing to vaccinate with a given probability. This probability to vaccinate is found by assuming that all individuals in the population rely on the same information and perceptions and make equally rational decisions. Specifically, individuals' perceptions of getting infected are based on an epidemic model; this is typically a deterministic *susceptible-infected-recovered* (SIR) or *susceptible-exposed-infected-recovered* (SEIR) model. This approach was first used to price vaccines [4] and to predict the voluntary vaccination coverage for pathogens that provide permanent immunity. For example, following the heightened fear of bioterrorism, there has been growing attention in modeling a smallpox outbreak [5] and individuals' preemptive vaccination behavior [6]. A game theoretic approach showed that a voluntary vaccination policy for smallpox could lead to the free-rider problem, where the achieved vaccination coverage is well below optimal for the group [7]. Similarly, it was shown that voluntary vaccination alone will not, by itself, eradicate childhood diseases such as measles because of the onset of *rational exemption*, a phenomenon whereby some informed and rational parents still decide not to vaccinate their children [8, 9].

These initial models predict a stationary stable vaccination coverage for the population. However, in a heterogeneous population with varying beliefs about the costs of infection and vaccination the coverage may oscillate over time [10]. Cyclic dynamics of vaccination coverage can also result from other behavioral mechanisms. In the case of childhood diseases, this can occur when parents imitate vaccination choices made by other parents [11] or when decisions are based on past epidemic information [12, 13]. Cyclic dynamics can also occur for immunizations that do not provide permanent immunity against the pathogen in question and, thus, where individuals face vaccination decisions multiple times in a lifetime.

For the case of seasonal influenza, decisions need to be made on an annual basis because of the high mutation rate of the virus. Moreover, not all strains of influenza propagating in a single year are covered by the annually reformulated vaccine. Consequently, by using inductive reasoning, people may rely on their past experiences with the flu and its vaccine to help make their yearly vaccination

decisions. This continuous learning and adaptation process could indeed give rise to complex cyclic dynamics. For example, repeated annual influenza vaccination of individuals and of those in their social sphere leads to herd immunity, which in turn may lead to complacency behavior and free riding.

Evolutionary game theory agent-based models provide an approach for describing the coupled dynamics of influenza epidemiology and vaccination decision-making. In particular, inductive reasoning games [14], initially applied to models of the interplay between financial markets and evolving agents trading strategies [15], have since been used for this purpose. The first model assumed a uniformly mixed population where individuals annually evaluate their decision to vaccinate based on their personal outcomes and rely on the vaccination coverage as a proxy of the severity of the flu [16, 17]. In this model, individuals' acquire different past experiences which results in different risk perceptions of getting infected. Consequently, individuals do not assume nor rely on the notion that others are as likely to decide to be vaccinated as themselves. The heterogeneity in vaccination behavior emerges from the model dynamics as a result of different individuals' experiences with the flu and flu vaccine. This model has also been extended to consider other population outcomes individuals may consider to be proxy measures of the severity of the flu [18]. Another important source of heterogeneity in vaccination decision-making is the interaction of individuals in complex social contact networks [19–22]. Recently, evolutionary games of flu vaccination decision-making based on learning by imitation and by inductive thought have been coupled to influenza epidemiology models on networks [23, 24].

In this chapter we review our inductive reasoning game model of influenza vaccination decision-making introduced in [16]. The outline of the chapter is organized as follows. In Sect. 2 we describe and analyze the basic model. In Sect. 3 we analyze the basic model when two types of vaccination incentives are used. We then move to illustrate how a mean-field approach described in [17] can be used to analyze the model dynamics by deriving a dynamical system for the expected coverage in Sect. 4. In Sect. 5 we discuss extensions of the basic model explored in [18]. Finally, in Sect. 6 we provide some insights of our model for the case where influenza spreads over a contact network.

2 The Basic Model

For influenza, the average number of secondary cases, R_0, caused by one infectious case at the beginning of an epidemic ranges from 2 to 3 [25]. In a uniformly mixed population, simple deterministic models of influenza transmission such as SIR and SEIR models have shown that the probability $q(p)$ of any susceptible individual being infected decreases monotonically with vaccination coverage p. For large populations, once the vaccination coverage reaches the *critical vaccination level* given by

$$\pi_c = 1 - R_0^{-1}, \tag{1}$$

the population achieves herd immunity and the probability of infection is effectively zero. According to Eq. 1, π_c ranges from 50% to 67%. If the coverage is below this critical level, influenza can spread, and an epidemic occurs. If the coverage is at or above this level, influenza epidemics are prevented. In our inductive reasoning game, $q(p)$ can be calculated via an influenza transmission model. However, the overall behavior of our model described below does not rely on the specific form of $q(p)$, provided that it decreases monotonically for $p < \pi_c$ and is 0 for $p \geq \pi_c$.

2.1 Description

Our model considers a population of N self-interested individuals who decide whether or not to seek vaccination against seasonal influenza on an annual basis. Their sole interest is to avoid getting infected, preferably without undergoing vaccination. For simplicity, we assume that (i) the vaccine is risk-free and those who are vaccinated are fully protected from infection; (ii) individuals do not communicate their vaccination decisions to each other; and (iii) individuals who decide to get vaccinated do so at the beginning of the season.

At the beginning of year n, an individual i will vaccinate with probability $w_n^{(i)}$ that depends on a weighted sum of past experiences with flu infections and vaccination, lending more importance to the more recent experiences. A past experience in a previous year m is quantified by a variable $\Delta_m^{(i)}$. In our basic model this variable can be either 0 or 1. If individual i considered vaccination necessary that year, this variable takes the value 1; otherwise, if it was considered unnecessary, the variable takes the value 0. The weighted sum of these experiences defines individual i's pro-vaccination experience $v_n^{(i)}$ and is given by

$$v_n^{(i)} = s v_{n-1}^{(i)} + \Delta_{n-1}^{(i)} = \sum_{m=1}^{n-1} s^{(n-1)-m} \Delta_m^{(i)}, \tag{2}$$

where the parameter s discounts the importance of past experiences ($0 \leq s < 1$).[1] Those individuals who vaccinate achieve a coverage p_n in year n given by

$$p_n = \sum_{i}^{N} x_n^{(i)} / N, \tag{3}$$

where $x_n^{(i)} \in \{0, 1\}$ is a Bernoulli variable with parameter $w_n^{(i)}$. Those who do not vaccinate risk infection with a probability $q(p_n)$. At the end of the flu season, each individual evaluates his vaccination decision based either on personal outcomes or on a population-level (i.e., global to the system) epidemiological outcome. Those

[1] For $s = 1$, the pro-vaccination experience of an individual simply represents the total number of the years that he/she would have benefited from vaccinating.

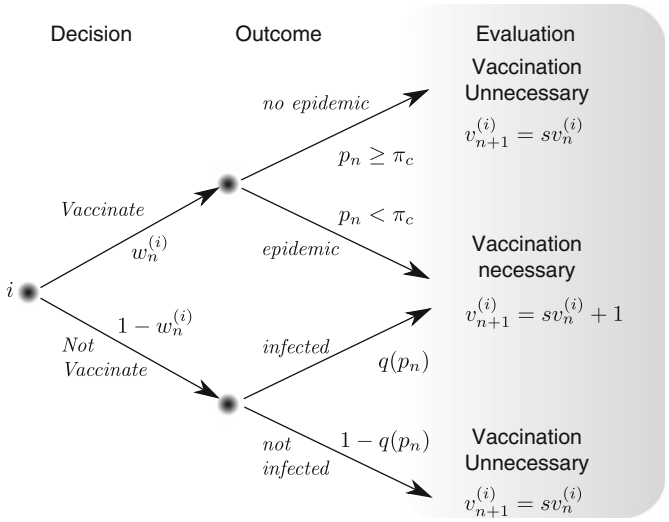

Fig. 1 A schematic diagram illustrating the decision, outcome, and evaluation tree for each individual. Those who decide to seek vaccination will evaluate their choice based on whether an epidemic occurs that season. Those that do not vaccinate will evaluate their choice based on whether or not they got infected. Both types of evaluations depend on the vaccination coverage p_n which they collectively determined through their vaccination decisions. See the main text for a detailed description

who vaccinate (and thus did not get infected) evaluate their decision based on feedback information they receive on the severity of the flu epidemic. In the basic model, the severity measure is determined by whether or not a flu epidemic occurred which explicitly depends on the vaccination coverage. If the achieved vaccination coverage was below the critical level (i.e., $p_n < \pi_c$) a flu epidemic occurred, and the choice to vaccinate was beneficial, and thus $\Delta_n^{(i)}$ takes the value 1. If no epidemic occurred, an individual who chose to get vaccinated is led to believe that vaccination was not necessary and thus $\Delta_n^{(i)}$ takes the value 0.[2] Those who do not get vaccinated evaluate their decision based on whether or not they were infected with the flu that year. If individual i was infected, vaccination would have been beneficial, and thus $\Delta_n^{(i)}$ is 1. Otherwise, if he/she was not infected, vaccination was not necessary, and $\Delta_n^{(i)}$ is 0. The feedback on the vaccination behavior of non-vaccinated individuals also depends on the achieved vaccination coverage, in this case implicitly via the probability $q(p_n)$. Figure 1 provides an illustration of the vaccination decision-making tree. Based on the evaluation $\Delta_n^{(i)}$ individuals update their pro-vaccination

[2]If no epidemic occurred, we assume that an individual who chose to get vaccinated is not attending to the fact that mass vaccination could have prevented the epidemic. He/she is purely self-interested and believes that in the next flu season he/she can choose not to vaccinate and free-ride on the protection provided by those that do get vaccinated. This assumption is relaxed in Sect. 5.

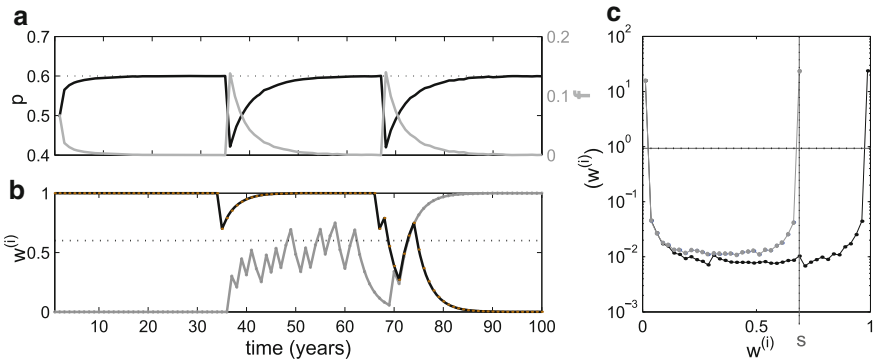

Fig. 2 Individual and population level vaccination dynamics using $s = 0.7$ and $\pi_c = 0.6$. **(a)** Dynamics of yearly coverage (p) for a population of $N = 10^5$ individuals (*black data*), and the corresponding dynamics of the prevalence (*gray data*). **(b)** Dynamics of the probability of vaccination $w_n^{(i)}$ for two example individuals in the population. **(c)** Normalized distributions ($\rho(w^{(i)})$) of the probability to vaccinate ($w_n^{(i)}$) for a population of size $N = 10^7$ for improved accuracy. The first distribution (*black data*) is obtained from a season when an epidemic does not occur. The second distribution (*gray data*) is obtained in successive seasons when severe epidemics occur. Figure taken from [16]

experience to $v_{n+1}^{(i)}$ as given by Eq. (2). Finally, the probability they use to decide whether or not to be vaccinated in the next flu season is given by

$$w_{n+1}^{(i)} = v_{n+1}^{(i)}(1-s)/(1-s^{n+1}). \tag{4}$$

The term $(1-s)/(1-s^{n+1})$ is a normalizing factor representing the maximum value the pro-vaccination experience could be if every year individual i evaluated that vaccination as necessary. The model is iterated from year to year by repeating these steps.

2.2 Numerical Results

Figure 2a shows the vaccination coverage dynamics obtained by simulating the basic model for a population size of $N = 10^5$ and with $s = 0.7$ and $\pi_c = 0.6$.[3] Here, our initial conditions assign a random vaccination probability for the first season to every individual. Therefore, $v_0^{(i)} = 0$ and $w_0^{(i)}$ is uniformly distributed between 0 and 1 for all i. It can be seen that as p approaches π_c from below, it

[3]We used an R_0 value of 2.5 and obtained $q(p)$ by integrating a deterministic SIR model with daily transmissibility rate of $5/6$ and an average infectious duration with flu of 3 days. Similar results can be obtained for the case where $q(p)$ is a linear function with $q(0) = 0.8$ that monotonically decreases to $q(p) = 0$ for $p \geq \pi_c$.

eventually fluctuates above π_c because of the stochastic nature of the individual-level adaptive decision-making process. In the following season, many individuals believe they no longer need to be vaccinated, as an epidemic did not occur in the previous season. Consequently, the vaccination coverage abruptly decreases. The vaccination coverage dynamics then repeat with a cycle of approximately 35 years. Figure 2b shows the dynamics of the probability $w_n^{(i)}$ versus time for two example individuals in the population. In contrast to the simple dynamics of the coverage, individuals go through complex vaccination decision behavior. Over the years, individuals who would commonly seek vaccination or commonly not seek vaccination may change their vaccination behavior. Figure 2c shows two different distributions for two separate seasons of the populations' probability of seeking vaccination. These distributions show that individuals segregate into two groups with different vaccination behaviors: those who commonly get vaccinated and those who do not. Individuals who were very likely to get vaccinated in the previous season decrease their vaccination probability, causing severe epidemics. Over the years, the distribution shown by the gray data slowly tend toward the distribution shown by the black data as epidemics decrease in severity. The segregation in the probability to seek vaccination results from the fact that in the model individuals rely on different past experiences and over the years this produces very different vaccination behaviors.

3 Basic Model with Public Health Incentives

The basic model showed that, although the vaccination coverage necessary for controlling seasonal influenza epidemics can occasionally be achieved by voluntary vaccination, it cannot be maintained. Furthermore, the model suggests that the vaccination coverage undergoes cyclic dynamics and can collapse to low values. However, public health programs based on incentives could help stabilize the vaccination coverage dynamics. Two classes of incentive-based public health programs can be investigated with the model. The first class uses incentives to correlate vaccination decisions among individuals in one influenza season. The second class uses incentives to correlate vaccination decisions for the same individual over many influenza seasons. Many additional incentive-based vaccination programs can be formulated by combining the defining characteristics of these two classes. Here we describe an example of each of these classes.

3.1 Family-Based Vaccination Incentive

In the first public health program that we explore, families pay a reduced price for vaccination if they get vaccinated together. We assume that the head of the family decides every year whether to enroll in the program based upon how many of his/her

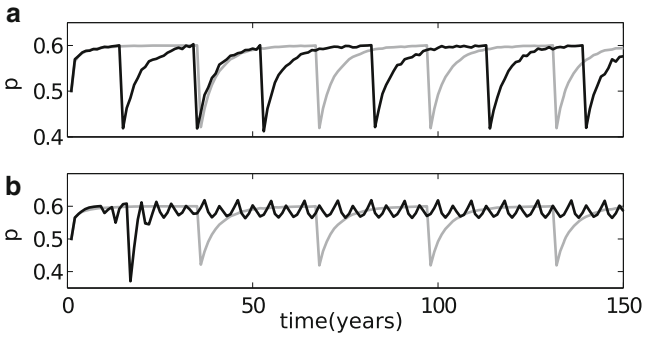

Fig. 3 Population level vaccination coverage dynamics using $s = 0.7$, $\pi_c = 0.6$, and $N = 10^5$. **(a)** Family-based incentive vaccination coverage dynamics for a family size of eight ($C = 8$) is shown in *black*. **(b)** Coverage dynamics for a commitment incentive to vaccinate for three additional years ($y = 3$) is shown in *black*. The coverage dynamics of the basic model with no incentives is shown in *gray* for comparison. Figure taken from [17]

family members were infected in the previous season. To model this vaccination program we considered our population to be grouped into F families, each with C members. As with the basic model with no incentive, each family keeps track of, and updates their pro-vaccination value based on the outcomes and evaluations made each flu season. Family j updates their pro-vaccination value $v_n^{(j)}$ as follows:

Decision	Outcome	Evaluation
Vaccinated	No epidemic	$v_{n+1}^{j)} = sv_n^{(j)}$
Vaccinated	Epidemic	$v_{n+1}^{j)} = sv_n^{(j)} + C$
Not vaccinated	k members infected	$v_{n+1}^{(j)} = sv_n^{(j)} + k$

(5)

where k is the number of family members who get infected if the family is not vaccinated and ranges from 0 to C via a binomial distribution. The probability that a family chooses to vaccinate is updated as follows:

$$w_{n+1}^{(j)} = v_{n+1}^{(j)} / [C(s^{n+1} - 1)/(s-1)], \tag{6}$$

where the normalizing factor, $C(s^{n+1} - 1)/(s-1)$, represents the maximum possible value for $v_{n+1}^{(j)}$ if family j would have benefited from vaccination in all of the n influenza seasons.

As shown in Fig. 3a, simulations of the basic model with family-incentive programs increase the frequency of severe epidemics. In the model, epidemic severity and frequency depend on the number of individuals who independently decide

whether to vaccinate. As the number of independent decision-makers decreases, the likelihood that the coverage fluctuates above π_c increases as it approaches from below. When this occurs, the coverage decreases abruptly in the next flu season resulting in a severe epidemic. Therefore, stochastic variation in the coverage and hence frequency of severe epidemics increases as the number of independent decision-makers decreases. In the basic model without incentives, each member of the population is a decision-maker and decides independently whether to be vaccinated or not. In the family-incentive program the family decides as a whole and therefore the number of independent decision-makers is reduced from the total number of individuals to the total number of families. Thus the family-incentive program increased the frequency of severe epidemics.

3.2 Commitment-Incentive Vaccination Program

The second public health program that we explore offers vaccination for a certain number of additional years at a reduced price to an individual who prepays in the first year. We assume that individuals obtain vaccinations for each year during their enrollment in the program, but they still evaluate the necessity of vaccination every year. The program is specified for $1 + y$ years, which includes the first year and the y additional years of vaccination. At the end of this period, individuals enrolled in the program evaluate whether to reenroll in the program. If they do not reenroll, they stay exposed to the flu that year and for subsequent years until they decide to reenroll. Although highly simplistic, we assume that only enrollees to the program can vaccinate.

As shown in Fig. 3b, simulations of the basic model with a three-year ($y = 3$) commitment-incentive program demonstrated substantially less severe, but more frequent, epidemics than a program without incentives. This result is a consequence of the relationship between the length of the commitment to the program and the time scale of the parameter s. In our simulations we used $s = 0.7$ which translates into a half-life of 1.9 years. In this case, when individuals decide whether or not to vaccinate in the current season, experiences acquired roughly three flu seasons earlier are half as important as the experiences of the previous year. Programs that require only a short-term commitment (e.g., $y = 3$) have a high turnover of participants and a time scale comparable to that of the half-life parameter. Individuals self-organize in such a way that the number of participants entering the vaccination program annually stays roughly the same. Consequently, the number of participants who leave the program in any one year is never very large leading to small frequent epidemics.

In contrast, programs that require long-term commitments (e.g., $y > 10$) have a relatively low turnover of participants and a time scale much longer than that of the half-life parameter. Individuals choose to enroll in the program as long as

the coverage is below π_c. Eventually, the coverage increases above π_c, but many participants are still locked into the program for many remaining years. Once this occurs, individuals not enrolled in the program no longer find it necessary to enroll in the program as they benefit from the repeated vaccination of those that are locked in. Consequently, these long-term commitment program prevent epidemics over the long term. However, at the end of the commitment, many individuals decide not to reenroll in the program because an epidemic has not occurred for many years. Consequently, vaccination coverage drops abruptly and a severe epidemic occurs. In this case, individuals fail to self-organize in a way that the number of participants entering the vaccination program annually stays roughly the same.

4 Mean-Field Analysis

In statistical physics, mean-field approaches were developed to describe systems made of many microscopic interacting bodies and to understand the emergence of macroscopic critical behavior. In a mean-field approach, the microscopic interactions among the bodies are replaced by interactions with an average external field (namely the mean field). In this case, the many-body model is replaced by an equivalent one-body model. The basic model is well suited for a mean-field analysis. Here our basic model describing many individuals is replaced with a mean-field model describing just one individual interacting with a field that describes the overall influence of the vaccination decisions made by the others in the population. Although the basic model includes no explicit individual-individual behavioral interactions, individuals do interact with each other through the vaccination coverage which defines our mean field. Individual vaccination decisions help determine the mean field, which in turn affects future vaccination decisions. In this section we illustrate the mean-field analysis for the basic model and show how it helps explain the observed dynamics of the simulations presented in Sects. 2 and 3. We will see that the nature of the cyclic dynamics in the basic model alone, and the basic model with family-based incentives, is fundamentally different to that of the basic model with commitment-based incentives.

4.1 Vaccination Coverage Iterative Map

For our analysis we define the mean-field coverage in the limit of large N as

$$\pi_n = \langle p_n \rangle = \sum_{i=1}^{N} \langle w_n^{(i)} \rangle / N \tag{7}$$

and define the mean pro-vaccination experience $u_n = \langle v_n^{(i)} \rangle$ where $\langle . \rangle$ represents an average over many independent realizations of the game.[4] Similar to Eq. (4), these realization averaged quantities are related by

$$\pi_{n+1} = (1-s)u_{n+1}/(1-s^{n+1}). \tag{8}$$

We use a piecewise linear approximation for the probability of infection $q(p)$ as a function of coverage p and therefore $\langle q(p) \rangle = q(\pi)$ is given by

$$q(\pi) = \begin{cases} 0, & \text{if } \pi \geq \pi_c; \\ q(0)[1-\pi/\pi_c], & \text{if } \pi < \pi_c. \end{cases} \tag{9}$$

Using the decision-outcome-evaluation tree diagram in Fig. 1, we find that

Population	Expected fraction	Update
Vaccinated	π_n	$u_{n+1} = su_n + 1 - \theta(\pi_n - \pi_c)$
Not vaccinated & infected	$(1-\pi_n)q(\pi_n)$	$u_{n+1}^{(i)} = su_n^{(i)} + 1$
Not vaccinated & not infected	$(1-\pi_n)[1-q(\pi_n)]$	$u_{n+1}^{(i)} = su_n^{(i)}$

(10)

where $\theta(x)$ is the discrete Heaviside step function, which is equal to 0 for $x < 0$ and equal to 1 otherwise. Taking the weighted average over Eqs. (10), we find that

$$u_{n+1} = su_n + (1-\pi_n)q(\pi_n) + \pi_n[1-\theta(\pi_n - \pi_c)]. \tag{11}$$

Substituting Eq. (8) into Eq. (11) and taking the long time limit $n \to \infty$, we obtain an autonomous asymptotic iterative map of the mean-field vaccination coverage given by

$$\pi_{n+1} = s\pi_n + (1-s)\{(1-\pi_n)q(\pi_n) + \pi_n[1-\theta(\pi_n - \pi_c)]\}. \tag{12}$$

The map is defined on the unit interval $\mathscr{I} = [0,1]$. However, the nature of the discontinuity at $\pi = \pi_c$ allows us to distinguish two complementary domains namely $\mathscr{I}_1 = [\pi_c, 1]$ and $\mathscr{I}_2 = [0, \pi_c)$. In the first domain, when the vaccination coverage π_n is between π_c and 1, the map reduces to

$$\pi_{n+1} = s\pi_n. \tag{13}$$

[4] When simulating the basic model, the achieved vaccination coverage p_n in year n represents only one realization as given by Eq. (3). However, using the same set of vaccination probabilities $w_n^{(i)}$, the Bernoulli process describing the vaccination decisions could have resulted in a different set of vaccination decisions and thus in a different vaccination coverage realization.

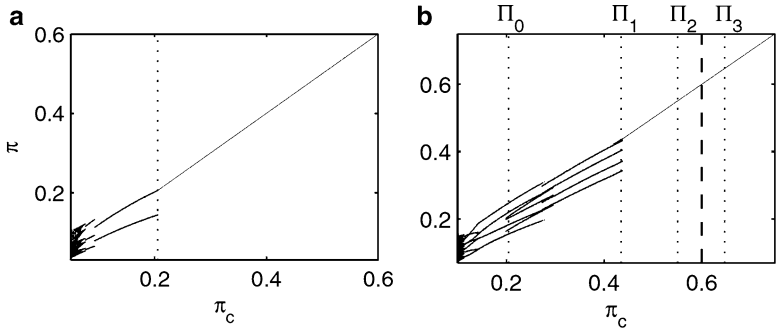

Fig. 4 **(a)** Bifurcation diagram of the iterative map given by Eq. (12) versus π_c for the case where $s = 0.7$ and $q(0) = 0.8$. As π_c decreases, a period-two orbit is created at $\pi_c = \Pi_0$; here its position is shown by the *vertical dotted line*. **(b)** Bifurcation diagram of the iterative map versus π_c of our basic model with a $y = 1$ commitment-incentive vaccination program. As π_c decreases, a period-five orbit is created at $\pi_c = \Pi_1$. Other critical points Π_0, Π_2, and Π_3, respectively, shown for y values of 0, 2, and 3 are also shown. The *dashed line* marks our chosen value of $\pi = 0.6$. The cases where $y = 1$ and $y = 2$ do not induce a qualitative change in the dynamics of the coverage, whereas, since $\Pi_3 > 0.6$, the dynamics for $y = 3$ are qualitatively different. Figures taken from [17]

Since s is positive but smaller than 1, the orbits in $\mathscr{I}_1$ will be attracted toward a vaccination coverage of 0. Therefore, orbits in $\mathscr{I}_1$ will take the vaccination coverage into the second domain $\mathscr{I}_2$ where π_n is between 0 and below π_c. Once in $\mathscr{I}_2$, the orbit is iterated with a different smooth map given by

$$\pi_{n+1} = \pi_n + q(0)(1-s)(1-\pi_n)(1-\pi_n/\pi_c). \tag{14}$$

In this domain $\pi_n < \pi_c$ and therefore the second term of this map is always positive. Depending on its magnitude, orbits in $\mathscr{I}_2$ may either stay in $\mathscr{I}_2$ or cross back into $\mathscr{I}_1$. The orbits' behavior can be determined by a fixed point analysis of the second map over the entire domain $\mathscr{I}$. We find that the map has two fixed points, one at $\pi_n = 1$ and the other at $\pi_n = \pi_c$; we denote the fixed point at π_c by π^*. The first fixed point at $\pi_n = 1$ is unstable since the derivative of the map at 1, given by $1 + q(0)(1-s)(\pi_c^{-1} - 1)$, is always greater than 1. Whereas, the derivative of the map evaluated at the second fixed point $\pi_n = \pi^*$ is given by

$$\lambda = 1 - q(0)(1-s)(\pi_c^{-1} - 1), \tag{15}$$

and since its range is $(-\infty, 1]$, the second fixed point can be stable. When $0 < \lambda < 1$, orbits always stay in $\mathscr{I}_2$ and they approach arbitrarily close to π^* from below but never quite reach this fixed point. In this case π^* is a stable attractor fixed point. When $\lambda \leq 0$, orbits take π_n back and forth between $\mathscr{I}_2$ and $\mathscr{I}_1$. In this case, π^* may still be an attractor fixed point. Depending on the parameters that enter the iterative map, if the orbit begins close to π^* within its basin of attraction, it will spiral and converge toward it. Figure 4a shows a bifurcation diagram for varying π_c using

parameter values $s = 0.7$ and $q(0) = 0.8$. We find that as long as π_c is greater than a critical value $\Pi_0 \approx 0.205$, the basin of attraction of the fixed point π^* is the entire domain $\mathscr{I}$. However, at $\pi_c = \Pi_0$, a period-two orbit is created between the points π_c and $s\pi_c$.[5] Eventually, the basin of attraction of this period-two orbit completely replaces the basin of attraction of π^*. At this point π^* is no longer a stable fixed point. Interestingly, as π_c is further decreased the basin of attraction of the period-two orbit is itself replaced and numerically we observe period doubling and chaotic behavior.

4.2 Stochastic Effects

The described analysis of the iterative map given by Eq. (12) is insufficient to explain the observed numerical dynamics of the vaccination coverage of the basic model presented in Sect. 2.2. According to our analysis, for $\pi_c = 0.6$, the vaccination coverage dynamics should always increase when approaching π_c from below. However, by considering a large set of independent realizations of the game for year n, we find that the resulting vaccination coverages are normally distributed with an average π_n and variance $\sigma_n^2 = \sum_i^N w_n^{(i)}(1 - w_n^{(i)})/N$ (i.e., the sum of the variances of the Bernoulli distribution). Thus, the dynamics of p_n at large finite N can be described by adding Gaussian noise to the dynamics of π_n. In most of the phase space of π, the noise does not change the qualitative dynamics of the orbit. However, when the orbit asymptotically approaches π^* from $\mathscr{I}_2$, the coverage p_n may fluctuate above π^* and into $\mathscr{I}_1$. Then, according to Eq. (13), in the next iteration, the orbit drops back into $\mathscr{I}_2$ in the vicinity of $s\pi_c$ and the dynamics repeat. The expected periodicity depends on the size of the fluctuations which, in turn, depends on the number of individuals in the system. When N is large, as long as π_n is still in $\mathscr{I}_2$ but close to π^*, the dynamics can be approximated as

$$\pi^* - \pi_n \sim \lambda^n. \tag{16}$$

However, since p_n is normally distributed, we expect a jump of the coverage p_n above π^* when $\pi^* - p_n$ is on the order of the standard deviation of p_n:

$$\pi^* - p_n \sim \frac{\sqrt{\sum_{i=1}^N \sigma_n^{(i)\,2}/N}}{N^{1/2}}. \tag{17}$$

As can be seen from Fig. 2c, we expect that the distribution of $w^{(i)}$ becomes asymptotically independent of n just before the drop and therefore the numerator of Eq. (17) approaches a finite constant. Combining Eqs. (16) and (17) and denoting

[5] Here, $\Pi_0 = \{s + 1/[(1-s)q(0)]\}^{-1}$ and is found by setting $\pi_n = s\pi_c$ and $\pi_{n+1} = \pi_c$ in the iterative map Eq. (14).

$\tilde{n}$ as the expected period of the dynamics, we obtain the following scaling result at large finite N:

$$\tilde{n} \sim -\frac{\log N}{2\log\lambda}. \tag{18}$$

4.3 Stochastic Versus Deterministic Periodicity

For the basic model with $\pi_c = 0.6$, our deterministic description of the dynamics suggests that the vaccination coverage approaches π^* from below. Were it not for stochastic fluctuations, the vaccination coverage would remain below π_c and would approach it asymptotically. However, due to the finite size of our population, stochasticity causes the vaccination coverage to fluctuate above π_c which leads to cyclic dynamics. As shown in [17], a mean-field analysis of the model with family-based incentives produces an identical iterative map as the basic model. However, using Eq. 18 and denoting the period for the basic model with family-based incentives by $\tilde{n}(C)$, where C is the family size, we find that

$$\tilde{n}(C)/\tilde{n}(1) \sim 1 - \ln C/\ln N < 1. \tag{19}$$

Hence, with the family-based incentives, we get shorter periods and more frequent, severe epidemics as observed by simulation. We have also seen that in the basic model with no incentives, when $\pi_c < 0.2$ the deterministic description of the dynamics changes such that we obtain cyclic dynamics, first via a period-two and then via a multi-period orbit. These deterministic cyclic dynamics are qualitatively different from the cyclic dynamics caused by stochastic fluctuations. Furthermore, the periodic orbit they create are robust to stochastic fluctuation for large population sizes. Although for the case of the basic model, these robust deterministic and periodic dynamics occur for unrealistically low values of π_c, this is not the case with a commitment-incentive vaccination program. As shown in [17], by following a mean-field analysis of the basic model with a commitment-incentive vaccination program, we obtain a different bifurcation diagram. In Fig. 4b we show the bifurcation diagram for the case where $y = 1$. For a value of π_c at or just below a critical value of $\Pi_1 \approx 0.435$, we obtain a deterministic period-5 orbit. Similar bifurcation diagrams can be obtained for $y = 2$, where we obtain a period-5 orbit forming at $\Pi_2 \approx 0.551$, and for $y = 3$ where we obtain a period-6 orbit forming at $\Pi_3 \approx 0.647$. Since, in our simulations, we used the realistic value of $\pi_c = 0.6$, which is below Π_3, our observed cyclic dynamics (shown in Fig. 3b) of the vaccination coverage are not explained by the stochastic nature of the model but rather by the deterministic periodic nature revealed by our mean-field analysis.

In summary, understanding the nature of the cyclic dynamics—whether more stochastically or deterministically driven—in inductive reasoning game models of influenza vaccination is important in order to better design incentive-based public health programs.

5 The Extended Model

Although novel in both methodology and findings, the basic model makes many idealizing simplifications. One prominent simplification is how individuals make their vaccination decisions. In real-life scenarios, many factors affect an individual's propensity to seek vaccination, including preconceptions—say, fearing pain from needles—that are not likely to change much over the years and risk perceptions that change yearly by an adaptation and learning process using evaluations of past experiences. Although our description of the basic model just considered the learning process, a simple extension that includes a variable preconception term has been described in [16]. The model also substantially simplifies how individuals adapt and evaluate their vaccination decisions. It assumes that $\Delta_n^{(i)}$ is given by a dichotomous variable taking only the values 0 or 1. In particular, the epidemic severity measure that vaccinating individuals use to make their evaluations is given by such a dichotomous variable determined by whether or not a flu epidemic occurred. However, individuals who choose to get vaccinated would probably evaluate their choice using a more continuous severity measure. This idea has recently been explored by Breban [18]. In this section we describe this extension.

5.1 Generalizing the Perception of Epidemic Severity

In the mean-field analysis of the extended model considered in [18], individuals who choose to get vaccinated update their pro-vaccination experience by

$$v_{n+1}^{(i)} = s v_n^{(i)} + F(\pi_n), \tag{20}$$

where $F(\pi_n)$ is a continuous and differentiable function everywhere in $\mathscr{I}$ except at $\pi = \pi_c$. Hence, $\Delta_n^{(i)} = F(\pi_n)$ for all individuals i who get vaccinated. Instead, individuals who do not choose to vaccinate update their pro-vaccination as before as given by Eq. (10). The model considers the case where at the end of a flu season, the media publicizes whether or not a flu epidemic occurred (i.e., $\theta(\pi_n - \pi_c)$), the achieved vaccination coverage (i.e., π_n), and the yearly incidence (i.e., $q(\pi_n)$).[6] Individuals who choose to get vaccinated would then use and combine these pieces of epidemiological information about the population-level outcomes in different ways to estimate the severity of the epidemic $F(\pi_n)$.

[6]Here, incidence is defined as the number of new cases per susceptible (i.e., non-vaccinated) individual. Since we assume a perfect vaccine, the incidence is equivalent to the risk of infection $q(\pi_n)$ that a vaccinated individual would have had if he/she had not been vaccinated at the beginning of the season.

The mean-field autonomous approximation of the coverage dynamics given by Eq. (20) is given by

$$\pi_{n+1} = s\pi_n + (1-s)[(1-\pi_n)q(\pi_n) + \pi_n F(\pi_n)]. \tag{21}$$

As for the basic model, this iterative map has no attractor in $\mathscr{I}_1$. However, a fixed point $\hat{\pi}$ to the map that satisfies

$$q(\hat{\pi}) = \hat{\pi}[1 - F(\hat{\pi})]/(1-\hat{\pi}) \tag{22}$$

exists in $\mathscr{I}_2$. Note that this fixed point is not necessarily equal to $\pi_c = \pi^*$ as in the basic model. In particular, the form of $F(\pi)$ could lead to a fixed point $\hat{\pi} < \pi_c$. This issue is relevant because, as we have seen in Sect. 4.2, such a situation would lead to a map that is more robust to stochastic fluctuations, which would reduce the frequency of severe epidemics.

Although the fixed point does not depend on the parameter s, its stability does. Deterministically, the stability condition of the map is found as before by taking its derivative at $\pi = \hat{\pi}$ and checking for the cases where its magnitude is less than one. Breban showed in [18] that the fixed point is stable as long as the parameter s is greater than a critical value given by

$$S = 1 + 2[q'(\hat{\pi})(1-\hat{\pi}) - q(\hat{\pi})/\hat{\pi} + \hat{\pi}F'(\hat{\pi})]^{-1}. \tag{23}$$

Furthermore, if $F(\pi) = 0$ when $\pi \geq \pi_c$, the vaccination coverage never drops below $s\pi_c$ when the map is iterated in $\mathscr{I}_1$. Therefore, a stable fixed point must further satisfy $\hat{\pi} > s\pi_c$. Putting these stability conditions together, we can define an interval $(S, \hat{\pi}/\pi_c)$ such that if the parameter s takes values within this range we get deterministically stable dynamics. The smaller the value of the boundary point S the larger this interval and the more stable the dynamics. As we have seen in Sect. 4.1, when $\hat{\pi}$ loses its stability we obtain deterministically periodic dynamics.

5.2 *Example Models for the Epidemic Severity*

Four models have been explored, each with a different severity measure $F(\pi)$ [18]. These are

Model	$F(\pi)$
1	$1 - \theta(\pi - \pi_c)$
2	$q(\pi)$
3	$(1-\pi)\,[1 - \theta(\pi - \pi_c)]$
4*a*	$\{q(\pi) + (1-\pi)[1-q(\pi)]\}\,[1 - \theta(\pi - \pi_c)]$
4*b*	$(1-\pi)q(\pi)$

(24)

Since $q(\pi)$ is given by Eq. (9), $F(\pi)$ is equal to 0 in all models when $\pi \geq \pi_c$. Therefore, at the end of the flu season, individuals who choose to vaccinate always know whether an epidemic occurred. Model 1 is a restatement of the basic model. In model 2, individuals that choose to get vaccinated measure the severity of the epidemic based on the incidence. In model 3, the severity measure is given by the proportion of individuals who do not choose to get vaccinated. In model 4a, individuals who choose to get vaccinated consider a severity measure that combines both a personal and a social benefit of having been vaccinated. They are aware of the personal benefit of having avoided the risk of infection (i.e., $q(\pi)$). Furthermore, they are aware of the social benefit of vaccination in providing added protection to those who did not obtain vaccinations, specifically those who directly benefited by not getting infected. Lastly, in model 4b, individuals who choose to get vaccinated measure the severity of the epidemic based on the proportion of individuals infected in the entire population.

Except for model 1 (i.e., the basic model), all models produce a fixed point $\hat{\pi}$ that is below π_c and obey the following ordering $\hat{\pi}_{4b} < \hat{\pi}_2 < \hat{\pi}_{4a}$, where the subscripts label the models. Furthermore, as long as $q(\pi)$ is piecewise linear, $\hat{\pi}_2 < \hat{\pi}_3 < \hat{\pi}_{4a}$. Hence, according to these models, no combination of epidemiological information broadcast by mass media would be able to achieve a stable vaccination coverage that is greater than the critical vaccination level year-after-year. Therefore, none of these combinations would eliminate flu epidemics. When epidemics do not occur for many years, individuals would eventually learn that vaccination to the flu is not as important and become complacent in non-vaccinating, regardless of the epidemiological information broadcast by mass media. Nevertheless, since these fixed points are below π_c, when compared to the basic model, their iterative map produces vaccination coverage dynamics that are more robust to stochastic fluctuations. Therefore, although epidemics cannot be prevented, severe epidemics would occur less frequently. A stability analysis of the fixed points produced by these models shows that S_{4a} is the smallest. Consequently, model 4a has the largest interval of stability with respect to the parameter s and the largest stable vaccination coverage fixed point that is robust to fluctuations. These results suggest that if individuals who choose to get vaccinated use a severity measure that combines both personal and social benefits of vaccination, then mass media broadcasting epidemiological information would lead to stable yearly vaccination coverages with less frequent severe epidemics. This goal could be achieved in principle without the need for incentive-based public health policies of the types described in Sect. 3.

6 Introducing Networks to the Vaccination Game

The basic model and its extensions considered up to this point rely on the underlying assumption that individuals are uniformly mixed. In this case, the transmission dynamics are based on an SIR model where any susceptible individual has an equal chance of being infected. Furthermore, we assumed that individuals update their

vaccination probability based on their own personal influenza experience and are not affected nor rely on observing influenza and vaccination outcomes of people they know. In a more realistic model, individuals interact and mix in complex contact networks. In this case, information diffuses across individuals through the underlying contact network which also offers preferential paths for transmission. Consequently the social structure may strongly affect how individuals change their vaccination behavior. For this reason, a new paradigm in the study of this class of models considers the epidemiological effects of network structure [23, 24]. Locally, network structure constrains the availability of alters that any individual can reach to pass on information or infection; globally, the network structure constrains total infection and vaccination rates achieved by the end of an influenza season. This, in turn, gives rise to faster or slower convergence to the critical vaccination coverage depending on that structure. In many networks, vaccination behavior, susceptibility, and infections will tend to group in local clusters of the contact network, knowledge of which may inform targeted vaccination policies. In this section, we will review how relatively simple models of human interaction gives rise to faster critical vaccination than randomly vaccinating individuals in a population and show that vaccinators will tend to cluster together more than expected by chance even though they do not share information about their decisions.

6.1 The Basic Model on an Erdös–Rènyi Graph

We define a contact network G as a binomial graph with 10^5 nodes and an average degree $\langle k \rangle = 20$ [24], drawn from the Erdös–Rènyi model [26]. The average degree represents the typical number of contacts an individual has during a contagious episode. In our model, we assume that transmission can only occur over the network and that infected actors transmit influenza to their susceptible nearest neighbors with transmission probability

$$T = 1 - \exp(-\beta/\gamma), \tag{25}$$

where β is the average rate of contact per individual weighted by the probability of a flu transmission and γ^{-1} is the average contagious period [27]. We consider the same SIR parameter values as those presented in Sect. 2.2 with a critical vaccination coverage π_c of 60%.[7] As we iterate in time from season to season, we use G to generate a transmission network G_n for season n: There is a probability $1 - T$ that ties connecting susceptible individuals are deactivated on G_n whereas ties to individuals who choose to vaccinate are always deactivated as they cannot transmit

[7]Here, R_0 is given by $\langle k \rangle T$. For the Erdös–Rènyi graph, the epidemic threshold condition is still expressed in terms of R_0, although this is not the case for a general network [19]. Therefore, Eq. (1) relating π_c to R_0 is still valid. It is however important to note that π_c gives the critical vaccination coverage needed if individuals vaccinate irrespective of their location on the network.

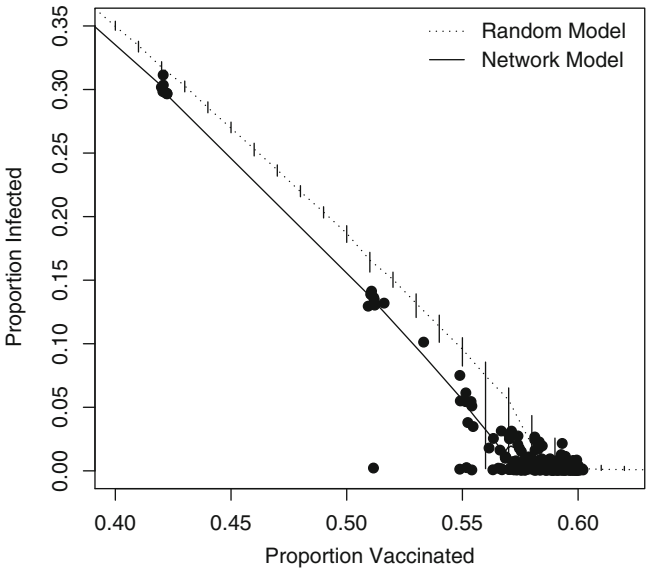

Fig. 5 The proportion of infected versus the vaccination coverage. The 300 seasons of the basic model on an Erdös–Rènyi graph with mean degree 20 are plotted as *black points*. A Friedman's kernel smoother of the points (*solid line*) shows the average behavior of the model. The basic model with uniform mixing with no underlying network structure is indicated by the *dotted-line* with standard error bars represents 100 independent and identically set up Monte Carlo replications of the network

influenza nor become infected by the virus. Hence, G_n is a seasonally varying instantiation of the contact network G. Individual vaccination behavior changes from season to season as described by our basic model. We continue to assume that individuals do not communicate their vaccination decisions to one another and further, we assume that individuals do not observe influenza outcomes of their alters. Thus, local network characteristics (i.e., nearest neighbors' vaccination and infection rates) only affect an individual's vaccination behavior indirectly by modifying their chances of getting infected.

When integrating the dynamics of the basic model on an Erdös–Rènyi graph we reproduce qualitatively similar dynamics to those observed in Sect. 2.2 for the basic model with no underlying network. However, for the basic model on an Erdös–Rènyi graph, over time, individuals learn about their relative vulnerability of getting infected. Those who have many contacts learn to vaccinate more often than those with fewer contacts. This process has compounding benefits as vaccination of the more connected individuals rapidly reduces available transmission paths which results in added herd immunity. Therefore, individuals do not choose to vaccinate irrespective of their location on the network. Consequently, they reach the effective critical vaccination coverage which is below π_c. Figure 5 illustrates this by comparing the basic model on an Erdös–Rènyi graph (which we call the network

Table 1 Odds ratios and standard errors comparing whether or not non-vaccinated and vaccinated actors are nearest neighbors with non-vaccinated and vaccinated alters, respectively

	Non-vaccinators			Vaccinators		
Model	μ	SE		μ	SE	
M1	0.95157	0.00082	***	1.04462	0.00031	***
M2	0.99464	0.00064	***	1.06922	0.00032	***
M1-M2	−0.04307	0.00059	***	−0.02461	0.00033	***

$*** = p - value < 2.2e^{-16}$

model) to the case where individuals on the graph are randomly selected to vaccinate (which we call the random model). The plot shows the proportion of infected individuals versus the proportion of vaccinated individuals. The points shown in the plot are produced by running the network model. The solid line represents a fit to the data points given by a Friedman's smoother. The dotted line represents the median of the random model found over 100 independent and identically set up Monte Carlo replications. Although not shown in the plot, it is important to note that this line is in agreement with a line produced by integrating the equivalently setup deterministic SIR model that assumes uniform mixing. Therefore, running the basic model with uniform mixing produces points that lie on the dotted line.

6.2 Adaptation to Local Information

The basic model on an Erdös–Rènyi graph considers individuals making their evaluations based on personal (i.e., whether they were infected or not) and global (i.e., whether there was an epidemic or not) outcomes. However, by including a network, we can assume that individuals may more readily rely on local outcomes (i.e., how many or what proportion of those they know were infected) than on global outcomes when making their evaluations. We consider a behavioral model where individuals who choose to get vaccinated measure the severity of an epidemic based on a local evaluations. Specifically, $\Delta_n^{(i)}$ of an individual i that chose to get vaccinated is equal to the proportion of alters that were infected in season n. Likewise, we assume that the $\Delta_n^{(j)}$ for an individual j that chose not to get vaccinated and did not get infected to be equal to a weighted sum of his personal and local evaluations. Instead, individuals who get infected continue to evaluate their decision using personal outcomes and are thus more likely to vaccinate in the following season. We call this the simple local behavioral model (M2).

Since network models impose that infections diffuse between connected individuals it is useful to consider how clustered vaccinated and non-vaccinated individuals are on average. Table 1 reports the odds ratios comparing the probability of non-vaccinated and vaccinated individuals being connected to similarly non-vaccinated and vaccinated nearest neighbors, respectively, relative to a baseline provided by the

random model. Values for two games are reported: the basic model on an Erdös–Rènyi graph (M1) and the simple local behavioral model an Erdös–Rènyi graph (M2). The results reveal that non-vaccinators are less likely to cluster together and that vaccinators are more likely to cluster together under both models. Moreover, M2 exhibits greater clustering of vaccinators and slightly more clustering of non-vaccinators than M1. Although these effects may seem small, they are statistically significant.

The reason we see a significant difference in clustering between the two models is subtle but illustrates why considering network structure in vaccination decision models is important. Take the susceptible (non-vaccinating) population, for example, in the simple local model an individual who is not very connected will tend to be less vulnerable and, over time, will be less likely to vaccinate. If this individual observes that his/her alters are not getting infected either then his/her probability to vaccinate decreases more rapidly. It is also likely that his/her alters are not being infected that often because they are also not highly connected. This is in sharp contrast to the process at play in M1, whereby the vaccination and infection history of an individual's alters do not directly influence that individual's own decision to vaccinate. While the non-vaccinators are slightly more clustered in M2 than in M1, they are nested within smaller clusters that are more sparsely connected than in M1. Thus, M1 gives rise to greater connectivity among subgraph clusters of susceptible individuals than M2. To test this, we compare the two models' average local structure for susceptible individuals at each instance of G from time 0 to time 300 ($G_0 \ldots G_{300}$). We expect that, averaging over all 300 seasons, the mean degree of nearest neighbors ($\langle knn \rangle$) in each cluster of susceptible individuals will be greater for M1 than M2. Indeed, we find that $\langle knn \rangle$ is 4.435 for M1, and 3.278 for M2 ($t = 38.2192, df = 596.192, p - value < 2.2e^{-16}$).

7 Discussion and Conclusion

Influenza is the leading cause of death among vaccine-preventable diseases in the USA, and is responsible for more than $10 billion in direct medical expenses and $16 billion in lost potential earnings annually [28]. As of February 2010, annual influenza vaccination has been recommended for all people in the USA aged 6 months and older. However, vaccination rates are well below this target, with less than 40% of the population receiving the vaccine each year [29]. An individual's decision to get vaccinated is affected by the trade-off between perceived risk of influenza infection and perceived benefits and risks of vaccination. Such perceptions can be influenced by past experiences, both one's own and those in one's social network, as well as media coverage. Given the suboptimal rates of annual influenza vaccination, we need a better understanding of how vaccination decisions and prevalence of influenza infections influence each other. Such information would help to better inform public health policy by allowing interventions to increase influenza vaccination coverage.

In this chapter, we presented the inductive reasoning game first introduced in [16] that models the interplay between influenza vaccination decisions and influenza epidemiology. The basic model introduces a simple construct where individuals' propensity to obtain vaccinations depends on personal experiences with getting infected in the past, as well as the overall epidemiological outcome of whether or not an epidemic occurred. The vaccination coverage that results from the collective actions of the population affects whether or not non-vaccinated individuals get infected, as well as determining the conditions for an epidemic. The achieved vaccination coverage changes individual propensities to seek vaccinations for the following year, which in turn determines that years' vaccination coverage.[8] The basic model showed that individuals' vaccination behavior, based on learning and adaptation, can lead to cyclic dynamics in vaccination coverage where severe epidemics may result even in the absence of a pandemic strain.

As we have seen, public health programs based on incentives could be used to promote vaccination and prevent the occurrence of severe epidemics. The basic model showed that public health intervention programs that focus on vaccinating families are likely to increase the frequency of severe epidemics. This result is explained by the fact that when the number of independent decision-makers is reduced, groups of individuals make the same vaccination decisions year after year. Then, following many years of non-severe epidemics, complacency to vaccination emerges, which causes many groups of individuals to forgo vaccination, resulting in a severe epidemic. If this effect is a real, the implication of our finding go beyond the potential success of a family-based incentive. Surveys show that many individuals follow the advice of their family physician when deciding to vaccinate [31]. The basic model indicates that if physicians base vaccination recommendations on their past influenza experiences and observations, such as how many patients showed influenza symptoms in the previous year, then the frequency of severe epidemics might increase. In contrast, when the basic model is used to model commitment-based incentives where individuals who are inclined to get vaccinated enter a program that provides vaccinations for multiple years, we find that severe epidemics can be prevented. However, the duration of the commitment is crucial in determining the success of the program. The likelihood of program success increases when the duration of commitment is similar to the number of years of experience an individual considers when evaluating the necessity to get vaccinated. If the program is longer, the model indicates that the severity of the epidemic increases. This result also has implications for the potential success of a universal influenza vaccine [32]. The development of such a vaccine, which would protect against many seasonal and pandemic flu strains for many years, has become a real

[8]This seemingly simple construct provides an example of what is known as a *complex-adaptive system* [30] since the emergence of the vaccination coverage (i.e., a macroscopic quantity) provides different types of feedback to the individuals (i.e., the microscopic agents) depending on both its achieved value and the actions taken by each individual.

possibility [33, 34]. The basic model with a commitment-based incentive suggests that a universal vaccine should be tailored to provide protection for a few years at most, in order to avoid increased complacency.

We have also presented recent work by Breban that modified the basic model so that individuals are made aware of more epidemiological information (e.g., incidence, coverage, or both) at the end of each flu season [18]. In this model, individuals who would not be likely to get vaccinated combine these pieces of epidemiological information and use them to evaluate the necessity of vaccination. We have seen that although it is unlikely that epidemics can be prevented by the release of more epidemiological information by the media, the cyclic dynamics of vaccination coverage, which results in periodic severe epidemics, can be suppressed. In particular this goal can be achieved if individuals who obtain vaccinations perceive both the personal benefit of vaccination and the social benefit of providing added protection for those who did not choose to be vaccinated.

Mathematically, these results can be analyzed and understood via a mean-field approach. For the basic model, we have presented and analyzed an iterative map of the vaccination coverage dynamics. We found that for biologically plausible parameters, the dynamics tend to approach the critical vaccination coverage from below. However, from time to time, the stochastic nature of the dynamics causes the vaccination coverage to fluctuate above the critical level. This upward fluctuation is then followed by a collapse of the vaccination coverage in the subsequent year, which results in a severe epidemic. When we reduce the number of independent decision-makers and allow groups of individuals to act together, stochastic fluctuations become larger. These larger fluctuations increase the frequency with which the vaccination rate exceeds the critical vaccination coverage level and triggers a severe epidemic the following year. When individuals enter an incentive-based program to obtain vaccinations for multiple years, the dynamics fundamentally change from fluctuation-sensitive to fluctuation-robust. Periodicity still occurs, but it is explained deterministically by a period doubling process of the iterative map. When mass media releases more epidemiological information, and individuals who normally obtain vaccinations use these to evaluate the necessity of vaccination, the iterative map produces a stable fixed point that is below the critical vaccination coverage. Consequently, fluctuations above the critical coverage becomes less likely and severe epidemics are suppressed.

We have also presented some first observations of the effects of combining a social network with our inductive reasoning game model for vaccination. We have found that network models offer great potential for understanding how individual decisions are constrained by social structure. While we acknowledge that the particular network we used, the Erdös–Rènyi graph, is a simplistic model of interpersonal contact, we also emphasize that our results show that networks affect the learning and adaptation process of individuals' vaccination behavior. Throughout this chapter we have referred to the critical vaccination coverage as the vaccination coverage required if individuals were uniformly mixed with no underlying network. However, as we have seen being connected to others, even in a simple world where no information is shared between alters and vaccination decisions are solely based

on individual infection experience and knowing whether or not there was a recent epidemic, reduces the effective critical vaccination coverage necessary to prevent an epidemic in a population. Furthermore, over the years we see that individuals who tend to vaccinate cluster together and that this clustering will vary depending on model choice.

In conclusion, memory and adaptation are principle biological and social attributes of individuals. Consequently, including a learning process in models of recurring voluntary vaccination is essential. However, many other social-cognitive factors influence vaccination motivation and participation [31]. Although recent survey-based studies suggest that past vaccination behavior strongly influences future intentions to vaccinate [35–37], the extent to which individuals learn from past experiences with the flu and its vaccine and use these experiences to modify their vaccination behavior is still unclear. These experiences could include a combination of personal experiences, observations of flu cases and vaccinations in their social network, and epidemiological information reported by mass media. The importance of each of these factors in contributing to the formation of risk perceptions remains an open question. Furthermore, the basic model assumes that individuals are self-interested and try to avoid the flu, preferably without getting vaccinated. Therefore, they are led to try to take advantage of herd immunity. However, the extent to which individuals are consciously or subconsciously aware of the concept of herd immunity is also still unclear. A recent survey by the ;American Life Panel at the RAND Corporation hopes to shed some light on these important behavioral issues. We hope to use the analyses of these survey data together with realistic social contact networks to construct a more sophisticated inductive reasoning game model of influenza vaccination and use it to test public health policies based on incentives.

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References

1. Fine, P.E.M.: Epidemiol. Rev. **15**, 265 (1993)
2. Groves, T., Ledyard, J.: Econometrica **45**, 783 (1977)
3. Funk, S., Salathé, M., Jansen, V.A.A.: J. R. Soc. Interface **7**, 1247 (2010)
4. Geoffard, P.Y., Philipson, T.: Am. Econ. Rev. **87**, 222 (1997)
5. Bozzette, S.A., Boer, R., Bhatnagar, V., Brower, J.L., Keeler, E.B., Morton, S.C., Stoto, M.A.: N. Engl. J. Med. **348**, 416 (2003)
6. Valle, S.D., Hethcote, H., Hyman, J.M., Castillo-Chavez, C.: Math. Biosci. **195**, 228 (2005)
7. Bauch, C.T., Earn, D.J.: Proc. Natl. Acad. Sci. USA **101**, 13391 (2004)
8. Bauch, C.T., Galvani, A.P., Earn, D.J.: Proc. Natl. Acad. Sci. USA **100**, 10564 (2003)

9. Manfredi, P., Posta, P.D., d'Onofrio, A., Salinelli, E., Centrone, F., Meo, C. Poletti, P.: Vaccine **28**, 98 (2009)
10. Reluga, T.C., Bauch, C.T., Galvani, A.P.: Math. Biosci. **204**, 185 (2006)
11. Bauch, C.T.: Proc. Biol. Sci. **272**, 1669 (2005)
12. d'Onofrio, A., Manfredi, P., Salinelli, E.: Theor. Popul. Biol. **71**, 301 (2007)
13. Buonomo, B., D'Onofrio, A., Lacitignola, D.: Math. Biosci. **216**, 9 (2008)
14. Arthur, W.B.: Amer. Econ. Review **84**, 406 (1994)
15. Challet, D., Marsili, M., Zhang, Y.-C.: Minority games: Oxford finance. Oxford University Press, Oxford, New York (2005): Book Oxford finance. ill.; 25 cm. Includes bibliographical references (p. [335]-342) and index. English
16. Vardavas, R., Breban, R., Blower, S.: PLoS Comput. Biol. **3**, e85 (2007)
17. Breban, R., Vardavas, R., Blower, S.: Phys. Rev. E. Stat. Nonlin. Soft. Matter Phys. **76**, 031127 (2007)
18. Breban, R.: PLoS One **6**, e28300 (2011)
19. Barrat, A., Barthelemy, M., Vespignani, A.: Dynamical Processes on Complex Networks. Cambridge University Press, Cambridge (2008)
20. Perisic, A., Bauch, C.T.: PLoS Comput. Biol. **5**, e1000280 (2009)
21. Perisic, A., Bauch, C.T.: BMC Infect. Dis. **9**, 77 (2009)
22. Salathé, M., Jones, J.H.: PLoS Comput. Biol. **6**, e1000736 (2010)
23. Fu, F., Rosenbloom, D.I., Wang, L., Nowak, M.A.: Proc. Biol. Sci. **278**, 42 (2011)
24. Cornforth, D.M., Reluga, T.C., Shim, E., Bauch, C.T., Galvani, A.P., Meyers, L.A.: PLoS Comput. Biol. **7**, e1001062 (2011)
25. Mills, C.E., Robins, J.M., Lipsitch, M.: Nature **432**, 904 (2004): 1476-4687 (Electronic) Historical Article Journal Article
26. Erdös, P., Rényi, A.: Publicationes Mathematicae **6**, 290 (1959)
27. Newman, M.E.J.: Phys. Rev. E. Stat. Nonlin. Soft. Matter Phys. **66**, 016128 (2002)
28. Molinari, N.-A.M., Ortega-Sanchez, I.R., Messonnier, M.L., Thompson, W.W., Wortley, P.M., Weintraub, E., Bridges, C.B.: Vaccine **25**, 5086 (2007)
29. Fiore, A.E., Shay, D.K., Broder, K., Iskander, J.K., Uyeki, T.M., Mootrey, G., Bresee, J.S., Cox, N.J.: C. for Disease Control, Prevention: MMWR Recomm. Rep. **58**, 1 (2009)
30. Miller, J., Page, S.: Complex Adaptive Systems: An Introduction to Computational Models of Social Life. Princeton University Press, Princeton (2007)
31. Szucs, T.D., Muller, D.: Vaccine **23**, 5055 (2005) 0264-410X (Print) Journal Article
32. Vardavas, R., Breban, R., Blower, S.: BMC Res. Notes **3**, 92 (2010)
33. Chen, G.L., Subbarao, K.: Nat. Med. **15**, 1251 (2009)
34. Du, L., Zhou, Y., Jiang, S.: Microbes Infect. **12**, 280 (2010)
35. Maurer, J., Harris, K.M., Parker, A., Lurie, N.: Vaccine **27**, 5732 (2009)
36. Ernsting, A., Lippke, S., Schwarzer, R., Schneider, M.: Adv. Prev. Med. **2011**, 148934 (2011)
37. Gidengil, C.A., Parker, A.M., Zikmund-Fisher, B.J.: Am. J. Public Health **102**, 672 (2012)

Modeling Voluntary Influenza Vaccination Using an Age-Structured Inductive Reasoning Game

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Abstract Recently, the impact of social behavior on the dynamics of voluntary vaccination coverage against seasonal influenza has been modeled using inductive reasoning games. This modeling technique allows for a natural approach to describing decision making, experience, and adaptation of individuals. However, so far, age structure has not been included in this type of models, despite the fundamental role that age plays in influenza epidemiology. Here, we build on the previous mathematical framework to include this feature missing from inductive reasoning games. Then, we discuss several results in contrast to previously developed theory. We find that including age structure may impact on the game dynamics not only for epidemiological, but also behavioral reasons. Although implausible for realistic parameter values, age structure allows for the possibility that individuals eliminate influenza through voluntary vaccination. Furthermore, we find that, in this case, period doubling is not the only type of generic bifurcation that could account for the stability loss of mean-field fixed-point dynamics of the vaccination coverage. Our study emphasizes the importance of including age structure in predictive models of voluntary vaccination against seasonal influenza.

1 Introduction

In the developed world, campaigns of voluntary vaccination rarely run into logistic problems: vaccines go hardly out of stock and qualified medical personnel is constantly available. Hence, the success of voluntary vaccination depends very much on human behavior, because individuals learn and adapt to maximize their personal benefit even when participating to public health programs for the common good.

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Game theory provides methods for the mathematical study of models of conflict and cooperation between intelligent, rational, adaptive decision makers. Although its major applications are in the fields of economics and political science, game theory has also offered a proper framework for modeling the impact of social behavior on the vaccination coverage—i.e., the proportion of the population that gets vaccinated—in countries of the developed world. Deductive reasoning games have been used to predict the voluntary vaccination coverage for pathogens that provide permanent immunity [1–5]. In the case of pathogens that do not provide permanent immunity, modeling studies have focused on influenza. Human behavior is particularly important for vaccination against influenza, which is a seasonal disease and remains a continual epidemic and pandemic threat. In this case, individuals make yearly vaccination decisions that are potentially biased by their perception of costs versus benefits of vaccination.

Several ideas of modeling influenza vaccination have been investigated. An evolutionary game was proposed where an individual copies the vaccination strategy of another with a probability depending on the success of the vaccination strategy [6]. A different approach is that based on inductive reasoning games [7] initially applied to modeling financial markets [8]. In this case, it is assumed that individuals make repeated vaccination decisions based on their expectations about future epidemics that are, in turn, determined by their collective vaccination coverage. Inductive reasoning games were applied to understanding the dynamics of influenza vaccination coverage assuming both homogeneous mixing of individuals [9–11] and mixing through complex contact networks [12].

Inductive reasoning games proved very instrumental in capturing the interplay of many fundamental concepts for the dynamics of the influenza vaccination coverage, such as (1) decision making based on past experience with vaccination, (2) competition for profiting from the immunity of others and avoiding vaccination (i.e., so-called *free-riding on herd immunity*), (3) cooperation to reduce the severity of epidemics, and (4) self-interested behavior and avoiding vaccination when epidemics are prevented [9–12]. Furthermore, inductive reasoning games have shown that public health programs ignoring behavioral aspects may have counterintuitive effects and sometimes make epidemics worse [9, 10]. However, they remain, so far, toy models of influenza vaccination because, for reasons of tractability, they ignore various practical behavioral and epidemiological issues and lose quantitative prediction power. For example, in absence of thorough empirical studies, the public perception of costs versus benefits of vaccination remains poorly modeled, subject to working assumptions [11]. Another major limitation is the lack of age structure, even though age structure is recognized as a fundamental feature of influenza epidemiology [13].

The purpose of this work is to introduce and discuss, for the first time, an inductive reasoning game with age structure as model for the dynamics of vaccination coverage against seasonal influenza. This modeling feature has already been implemented in compartmental models of seasonal influenza expressed using ordinary differential equations [14, 15] or stochastic processes [16]. Previous work has used age structure for accurate descriptions of influenza susceptibility, morbidity

and mixing patterns [14–16] which we also address in this work. In addition, our game theoretic framework allows for the study of how age impacts on the perceived costs versus benefits of vaccination.

2 Model Definition

Our model is defined by assumptions which we present below grouped into three broad categories: demographic, epidemiologic, and behavioral. We explain how the assumptions were made with regard to real world data and formalize them mathematically. Then, we investigate the model analytically and discuss the impact of age structure in contrast to results obtained for models lacking this feature [9–11].

2.1 Demographic Assumptions

To establish the age distribution of the game players, we investigated recent demographical data about developed countries. In these settings, the probability of survival up to a certain age as a function of age (i.e., so-called *survival function*) is well approximated by a rectangular shape, remaining close to one up to nearly the life expectancy then dropping abruptly to zero [17]. Furthermore, survival functions of developed countries are expected to become even more rectangular in the future [18, 19]. Typically, age distributions are reported as *age pyramids* which consist of two back-to-back histograms, with the population plotted on the horizontal axis and age on the vertical axis, one reporting on males and the other on females [20]. For developed countries, age pyramids have tall, nearly parallel walls and nearly flat tops [20], suggesting a stable population with long life expectancy that dies of old age. Hence, we propose the following demographic assumption.

Assumption D 1: We consider a number of N individuals that make yearly vaccination decisions. Their age pyramid is rectangular; i.e., ages are uniformly distributed with the discrete support $\{1,2,3,\ldots A\}$ with N/A individuals of each age, where A is the maximum age reached by the individuals.

2.2 Epidemiologic Assumptions

Compartmental models of influenza transmission typically have a *susceptible-infected-recovered* (*SIR*) or a *susceptible-exposed-infected-recovered* (*SEIR*) structure which reveals the existence of an epidemic threshold expressed by the basic reproduction ratio of the model, R_0—i.e., if $R_0 > 1$, an outbreak becomes an epidemic, otherwise, the outbreak goes extinct. Analysis of age-structured models

of influenza epidemics [14] yields essentially the same basic structure providing that all ages mix (i.e., the mixing matrix between age groups is not block-diagonal). If the model also includes vaccination, it is found that various configurations of the age-stratified vaccination coverage may render $R_0 < 1$, preventing epidemics (see, e.g., [22] Part I.7 and [23]).

Our game theoretic model includes an unrestrictive axiomatic description of this threshold phenomenon. We denote by q_a the probability that unvaccinated individuals aged a eventually become infected during the course of an epidemic and by p_a the fraction of individuals of age a that got vaccinated. We also introduce the vector notation $\mathbf{p} \equiv (p_1, p_2, \ldots, p_A)$ to refer to all the components of the age-stratified coverage. The equation $R_0(\mathbf{p}) = 1$ provides a constraint that typically defines a compact manifold, called *threshold surface* [23], dividing the space $\mathscr{P} \equiv [0,1]^A$ of all age-stratified coverage configurations into two disjoint domains:

$$\mathscr{P}_- \equiv \{\mathbf{p} \in \mathscr{P} : R_0(\mathbf{p}) < 1\}, \quad \mathscr{P}_+ \equiv \{\mathbf{p} \in \mathscr{P} : R_0(\mathbf{p}) > 1\}, \tag{1}$$

where vaccination succeeds or fails to prevent epidemics, respectively. We use the notation $\partial \mathscr{P}_\pm$ for the boundaries of the domains $\mathscr{P}_\pm$, and $\tilde{\mathscr{P}}_\pm$ for $\partial \mathscr{P}_\pm \cup \mathscr{P}_\pm$.

As a function of $\mathbf{p}$, q_a must illustrate the epidemic threshold and a herd immunity effect (i.e., overall protection increases if coverage increases in one age group and remains the same in all others). As a function of a, q_a must illustrate the age-dependent susceptibility to influenza infection. Studies of animal populations [24], animal models of human influenza [25], and surveillance data about human communities suggest [13] that the early and the elderly ages are more susceptible than the adults. All these conditions are formulated mathematically by the following assumptions.

Assumption E 1: $q_a(\cdot) : \mathscr{P} \to [0,1]$ is continuous. We also require that $q_a(\cdot)$ is differentiable everywhere in the domain except on the threshold surface $R_0(\mathbf{p})=1$.

Assumption E 2: $q_a(\mathbf{p}) = 0, \forall \mathbf{p} \in \mathscr{P}_-$, $q_a((0,0,\ldots,0)) < 1$, and $\partial q_a(\mathbf{p})/\partial p_b < 0$, $\forall \mathbf{p} \in \mathscr{P}_+$, $\forall a, b \in \{1,2,\ldots,A\}$.

Assumption E 3: $q_a(\mathbf{p})$ is a decreasing function of a for a close to 1, and an increasing function of a for a close to A.

We also assume that the vaccine offers complete protection against influenza infection for one season for two reasons. First, the efficacy of the influenza vaccine is quite high, in the range of 70–90 % [26]. Second, effects of imperfect vaccines may be accounted by increasing the value of the critical vaccination coverage.

We may obtain functions $q_a(\cdot)$ in agreement with Assumptions E1–E3 from a paradigm within-season influenza epidemic model with age structure and preseason vaccination. Consider the following *SIR* model without vital dynamics (i.e., no births, deaths, or aging)

$$\mathrm{d}S_a/dt = -\sum_{b=1}^{A} \beta_{ab} S_a I_b, \tag{2}$$

$$\mathrm{d}I_a/\mathrm{d}t = \sum_{b=1}^{A} \beta_{ab} S_a I_b - \gamma_a I_a, \tag{3}$$

$$\mathrm{d}R_a/\mathrm{d}t = \gamma_a R_a, \tag{4}$$

$$\mathrm{d}V_a/\mathrm{d}t = 0, \tag{5}$$

where S_a, I_a, R_a, and V_a represent the number of susceptible, infected, recovered, and vaccinated individuals of age a, respectively. The notation γ_a represents the age-stratified recovery rate and β_{ab} are the elements of the "who acquires infection from whom" (WAIFW) matrix (c.f., [21] and [22] Part I.9.2). Another option would be to use the slightly more complex age-stratified influenza model presented in [14] and include vaccination. However, the computation of $q_a(\cdot)$ would proceed similarly, as we illustrate bellow.

We assume that at the beginning of each season, $p_a N/A$ individuals of age a vaccinate, while $S_a(0) = N(1-p_a)/A$ remain susceptible. Equation 3 shows that epidemics are averted starting with the beginning of the season if and only if the matrix with the elements $\beta_{ab} S_a(0) - \mathbf{1}_{ab}\gamma_a$ (where $\mathbf{1}_{ab}$ are the elements of the unit matrix and $a, b = 1, \ldots, A$) has all the eigenvalues less than zero. The condition that the largest eigenvalue equals zero is equivalent to the condition that $R_0 = 1$. Hence, $\mathscr{P}_-$ is the region in $\mathscr{P}$ where all eigenvalues are negative and $\mathscr{P}_+$ is the region where at least one eigenvalue is positive. The function $q_a(\cdot)$ is then given by the cumulative number of cases in age group a over the duration of the season divided by the size of the age group

$$q_a(\mathbf{p}) = \int_0^T \frac{\sum_{b=1}^{A} \beta_{ab} S_a I_b}{N/A} \mathrm{d}t, \tag{6}$$

where by T we denoted the duration of the influenza season. Of note, for an *SIR* model without age structure, it was found that $q(p)$ is approximately piece-wise linear [9].

2.3 Behavioral Assumptions

The game theoretic core of our model is defined for a large population of self-interested individuals according to the principles of the inductive reasoning games [9–12]. The game proceeds in two steps per influenza season. The first step is at the beginning of the season when every individual makes his vaccination decision depending on his experience with flu vaccination. An epidemic may occur every influenza season, depending on the achieved $R_0(\mathbf{p})$. The second step is at the end of the influenza season when every individual scores his last vaccination decision.

We assume that, if he did not get vaccinated, an individual evaluates their decision favorably if they avoided infection and unfavorably if he got infected. Vaccinated individuals establish the scores of their decisions based on the available epidemiological information. Then, each individual updates his vaccination experience using the score of his last vaccination decision. (For early ages, it is assumed that the decisions and the experience updates are made by the guardian of the individual.) The whole process repeats in the next influenza season. Explicit mathematical assumptions are provided below.

Assumption B 1: The interest of the individuals is to avoid getting infected, preferably without having to vaccinate. They act in their own interest and do not communicate their vaccination decisions to each other.

Assumption B 2: To make his vaccination decision, each individual uses his past experience of vaccination outcomes. Thus, individuals independently decide whether or not to vaccinate using inductive reasoning. A factor s determines how important his previous vaccination outcomes are with respect to his most recent vaccination outcome ($0 \leq s \leq 1$).

Assumption B 3: We define a vaccination decision of an individual of age a as a realization $x_n^{(i_a)}$ of a Bernoulli variable with parameter $w_n^{(i_a)}$, where $w_n^{(i_a)}$ is the probability that individual i_a vaccinates in season n. In turn, $w_n^{(i_a)}$ further depends on a variable $v_n^{(i_a)}$ that characterizes the *pro-vaccination experience* of the i_ath individual (see details in Assumption B7). The indices i_a and n are positive integers; $i_a = 1, 2, \ldots, N/A$ labels the individual of age a and $n \geq 0$ labels the season. If individual i_a decides to get vaccinated in season n then $x_n^{(i_a)} = c_a$, otherwise $x_n^{(i_a)} = 0$. The variable c_a represents the *cost of infection* and depends on age similarly to the probability of infection q_a (see Assumption E3). The domains of the variables are as follows: $x_n^{(i_a)} \in \{0,1\}$, $w_n^{(i_a)} \in [0,1]$, $c_a \in [0,1]$, and $v_n^{(i_a)} \in [0, 1/\sum_{a=1}^{A} c_a s^{A-a}]$.

Assumption B 4: Newborns join society with no vaccination experience and a constant probability of vaccination given by public health guidelines; i.e., $w_n^{(i_1)} \equiv \varepsilon = \text{const}$.

Assumption B 5: In year n, a set of N vaccination decisions is made $\{x_n^{(i_a)}; 1 \leq i_a \leq N/A, 1 \leq a \leq A\}$, which, together with the pro-vaccination experiences in year n, determines the pro-vaccination experiences of all individuals in year $(n+1)$, $\{v_{n+1}^{(i_a)}; 1 \leq i_a \leq N/A, 1 \leq a \leq A\}$. In turn, the pro-vaccination in year $(n+1)$ determine $\{w_{n+1}^{(i_a)}; 1 \leq i \leq N/A, 1 \leq a \leq A\}$, the parameters of the Bernoulli variables in year $(n+1)$. Hence, the set of vaccination decisions in year $(n+1)$ is obtained $\{x_{n+1}^{(i_a)}, 1 \leq i \leq N/A, 1 \leq a \leq A\}$. Our inductive reasoning game is an array of sets of vaccination decisions.

Assumption B 6: The infection event of individual i_a in year n is described by a variable $z_n^{(i_a)}$. (If individual i_a got infected in season n then $z_n^{(i_a)} = 1$, otherwise

$z_n^{(i)} = 0$.) The infection process is as follows. If $x_n^{(i_a)} = 1$ then $z_n^{(i_a)} = 0$. If $x_n^{(i_a)} = 0$, then $z_n^{(i_a)}$ is a realization of a Bernoulli variable with parameter $q_a(\mathbf{p}_n)$. That is, if individuals vaccinate of age a, they are fully protected, otherwise they risk infection with probability $q_a(\mathbf{p}_n)$.

Assumption B 7: At the end of the influenza season of year n, each individual provides a score between 0 and 1 for his vaccination decision $x_n^{(i_a)}$ based on his infection status $z_n^{(i_a)}$ and available epidemiological information. We have three cases: (a1) if $x_n^{(i_a)} = 0$ and $z_n^{(i_a)} = 1$ then the score is c_a and $v_{n+1}^{(i_{a+1})} = sv_n^{(i_a)} + c_a$; i.e., if individual i did not get vaccinated and got infected, then he considers that the vaccination would have been necessary to avoid the cost of infection c_a; (a2) if $x_n^{(i)} = 0$ and $z_n^{(i)} = 0$ then the score is 0 and $v_{n+1}^{(i_{a+1})} = sv_n^{(i_a)}$; which means that if individual i did not get vaccinated and did not get infected, then he considers that the vaccination was unnecessary and (b) if $x_n^{(i_a)} = 1$, then the score of the vaccination decision is $F_a(\mathbf{p}_n)$ and $v_{n+1}^{(i_{a+1})} = sv_n^{(i_a)} + F_a(\mathbf{p}_n)$. That is, if individual i_a got vaccinated then he did not get infected and uses epidemiological information to evaluate their vaccination decision (see discussion below).

Assumption B 8: The probability that an individual chooses to get vaccinated is updated as follows:

$$w_{n+1}^{(i_a)} = v_{n+1}^{(i_a)} / \sum_{\alpha=1}^{a} c_\alpha s^{a-\alpha}. \tag{7}$$

That is, an individual's probability to get vaccinated in the next season is given by the updated cumulative vaccination experience. We have normalized $v_{n+1}^{(i_a)}$ by $\sum_{\alpha=1}^{a} c_\alpha s^{a-\alpha}$ because this factor is the maximum value of $v_{n+1}^{(i_a)}$ if individual i_a benefited from vaccination in all seasons up to age a.

The score function $F_a(\cdot)$ may be interpreted as the *perceived benefit of vaccination*, normalized between 0 and 1. It depends both on the epidemiological information available to vaccinated individuals, which we express in terms of the age-stratified vaccination coverage, and how they react to this information. Such a function could be grounded in terms of how individuals seek to maximize their utility, given their estimates of infection risk. We make assumptions on the analytic form of $F_a(\cdot)$ to reflect the fact that the individual tries to benefit from herd immunity and that he is not fully satisfied to have had vaccinated when epidemics were prevented [11].

Assumption BF 1: $F_a : \mathscr{P} \to [0,1]$ is continuous and differentiable everywhere in the domain except on the threshold surface $R_0(\mathbf{p}) = 1$.

Assumption BF 2: $\partial F_a(\mathbf{p})/\partial p_\alpha \leq 0$, $\forall a, \alpha \in \{1,2,\ldots,A\}$, wherever $F(\cdot)$ is differentiable. That is, individuals try to benefit from herd immunity; as coverage increases, the pro-vaccination experience gained by individuals who got vaccinated decreases.

Assumption BF 3: $F_a(\mathbf{p}) < 1, \forall a \in \{1,2,\ldots,A\}, \forall \mathbf{p} \in \mathscr{P}_+$. That is, individuals are not fully satisfied to have had vaccinated when epidemics were prevented.

3 Results

We follow the strategy of previous work [10, 11] and develop the mean-field approximation (i.e., the limit of large populations, $N \to \infty$) of the dynamics of the expected coverage predicted by the inductive reasoning game. Then, we proceed by analyzing the resulting deterministic dynamical system.

3.1 Mean-Field Approximation of the Coverage Dynamics

We denote by $\langle \cdot \rangle$ the average over the realizations of the game in the mean-field approximation and introduce the variable $\mathbf{m}_n \equiv \langle \mathbf{p}_n \rangle$ for the expected age-stratified vaccination coverage. By an argument similar to that employed in previous work [10, 11], the dynamics of $\mathbf{p}_n$ at large finite N can be approximated by adding Gaussian noise with amplitude $\sim \sqrt{N^{-1}}$ to the dynamics of $\mathbf{m}_n$. However, in most of the phase space of $\mathbf{m}$, the noise will not change the qualitative dynamics of the orbit and mean field will be a suitable approximation. Furthermore, since the noise amplitude is small and $q_a(\cdot)$ and $F_a(\cdot)$ are continuous, we have $\langle q_a(\mathbf{p}) \rangle \approx q_a(\mathbf{m})$ and $\langle F_a(\mathbf{p}) \rangle \approx F_a(\mathbf{m})$.

From the definition of p_n^a, we immediately obtain $m_n^a = \sum_{i_a=1}^{N/A} \langle w_n^{(i_a)} \rangle / (N/A)$. According to Assumption 7, it is straightforward to arrive at the following equations based on the scoring tree for vaccination decisions of individuals of age a:

branch	expected population fraction	expected $v^{(i_a)}$ update
(a1)	$(1-m_n^a)q_a(m_n)$	$v_{n+1}^{(i_{a+1})} = s v_n^{(i_a)} + c_a;$
(a2)	$(1-m_n^a)[1-q_a(m_n)]$	$v_{n+1}^{(i_{a+1})} = s v_n^{(i_a)};$
(b)	m_n^a	$v_{n+1}^{(i_{a+1})} = s v_n^{(i_a)} + F_a(m_n).$

(8)

The weighted average of Eq. 8 yields

$$u_{n+1}^{a+1} = s u_n^a + (1-m_n^a) c_a q_a(\mathbf{m}_n) + m_n^a F_a(\mathbf{m}_n), \tag{9}$$

where u^a denotes the average of $v^{(i_a)}$ over the population of age a. Taking the population average of Eq. 7, we obtain

$$m_{n+1}^{a+1} = u_{n+1}^{a+1} / \sum_{\alpha=1}^{a} c_\alpha s^{a-\alpha}. \tag{10}$$

Combining Eqs. 9 and 10, and using the fact that $m_{n+1}^1 = \varepsilon$, we obtain the mean-field approximation of the coverage dynamics of the inductive reasoning game

$$m_{n+1}^{a+1} = sm_n^a + [(1 - m_n^a)c_a q_a(\mathbf{m}_n) + m_n^a F_a(\mathbf{m}_n)] / \sum_{\alpha=1}^{a} (c_\alpha s^{a-\alpha}), \tag{11}$$

a dynamical system defined on the phase space of the age-stratified expected coverage $\mathscr{P}$.

3.2 On the Achieved Coverage When Epidemics Are Prevented

Proposition 1: *The mean-field model given by Eq. 9 predicts that epidemics could be always prevented if and only if the following dynamical system*

$$m_{n+1}^{a+1} = m_n^a \left[s + F_a(\mathbf{m}_n) / \sum_{\alpha=1}^{a} (c_\alpha s^{a-\alpha}) \right], \tag{12}$$

where $m_{n+1}^1 = \varepsilon$, *has an attractor in* $\mathscr{P}_-$.

Proof: The above dynamical system represents the restriction of the mean-field model (c.f., Eq. 11) to $\mathscr{P}_-$ where $q_a(\mathbf{m}) = 0$. Hence, if it has an attractor in $\mathscr{P}_-$, then the mean-field model has an attractor in $\mathscr{P}_-$ where $R_0(\mathbf{m}) < 1$ and epidemics are prevented. That is, the evolution of the coverage may assure that epidemics are prevented for all time given suitable initial conditions. □

Remark 1: Previous inductive reasoning games have ignored age structure in modeling voluntary vaccination against seasonal influenza. Within a general axiomatic framework similar to the one employed here, they yield mean-field approximations whose restriction to $\mathscr{P}_-$ converge to zero coverage, which belongs to $\mathscr{P}_+$ (see [11], Proposition 1). Hence, inductive reasoning games without age structure predict that, under very general conditions, voluntary vaccination will fail to eliminate influenza epidemics every season.

Remark 2: Including age structure in an inductive reasoning game suggests that voluntary vaccination could be efficient in always preventing influenza epidemics. To make this result more transparent, we consider a simple example where the perceived benefit of vaccination is proportional to the individual-level risk of infection $F_a(\mathbf{m}) \propto q_a(\mathbf{m})$ [11]. Hence, Eq. 12 becomes

$$m_{n+1}^{a+1} = sm_n^a, \tag{13}$$

a dynamical system with the following fixed-point attractor:

$$\hat{\mathbf{m}} = \{\varepsilon, s\varepsilon, \ldots s^{A-1}\varepsilon\}. \tag{14}$$

If $\hat{\mathbf{m}} \in \mathscr{P}_-$, then epidemics are always prevented; this could, in principle, be the case for large values of ε and s.

Remark 3: We recall that s represents a memory parameter that weights the previous vaccination experience with respect to the most recent vaccination outcome; i.e., for $s = 0.7$ [9], last year's memories about vaccination outcome contribute 70 % toward the total vaccination experience and previous to last year's memories only 49 %. It is unlikely that, for $s = 0.7$, $\hat{\mathbf{m}}$ belongs to $\mathscr{P}_-$ when $F_a(\mathbf{m}) \propto q_a(\mathbf{m})$, even if $\varepsilon = 1$. Assuming $A = 80$ years, the coverage over all age groups is $\sum_{a=1}^{A} \hat{m}_a/A \approx 4.2\,\%$, much less than the critical vaccination coverage for seasonal influenza estimated at 50–70 % [9]. Hence, it is unlikely that, under reasonable parameterization, the age stratified coverage $\hat{\mathbf{m}}$ given by Eq. 14 would prevent influenza epidemics.

3.3 Analysis of an Example Model

Proposition 2: *Consider* $F_a(\mathbf{m}) = c_a q_a(\mathbf{m})$ *and* $s = 0$. *Then the following statements hold.*

(1) The mean-field model given by Eq. 11 becomes

$$m_{n+1}^{a+1} = q_a(\mathbf{m}_n), \tag{15}$$

where $m_{n+1}^1 = \varepsilon$.

(2) The model may only have $\hat{\mathbf{m}}_- = \{\varepsilon, 0, 0, \ldots, 0\}$ *as an attractor in* $\tilde{\mathscr{P}}_-$.

(3) If $\hat{\mathbf{m}}_-$ *does not belong to* $\tilde{\mathscr{P}}_-$, *then there exists a unique fixed point* $\hat{\mathbf{m}}_+$ *in* $\tilde{\mathscr{P}}_+$.

Proof: (1) Equation 15 is obtained by making the appropriate substitutions in Eq. 9.

(2) This result follows directly from the discussion in Sect. 3.2. □

(3) The fixed-point equations are

$$m_+^{a+1} = q_a(\mathbf{m}_+). \tag{16}$$

Because $m_+^1 = \varepsilon$, we relabel the components of $\hat{\mathbf{m}}_+$ using the shift $a \to a - 1$. Since each function $q_a : \mathscr{P} \to [0,1]$ is continuous (see Assumption E1), the vector function $\mathbf{q} \equiv (q_1, q_2, \ldots, q_A) : \mathscr{P} \to \mathscr{P}$ is continuous, as well. Furthermore, since $\mathscr{P}$ is closed and convex, the Brouwer fixed-point theorem [27] guarantees the existence of a fixed point of the function $\mathbf{q}$ in $\mathscr{P}$ which, in turn, implies the existence of a fixed point for the dynamical system given by Eq. 15. If this fixed point does not belong to $\tilde{\mathscr{P}}_-$, it belongs to $\mathscr{P} \setminus \tilde{\mathscr{P}}_- = \tilde{\mathscr{P}}_+ \setminus \partial\mathscr{P}_-$; in this case, we denote it by $\hat{\mathbf{m}}_+$. Furthermore, $\hat{\mathbf{m}}_+$ is unique

because the $q_a(\cdot)$ functions ($a = 1, 2, \ldots, A$) are strictly decreasing in $\tilde{\mathscr{P}}_+$ (see Assumption E2). □

Remark 4: The choice $F_a(\mathbf{m}) = c_a q_a(\mathbf{m})$ represents the situation where the perceived benefit of vaccination at age a equals the individual-level risk of infection normalized between 0 and the cost of infection at age a, c_a. By considering $s = 0$ we model the case where individuals use only last year's experience to make their vaccination decisions for the current year.

Remark 5: The fixed point $\hat{\mathbf{m}}_+$ is linearly stable if and only if the eigenvalues of the jacobian matrix with elements $(\partial q_a / \partial m^b)_{\hat{\mathbf{m}}_+}$ belong to the interior of the unit disk in the complex plane [28]. Our assumptions are not sufficient for the resolution of this condition. Depending on the eigenvalues, loss of fixed-point stability typically occurs through a generic bifurcation: the saddle-node, period doubling, or Sacker-Neimark [28]. This is in contrast to results from studies of models without age structure where stability loss typically occurs only through a period-doubling bifurcation [11].

4 Discussion

Inductive reasoning games have recently emerged as a new class of models for studying the dynamics of voluntary vaccination against seasonal influenza. While instrumental at capturing key features of human behavior, they have, so far, used simplified demographical and epidemiological assumptions. In this work we expanded the previous mathematical framework to include age structure in inductive reasoning games. This addition, based on the demography of developed countries, impacts on modeling both influenza epidemiology and human behavior. Since the natural history of influenza infection and the prevention measures depend significantly with age, considering age structure in inductive reasoning games is a major step forward for making them more realistic models of influenza vaccination.

Age structure has important consequences for the modeling of human behavior. In previous work, it was considered that individuals live very many influenza seasons (essentially an infinite number) and, as a consequence, they end up finely tuning their vaccination strategies. As a result, it was noted that severe epidemics are periodically expected (approximately once every 35 years) as a result of human behavior, even without introduction of pandemic strains [9]. Furthermore, it was inferred that, due to self-interested behavior, a community will always fail to self-organize to eliminate influenza epidemics [11]. Considering age structure yields two important comments on these previous results. First, within the previous modeling framework, predictions of periodic epidemics on the time-scale of human life expectancy should be made with care as they may fall outside the validity of the model. Second, the modeling of age structure shows that, in principle, it is possible that a community eliminates influenza epidemics by voluntary vaccination (see Proposition 1). This is due to the fact that individuals do not actually reach

their optimal vaccination strategies as they live for a finite number of influenza seasons. The community continuously loses individuals that are very experienced with seasonal vaccination. Instead, they are replaced with newborns that may easily accept (themselves or their guardians) an initial vaccination probability according to the standard of care; then they will take time to search for a better vaccination strategy and adapt. Further work on the parameterization of the games is necessary to decide to what degree this phenomenon may contribute to the elimination of influenza epidemics. We determined that its impact increases exponentially with the degree to which individuals remember their vaccination outcomes (i.e., the memory parameter s).

Mathematically, age structure turns the mean-field model of the vaccination coverage from a one-dimensional into a multi-dimensional map. As demonstrated by the analysis of a game example (see Proposition 2), fixed-point coverage dynamics of the mean-field map when epidemics are not prevented remains possible. However, the fixed point may typically lose stability through any generic bifurcation, not just period doubling. Further refinement of this theory and a better understanding of the discrepancies between age-structured and age-unstructured inductive reasoning games may reside in restricting the form of the WAIFW matrix using realistic assumptions based on contact data [29–31]; see [14] for a sample calculation. In turn, this will constrain how the probability of infection depends on coverage and age.

In conclusion, including age structure in influenza vaccination models based on inductive reasoning games impacts on the description of both human behavior and epidemiology, and represents a key step forward in increasing models' realism.

References

1. Bauch, C.T., Galvani, A.P., Earn, D.J.: Proc. Natl. Acad. Sci. USA **100**(18), 10564 (2003)
2. Bauch, C.T., Earn, D.J.: Proc. Natl. Acad. Sci. USA **101**(36), 13391 (2004)
3. Manfredi, P., della Posta, P., d'Onofrio, A., Salinelli, E., Centrone, F. Meo, C., Poletti, P.: Vaccine **28**(1), 98 (2009)
4. d'Onofrio, A., Manfredi, P., Poletti P.: J. Theor. Biol **273**, 63 (2011)
5. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **264**, 237 (2010)
6. Fu, F., Rosenbloom, D.I., Wang, L., Nowak M.A.: Proc. Biol. Sci. **27**, 1702, 42 (2011)
7. Arthur, W.B.: Am. Econ. Rev. **84**(2), 406 (1994)
8. Challet, D., Marsili, M., Zhang, Y.C.: Minority Games. Oxford University Press, Oxford (2005)
9. Vardavas, R., Breban, R., Blower S.: PLoS Comput. Biol. **3**(5), e85 2007.
10. Breban, R., Vardavas, R., Blower S.: Phys. Rev. E **76**(3), 031127 (2007)
11. Breban, R.: PLoS ONE **6**(12), e28300 (2011)
12. Cornforth, D., Reluga, T., Shim, E., Bauch, C.T., Galvani, A.P., Meyers, L.A.: PLoS Comput. Biol. **7**(1), e1001062 (2011)
13. WHO. URL http://www.who.int/topics/influenza/en/
14. Glasser, J., Taneri, D., Feng Z., Chuang, J., Tüll, P., Thompson, W., McCauley, M., Alexander, J.: PLoS One **5**(9), e12777 (2010)
15. Truscott, J., Fraser, C., Cauchemez, S., Meeyai, A., Hinsley, W., Donnelly, C.A., Ghani, A., Ferguson, N.J.: Roy. Soc. Interface **9** (67), 304 (2012)

16. Chao, D.L., Halloran, M.E., Obenchain, V.J., Longini, I.M.: PLoS Comput. Biol. **6** (1), e1000656 (2010)
17. WHO, Life tables for WHO Member States. URL http://www.who.int/healthinfo/statistics/mortality_life_tables/en/
18. Wilmoth, J.R., Horiuchi, S.: Demography **36**(4), 475 (1999)
19. Cheung, S.L.K., Robine, J.-M., Tu, E.J.-C., Caselli G.: Demography **42**(2), 243 (2005)
20. World population prospects: The 2010 revision. New York (2011). URL http://esa.un.org/unpd/wpp/population-pyramids/population-pyramids.htm
21. Schenzle, D.: IMA J. Math. Appl. Med. Biol. **1**, 169 (1984)
22. Anderson, R.M., May, R.M.: Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford (1991)
23. Hill, A.N., Longini, I.M.: Math. Biosci. **181**, 85 (2003)
24. Lavoie, E.T., Sorrell, E.M., Perez, D.R., Ottinger, M.A.: Dev. Comp. Immunol. **31**(4), 407 (2007)
25. Coates, D.M., Husseini, R.H., Rushton, D.I., Sweet, C., Smith, H.: Br. J. Exp. Pathol. **65**(5), 543 (1984)
26. CDC. URL http://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm
27. Granas, A., Dugundji, J.: Fixed Point Theory. Springer Monographs in Mathematics. Springer (2010)
28. Kuznetsov, Y.A.: Elements of Applied Bifurcation Theory. Springer, New York (2004)
29. Mossong, J., Hens, N., Jit, M., Beutels, P., Auranen, K., Mikolajczyk, R., Massari, M., Salmaso, S., Scalia Tomba, G.S., Wallinga, J., Heijne, J., Sadkowska-Todys, M., Rosinska, M., Edmunds, W.J.: PLoS Med. **5**(3), e74 (2008)
30. Zagheni, E., Billari, F.C., Manfredi, P., Melegaro, A., Mossong, J., Edmunds, W.J.: Am. J. Epidemiol. **168**(9), 1082 (2008)
31. Iozzi, F., Trusiano, F., Chinazzi, M., Billari, F.C., Zagheni, E., Merler, S., Ajelli, M., Del Fava, E., Manfredi P.: PLoS Comput. Biol. **6**(12), e1001021 (2010)

Emergent Dynamical Features in Behaviour-Incidence Models of Vaccinating Decisions

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Abstract Vaccination is a cornerstone of infectious disease prevention. However, individual vaccinating behaviour does not always result in population-level vaccine coverage patterns that are optimal for protecting public health. For example, vaccine coverage may fall below the elimination threshold due to nonvaccinators who "free-ride" on the herd immunity provided by vaccinators. Routine vaccination programs for many paediatric infectious diseases now have an almost worldwide coverage, but vaccine scares fuelled by such behaviours threaten eradication goals. This free-riding behaviour can be seen as a manifestation of policy resistance, where humans respond to an intervention in such a way that tends to undermine the intervention. However, policy resistance is only one such example of the types of dynamics that emerge from the interaction between vaccinating behaviour and disease incidence or prevalence. Here we explore four types of emergent dynamics of behaviour-incidence systems: policy resistance, policy reinforcement, outcome inelasticity, and outcome variability. We discuss examples of each of these dynamics in the behaviour-incidence modelling literature, and suggest potential implications for vaccination policy.

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1 Introduction

Despite widespread controversies among the public, vaccination has proved to be one of the most successful infectious disease interventions ever and remains one of the greatest public health achievements in the twenty-first century. Vaccination against major infectious diseases, and the complete or near-complete eradication of some diseases (such as smallpox and polio), has completely changed the demography of many developed and developing countries worldwide [13].

The most common strategy is universal mass vaccination (UMV), which requires covering as much of the population as possible, either through large-scale periodic campaigns or through regular school-based programs. However, ring vaccination has also been applied. Ring vaccination involves identifying infectious index cases and vaccinating their close contacts to prevent them from being infected [29, 37]. Ring vaccination may perform better than UMV when the outbreak is localized and infected individuals or their exposed contacts can be rapidly identified. Ring vaccination has been applied to outbreak control for hepatitis A [17], foot-and-mouth disease in cattle [32, 41], and smallpox [21].

Large-scale vaccination programs confer population-wide benefits. Vaccination not only prevents infection in vaccinated individuals but also protects the unvaccinated through a "herd immunity" effect that slows down the circulation of a pathogen in the entire population [1]. Herd immunity operates through disrupting the chain of transmission between individuals. The greater the proportion of vaccinated individuals, the smaller the probability that a susceptible individual will come into contact with an infectious individual and thereby become infected.

The epidemiology of many well-known vaccine-preventable diseases is subject to the effects of human belief and awareness of disease or vaccine [15, 22]. Human behaviour plays an important role in determining whether target vaccination coverage can be reached in a given population. Common childhood diseases such as measles or pertussis are timely examples [38]. While there has long been enthusiastic debate in some higher-income countries about the relative merits and implications of mandatory versus voluntary vaccination [16], it is clear that voluntary vaccination policies sometimes fail. Measles-Mumps-Rubella (MMR) vaccination in Great Britain in the 1990s is one such example of failure due to a vaccine "scare" [31].

Vaccination coverage for seasonal influenza also remains suboptimal in many countries, including the USA and Canada. Suboptimal coverage has been observed even among health care workers (HCWs). For example, a recent study indicates that vaccination coverage for seasonal influenza among HCWs in Canada remains below 50 % [33]. Influenza vaccination coverage among children and individuals at high risk was also very low and significantly below the target level. This is a worldwide phenomenon, with suboptimal influenza vaccine coverage among HCWs having also been identified in Middle East countries (United Arab Emirates (UAE), Kuwait, and Oman), due to doubts about vaccine efficacy, lack of information about the importance of immunization, and concerns about vaccine side effects [28]. A low

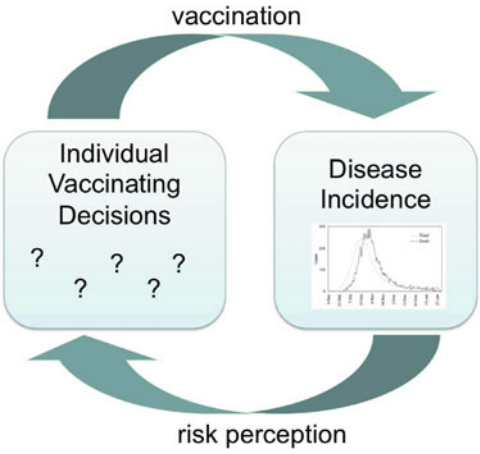

Fig. 1 Feedback loop arising from interactions between vaccinating behavior and disease incidence. Figure taken from [10]

perceived risk of becoming infected, whether justified by historically low infection rates or not, can contribute as much as inflated perception of vaccine risk does: studies identify perceived lack of infection risk as a factor in non-uptake of influenza vaccine [35]. If reduced infection rates due to previous vaccinations lead to reduced perception of infection risks, then herd immunity can, ironically, lead to reduced infection risk perception and thus reduced vaccine uptake.

An emerging fear of vaccine complications can combine with the temptation to rely on herd immunity provided by those who have already vaccinated to impel individuals to exempt themselves or their children from vaccination. Thus, herd immunity introduces a social dilemma in voluntary vaccination policy that amounts to "free-riding" or a "tragedy of the commons" [22, 30]. Equivalently, this dynamic implies a feedback loop between vaccinating decisions and disease dynamics: individual vaccinating choices influence disease prevalence, but the level of disease prevalence in turn influences how many individuals choose to seek vaccination [7, 9, 11] (Fig. 1).

Classical game theory provides a useful tool to analyse and predict the outcomes of strategic interactions [18, 20, 43, 44], including those arising from the interaction between disease dynamics and human vaccinating behaviour [5, 14]. According to a game theoretical perspective, individuals make a rational decision in weighing up the costs and benefits related to vaccination against the cost of risking infection, making assumptions about how much herd immunity will be provided by others in the population. Although further empirical study is warranted regarding how well game theory captures vaccinating behaviour and risk perception, game theoretical modelling of individual vaccinating decisions is growing. This models often predict that rational self-interest leads to a Nash equilibrium vaccine coverage that is suboptimal for the population, being below the level required to eliminate the infection [5, 6]. However, a variety of other non-game-theoretical approaches have also been adopted to capture the interplay between disease dynamics and vaccinating behaviour, and they often yield similar predictions [2, 7, 19].

The nonlinear feedback loop that springs from interaction between individual vaccinating behaviour and disease dynamics can create interesting dynamical consequences, including policy resistance, policy reinforcement, outcome inelasticity, and outcome variability. In the next few sections, we will define these terms and discuss how they arise in models of the interplay between vaccinating behaviour and disease dynamics.

2 Policy Resistance

The most common implication of herd immunity for behaviour-incidence dynamics is *policy resistance*, which is "the tendency for interventions to be defeated by the systems response to the intervention itself" [40]. The vaccine coverage necessary to achieve perfect herd immunity and thus elimination vary greatly from one infectious disease to the next but generally range from 80 % to 95 % for common paediatric infectious diseases [1]. If this level of vaccination is attained, those who refuse to be vaccinated are nonetheless protected through the strong likelihood that they will never be infected. As a result, there is a temptation not to seek vaccination when vaccine coverage is very high. If this temptation translates into individual action not to seek vaccination, vaccine coverage will drop below the elimination threshold. Hence, as a result of herd immunity and the nonlinear interplay between disease dynamics and vaccinating behaviour, voluntary vaccination is subject to policy resistance.

Policy resistance is often cast as a conflict between the Nash equilibrium vaccine coverage and the *social optimum* vaccine coverage. The social optimum can be defined as the vaccine coverage such that the total population burden from either vaccination or infection across all individuals is minimized, and in these models the goal of public health is often conceived as being to reach the socially optimal coverage level (although typically, this definition ignores issues of equity). In contrast to the socially optimal coverage, the Nash equilibrium driven by rational self-interest in most models leads to a vaccine coverage that is different (often lower) than the social optimum vaccine coverage (Fig. 2). Some models indicate that this free-riding manifestation of policy resistance can emerge relatively quickly upon introduction of a new immunization program and that it can result in considerable instabilities in vaccine coverage [8, 19, 42]. For example, new generation vaccines for childhood immunization programs are launched in the United States every few years [3], and the success of the immunization program depends to some extent on how the population will respond to it, which may only partly be a function of demonstrated safety and efficacy of the vaccine. A recent game theoretical model describes how populations respond to a new paediatric infectious disease vaccine implemented through a universal mass vaccination program administered at a specified age every year [8]. This model predicts that, due to initially high infection prevalence, vaccine coverage remains reasonably high immediately after introduction but can succumb to free-riding on herd immunity within 4–5 birth

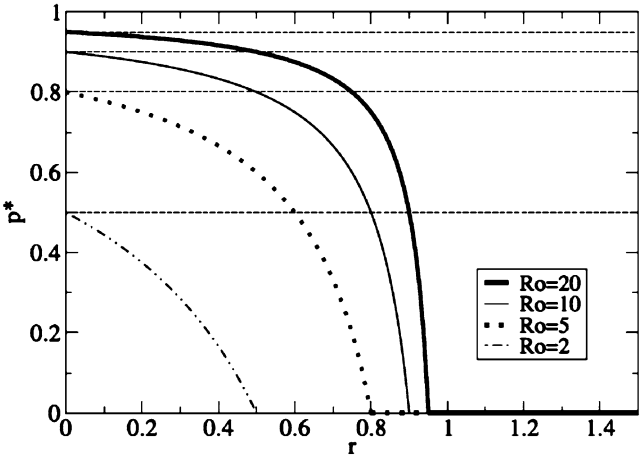

Fig. 2 Policy resistance in vaccination for paediatric infectious diseases. Vaccine coverage p^* at the Nash equilibrium versus relative risk r, the ratio between risk of vaccination and risk of infection, for various values of R_0. *Dashed horizontal lines* demarcate the critical coverage level that eliminates the disease from the population. Figure taken from [5]

cohorts (years). These drops occurs sooner (within 2–3 birth cohorts) when the disease risk is low or vaccine efficacy is low. Moreover, due to instabilities in behaviour-incidence dynamics, vaccine coverage can vary considerably from one birth cohort to the next. The model also enables calculating the smallest vaccine risk tolerable for each birth cohort so that an individual makes a rational decision of considering vaccination; this information may be useful for designing phase III trials and phase IV safety studies for vaccines [3].

Somewhat similar dynamics have been explored in the context of influenza vaccination [42]. Influenza management is one of the most significant current concerns for public health policy makers. While it is recommended that nearly 80 % of individuals should get annual influenza vaccine, it is estimated that only 40–50 % actually do so [23]. In response to the need to revaccinate for influenza every year, universal influenza vaccines conferring long-term immunity are being developed, and it is hoped that this might increase vaccine coverage [46]. However, a game theoretical model linking human cognition and memory for universal influenza immunization and influenza epidemiology forces us to consider the potential for policy resistance against universal influenza vaccines. This model predicts that a universal vaccine which provides short-term protection will on average increase the vaccine coverage, compared to the standard seasonal vaccine: short-term protection maintains risk communication of influenza among populations, resulting in stable vaccine coverage, which in turn creates small groups of free-riders and thus frequent but small-size epidemics. In contrast, a universal vaccine that provides longer-term protection may be counter-productive in some respects. Long-term protection creates large groups of free-riders who accept vaccination only after a severe epidemic occurs. Because of long-term immunity, individuals mostly free-ride, or

accept vaccination only once in a large time frame, and this results in drop of vaccine coverage after many years, in turn causing infrequent but very severe epidemics.

The imbalance between perceived and real risk and its negative effect on vaccine coverage is also reflected by several other examples of research. For example, population surveys have been used to parameterize game theoretical vaccinating behaviour models for influenza and human papillomavirus (HPV) vaccination [4, 27]. These models confirm that rational individual vaccinating decision-making would not allow populations to reach vaccine coverage levels that minimize disease prevalence in the population.

Another manifestation of policy resistance is individuals who vaccinate, but only after a period of delay. Delaying behaviour has been observed in some real-world immunization programs, and the game theoretical aspects of such behaviour have been explored for the case of paediatric infectious diseases [11] and pandemic influenza [12]. Using a game theoretical model of vaccination the authors have shown that relatively low disease incidence causes individuals to delay vaccination, for a year or two in the case of school-based programs for paediatric infectious diseases, or many weeks in the case of pandemic influenza. Naturally, delaying behaviour also hinders disease control and can cause subsequent incidence spikes.

3 Policy Reinforcement

Models of vaccinating behaviour can also exhibit *policy reinforcement*, which can be defined as the tendency for interventions to be *boosted* by the system's response to the intervention. Instead of the negative feedback loop of policy resistance, where an increase in vaccine coverage tends to create a disincentive for further vaccination activity, the feedback loop in the case of policy reinforcement is positive, where increased vaccination activity stimulates still further vaccination activity.

One situation in which policy reinforcement can occur in such models is during the transient period when a new vaccine has been introduced and there is some social learning process, whereby individuals adopt a vaccinator strategy only if they have learned that behaviour from someone else [7, 9, 20, 26, 39]. In that scenario, disease is initially widespread and there is little herd immunity, and so it is optimal for individuals to get vaccinated. At the same time, if individuals "sample" other individuals at some rate and only switch to being a vaccinator when they sample someone who is a vaccinator, then an increase in the abundance of vaccinators will lead to more instances of vaccinators being "sampled" and hence more opportunities for new vaccinators to be created. As a result, there is a virtuous cycle of increasing vaccine coverage, at least until herd immunity creates a disincentive large enough to outweigh the effect of increasing numbers of vaccinators.

There are also other potential sources of policy reinforcement. For some infections (such as chickenpox), pathogenicity of an infection can increase with age, which can reverse the usual relationship between Nash equilibrium vaccine coverage and socially optimal vaccine coverage [34]. Unlike for a non-age-structured

model, vaccination against chickenpox may either help or harm the unvaccinated. While vaccination decreases the probability of being infected, it also shifts the average age at infection upward, and for an infection like chickenpox that can become more severe with age, this could end up harming the unvaccinated. It could also harm vaccinated individuals in whom the vaccine was not efficacious, leading to breakthrough infection. At high vaccine efficacy, while the infection probability for unvaccinated juveniles decreases with vaccination coverage, it actually increases for adults. For example, the infection probability for adults peaks at 18 %, when the background vaccine coverage is 77 %, though it starts declining as full herd immunity is approached at 92 % coverage. For low vaccine efficacy, the infection probability peaks at 17 %, even if the entire population is vaccinated. The probability of breakthrough infection is also dependent on the vaccine coverage. For partial vaccine efficacy, the probability of breakthrough infection for both juveniles and adults increases with increasing vaccine coverage. With increasing vaccine coverage, fewer individuals are exposed to the disease thereby decreasing the total number of fully protected individuals relative to partially protected individuals. The probability of acquiring disease for partially protected individuals remains high when especially the coverage is low, though it drops very quickly as the herd immunity approached.

As a result of these effects, the Nash equilibrium vaccine coverage in this game theoretical chickenpox model can actually exceed the socially optimal vaccine coverage (Fig. 3).

From the perspective of the social optimum, this is not truly an example of policy reinforcement since the total health burden at the Nash equilibrium vaccine coverage still differs from the total health burden at the socially optimal vaccine coverage. However, from the perspective of universal vaccine coverage as a public health goal, we could view this as an example of policy reinforcement, since the emergence of high vaccine coverage is facilitated by the population response to the vaccine program.

4 Outcome Inelasticity

The consequences of a vaccination game played out over the course of a single outbreak where the vaccine is new to the population has also been investigated, in the context of pandemic influenza vaccination [12]. This can lead to an effect termed *outcome inelasticity*, whereby a given outcome (such as prevalence of infection, or timing of an epidemic peak or number of deaths) is conserved across a given range of parameter values, due to nonlinear feedbacks in the model.

In a situation where a new vaccine has been introduced to a population experiencing an outbreak of an infectious disease, many individuals may opt to "wait and see" regarding vaccine risks. In particular, they may avoid vaccination until enough other individuals around them have been vaccinated to convince them that the vaccine is safe. As a result, perceived vaccine risk decreases as a function of

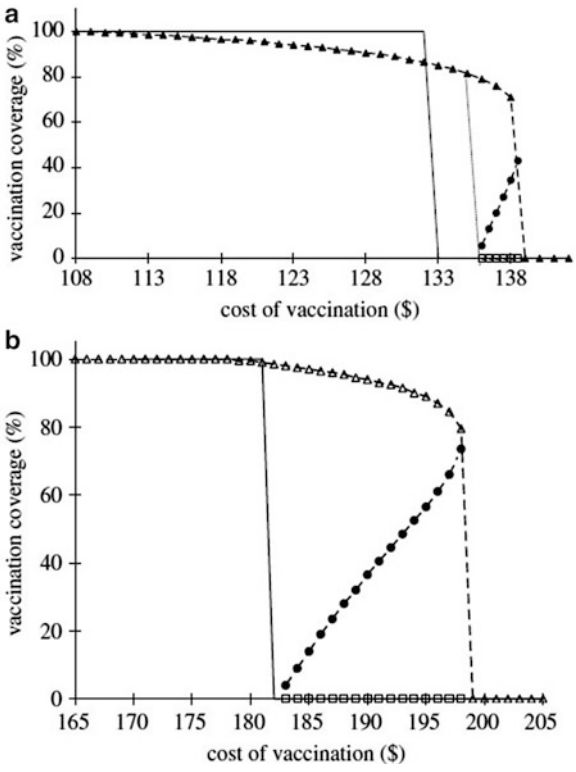

Fig. 3 Policy enhancement in chickenpox vaccination. Nash equilibria versus social optimum for a range of cost of vaccinations in (**a**) USA and (**b**) Israel. Depending on the vaccination cost, there are three Nash equilibria indicated by *triangles*, *squares*, and *filled circles*. *Solid line* (without symbols) indicates the social optima as a function of cost of vaccination. Figure taken from [34]

the number of individuals vaccinated to date. This amounts to a form of free-riding, where early vaccination by the entire population would have prevented the outbreak, but instead late vaccinators use early vaccinators as "guinea pigs." On the other hand, late vaccinators also accept an increased risk of being infected before they can get vaccinated. On top of this interaction, herd immunity also plays a role, with herd immunity provided by early vaccinators helping to protect late vaccinators or nonvaccinators.

In a game theoretical model capturing these strategies, it is possible to show how the strategic behaviour causes the timing of the pandemic peak to be strongly conserved across a broad range of plausible transmission rates, which is generally not possible without strategic behaviour. As the basic reproductive number R_0 increases it causes a more rapid development of the epidemic, which forces late vaccinators to vaccinate a little earlier, thus counteracting the effects of a higher R_0. The net effect is that the peak occurs at approximately the same week regardless of R_0, i.e., the outcome is inelastic with respect to R_0 (Fig. 4) [12].

We note in passing that this model also exhibits policy reinforcement with respect to the initial perceived vaccine risk: an effort to decrease the initial perceived vaccine risk would supply benefits throughout the epidemic, because a lower initial perceived vaccine risk means more early vaccinators, which in turn means more

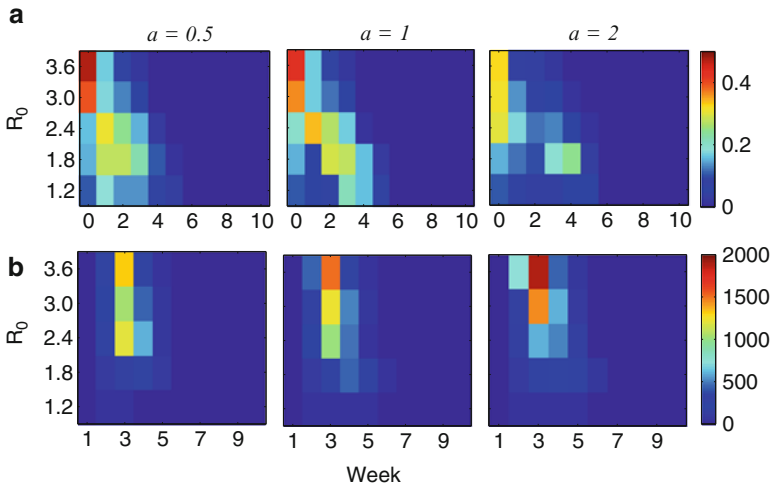

Fig. 4 Outcome inelasticity in pandemic influenza vaccination. (**a**) Nash equilibrium vaccine coverage and (**b**) resulting influenza incidence, at different R_0 values and different values of the parameter a governing perceived risk evolution during the pandemic, over each week of the outbreak. Figure taken from [12]

"guinea pigs" from which late vaccinators can form an impression of vaccine safety, which means more late vaccinators and lower perceived vaccine risk later in the outbreak.

An example of outcome inelasticity with respect to total mortality in a population is observed in a non-game-theoretical model of vaccinating behaviour for an infection transmitted through an evolving social contact network [36]. In this model, individuals who become infected have a probability d_{inf} of dying, and this risk is part of the individual payoff functions. As the parameter d_{inf} increases, the payoff for not vaccinating decreases, making vaccination a more appealing option. As a result, vaccine coverage increases as d_{inf} increases, which counteracts the effects of a higher d_{inf} to make the total number of deaths relatively constant across a range of values for d_{inf}.

5 Outcome Variability

Outcome variability is a situation where, due to stochastic effects, qualitatively different outcomes are possible for different stochastic realizations of the same underlying model parameter distributions. This may occur at the boundary of basins of attraction for two steady states and is a possible outcome of vaccinating behaviour models where some processes of social learning or imitation is present [7,9,39,45].

For example, in a model of voluntary ring vaccination where individuals must weigh whether to get vaccinated given that their contact is an index case, outcome

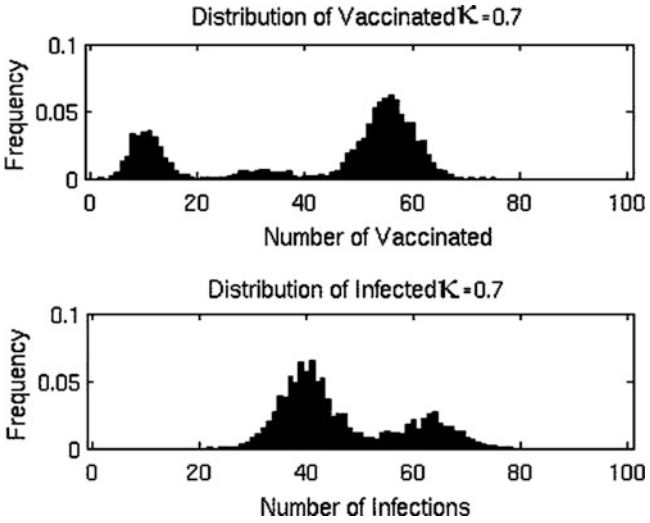

Fig. 5 Outcome variability in voluntary ring vaccination. The distribution across many stochastic realizations of the number vaccinated (*top*) and the number of secondary infections (*bottom*) in 100 neighbours of an index case, for imitation strength $\kappa = 0.7$. Figure adapted from [45]. For details see this reference

variability can occur when individuals are prone to imitate the decisions of other contacts of the index case [45]. For the same underlying model parameter distributions, some stochastic realizations result in the majority of contacts getting vaccinated, while other stochastic realizations result in the majority of contacts not getting vaccinated (Fig. 5). As a result, the number of contacts who get infected can be either large or small. The implications of such social "clumpiness" in vaccine strategies due to imitation tendencies for the success of ring vaccination strategies are clear, since this can make the difference between control or no control of the outbreak.

Likewise, in a social learning model where the population is split evenly between vaccinators and non-vaccinators and where individuals tend to copy more successful strategies, the long-term outcome can be high vaccine coverage or low vaccine coverage depending on which basin of attraction the system is tipped into, based on stochastic effects.

6 Discussion and Conclusion

Human behaviour can be a key driver of infectious disease dynamics [25], particularly as it relates to vaccinating decisions [9]. Behaviour-incidence dynamics can thereby have significant implications for public health policy. The clash between Nash equilibrium and social optimum, where free-riding behaviour results in

suboptimal vaccine uptake, is an example of policy resistance, which is the most commonly explored outcome of behaviour-incidence dynamics. However, here we have discussed other possible outcomes such as policy reinforcement, outcome inelasticity, and outcome variability. These effects nuance the standard "cartoon" of voluntary vaccination as a free-rider problem.

Such nuances can have important implications for vaccine policy. For example, the game theoretical model of chickenpox vaccination described in Sect. 3 provides diverging recommendations for chickenpox vaccination policy in Israel versus the United States [34]. The authors suggest that external regulation such as subsidies for vaccination may be unnecessary or may even worsen the situation depending on the relationship between the Nash equilibrium and the social optimum. According to their analysis, subsidies or external regulation are required to achieve target coverage for the United States, whereas an information campaign on chickenpox awareness and vaccine safety is sufficient to optimize vaccine coverage in Israel.

Similarly, outcome inelasticity and outcome variability have implications for disease management. Reaction to a new vaccine during a pandemic outbreak and the potential for behavioural feedbacks to shape the epidemic curve have implications for risk messaging, prioritization of vaccination for high-risk groups, and logistics of vaccine rollout during a pandemic [12]. Similarly, ring vaccination may need to consider the social context (with specific emphasis on beliefs regarding vaccination) given the potential for social learning effects to influence local acceptance or rejection of a vaccine and thus determine success of local containment [24,45].

The list of emergent dynamical effects of behaviour-incidence models we have provided here is not exhaustive, and more effects may come to light as the theory is developed. However, as the theory continues to develop, we hope that more efforts will be made to better validate these models against empirical data and apply them to specific questions concerning real-world vaccine policies. As a result, we will better understand how to recognize, mitigate, and harness the emergent dynamics of behaviour-incidence systems in order to improve public health.

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References

1. Anderson, R.M., May, R.M.: Infectious Diseases of Humans. Oxford Science Publications, Oxford (1991)
2. Auld, C.: J. Health Econ. **22**, 361 (2003)
3. Ball, L., Ball, R., Gellin, B.: Developing safe vaccines. In: Levine, M., Kaper, J., Rappuoli, R., Liu, M., Good, M. (eds.) New Generation Vaccines. Dekker, New York (2004)
4. Basu, S., Chapman, G.B., Galvani, A.P.: Proc Natl Acad Sci. USA **105**, 19018 (2008)
5. Bauch, C.T, Earn, D.J.D.: Proc Natl Acad Sci. USA **101**, 13391 (2004)
6. Bauch, C.T., Galvani, A.P., Earn, D.J.D.: Proc. Natl Acad. Sci. USA **100**, 10564 (2003)
7. Bauch, C.T.: Proc. R. Soc. B. **272**, 1669 (2005)

8. Bauch, C.T., Bhattacharyya, S., Ball, R.F.: PLoS ONE **5**(9), e12594 (2010)
9. Bauch, C.T., Bhattacharyya, S.: PLoS Comp Biol. **8**(4), e1002452 (2012)
10. Bhattacharyya, S., Bauch, C.T.: Hum. Vaccine and Immunotherapeutics **8**, 842 (2012)
11. Bhattacharyya, S., Bauch, C.T.: J. Theor. Biol. **267**, 276 (2010)
12. Bhattacharyya, S., Bauch, C.T.: Vaccine **29**, 55195 (2011)
13. Bonanni, P.: Vaccine **17**, 120 (1999)
14. Brito, D.L., Sheshinski, E., Intriligator, M.D.: J. Public. Econ. **45**, 69 (1991)
15. Coelho, F.C., Codeço, C.T.: PLoS Comput Biol **5**, e1000425 (2009)
16. Colgrave, J.: State of Immunity: The Politics of Vaccination in Twentieth-Century America. University of California Press, Berkeley (2006)
17. Diel, R., Rappenhoener, B., Schneider, S.: Eur. J. Health Econ. **2**(3), 963 (2000)
18. d'Onofrio, A., Manfredi, P., Salinelli, E.: Math. Med. Biol. **25**, 337 (2008)
19. d'Onofrio, A., Manfredi, P., Salinelli, E.: Theor. Popul. Biol. **71**, 301 (2007)
20. d'Onofrio, A., Manfredi, P., Poletti, P.: J. Theor. Biol. **273**(1), 63 (2011)
21. Fenner, F.D.A., Henderon, D.A., Arita, I., Jezek, Z., LAdnyin, I.D.: Smallpox and Its Eradication. World Health Organization Press, Geneva (1988)
22. Fine, P.E., Clarkson, J.A.: Am. J. Epidemiol. **124**, 1012 (1986)
23. Fiore, A.E., Shay, D.K., Broder, K., Iskander, J.K., Uyeki, T.M., Mootrey, G., Bresee, J.S.: Cox NJ MMWR Recomm Rep. **58**(RR-8), 1 (2009)
24. Funk, S., Gilad, E., Jansen, V.A.A.: J. Theor. Biol. **264**, 501 (2010)
25. Funk, S., Salathe, M., Jansen, V.A.A.: J. R. Soc. Interface **7**, 1247 (2010)
26. Fu, F., Rosenbloom, D.I., Wang, L., Nowak, M.A.: Proc. R. Soc. B **278**, 42 (2011)
27. Galvani, A.P., Reluga, T.C., Chapman, G.B.: Proc. Natl. Acad. Sci. USA **104**, 5692 (2007)
28. Gharbieh, E.A., Fahmy, S., Rasool, B.A., Khan, S.: Int. J. Med. Sci. **7**(5), 319 (2010)
29. Greenhalgh, D.: Commun. Stat. Stoch. Models **2**, 339 (1986)
30. Hardin, G.: Science **162**, 1243 (1968)
31. Jansen, V.A., Stollenwerk, N., Jensen, H.J., Ramsay, M.E., Edmunds, W.J, Rhodes, C.J.: Science **301**, 804 (2003)
32. Keeling, M.J., Woolhouse, M.E.J., May, R.M., Davies, G., Grenfell, B.T.: Nature **421**, 136 (2003)
33. Lam, P.P., Chambers, L.W., MacDougall, D.M., McCarthy, A.E.: CAMJ **182**(12), E542 (2010)
34. Liu, J., Kochin, B.F., Tekle, Y.I., Galvani, A.P.: J. R. Soc. Interface **9**(66), 68 (2012)
35. Madjid, M., Alfred, A., Sahai, A., Conyers, J.L., Casscells, S.W.: Tex Heart Inst. J. **36**(6), 546 (2009)
36. Morsky, B., Bauch, C.T.: Outcome inelasticity and outcome variability in behavior-incidence models: an example from an SIR infection on a dynamic network. Submitted in Computational and Mathematical methods in Medicine (2012)
37. Muller, J., Schonfisch, B., Kirkilionis, M.: J. Math. Biol. **41**, 143 (2000)
38. Philipson, T.: J. Hum. Resour. **31**, 611 (1996)
39. Reluga, T.C., Bauch, C.T., Galvani, A.P.: Math. Biosci. **204**, 185 (2006)
40. Sterman, J.D.: Am. J. Pub. Health **96**, 505 (2006)
41. Toma, B., Moutou, F., Dufourc, B., Durand, B.: Comp. Immunol. Microbiol. Infect. Dis. **25**, 365 (2002)
42. Vardavas, R., Breban, R., Blower, S.: BMC Research Notes **3**, 92 (2010)
43. Von Neumann, J., Morgenstern, O.: Theory of Games and Economic Behavior. Princeton University Press, Princeton (1944)
44. Weibull, J.W.: Evolutionary Game Theory. MIT Press, Cambridge (1995)
45. Wells, C.R., Tchuenche, J.M., Meyers, L., Galvani, A.P., Bauch, C.T.: Bull. Math. Biol. **73**, 2748 (2011)
46. Wilkinson, E.: Universal flu vaccine tests start (2008) http://news.bbc.co.uk/2/hi/health/7577501.stm

Impact of Vaccine Behavior on the Resurgence of Measles

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Abstract Widespread avoidance of the measles-mumps-rubella vaccination (MMR) demonstrates that the effectiveness of vaccination programs can be thwarted by public misperceptions of vaccine risk. By coupling game theory and epidemic models, we examine vaccination choice among populations stratified into vaccine skeptics and vaccine believers. The two behavioral groups are assumed to be heterogeneous with respect to their perceptions of vaccine and infection risks. We demonstrate that the pursuit of self-interest among vaccine skeptics often leads to vaccination levels that are suboptimal for a population, even if complete coverage is achieved among vaccine believers. Furthermore, as the number of vaccine skeptics increases, the probability of infection among vaccine skeptics increases initially, but it decreases once the vaccine skeptics begin receiving the vaccination, if both behavioral groups are vaccinated according to individual self-interest. This research illustrates the importance of public education on vaccine safety and infection risk in order to achieve vaccination levels that are sufficient to maintain herd immunity.

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1 Introduction

During the past century, developments in vaccination have led to effective control of the transmission and outbreaks of many infectious diseases. In 2000, the endemic transmission of measles was eliminated in the USA due to public policies regarding vaccination, such as requiring students to be vaccinated before entering schools [16]. However, measles elimination was hampered when a connection between the MMR vaccine and autism was proposed by Wakefield in 1998 [11]. This suggestion led many parents to refuse the MMR vaccine. Although the hypothesis by Wakefield was discredited in 2010, the impact of the idea linking the MMR vaccine and autism could not be withdrawn so easily [11].

Prior to the supposed autism-MMR connection in 1998, coverage in England was 92%, and only 56 cases of measles were reported in Wales and England in 1998 [11]. By 2001, the level of MMR coverage dropped to 80%, resulting in 1,370 measles cases in 2008 [11]. The drop in MMR vaccination also occurred in France, the European country with the highest number of outbreaks [6]. In the USA, the number of measles cases increased drastically as well. In 2001, the estimated number of children in the USA who did not receive the suggested three doses of the MMR vaccine due to safety concerns was 42,937, 15% of underimmunized children [12]. As in other developed countries, the main reasons for MMR refusal were reported to be the harmful effects of vaccines and the relatively low risk of the diseases. In 2011, the USA had 17 measles outbreaks with 222 confirmed cases, the highest number of cases since 1996 [18].

To understand the impact of the publics health-related perceptions on the success of interventions, several game-theoretical models in epidemiology have been proposed [1, 4, 8–10, 13, 20–22]. In the case of vaccination, these studies have shown potential conflicts between individual incentives and population incentives. From the perspective of the population, vaccination reduces the transmission of infectious diseases and has the potential to eliminate diseases when herd immunity is achieved. For individuals driven by self-interest, game-theoretic decisions are expected to tend toward the Nash strategy, where no player can increase his or her individual payoff by changing his or her own strategy [15].

Here, we propose a game-theoretic dynamic model of measles transmission in order to examine the impact of perceived risks of measles vaccination on the vaccine uptake. Using our model, we explore how vaccine refusal may lead to the failure of herd immunity. Our results highlight the role of vaccine skeptics in reducing overall vaccine coverage in populations, making the discrepancies between the Nash and utilitarian strategies of vaccination larger. Based on our results, we conclude that the probability of measles infection and incidence of measles are more sensitive to the proportion of vaccine skeptics than to individual misperceptions about vaccine risks. Our study also highlights the impact of discrepancies between perceived and actual risks in the general population on the individual vaccine uptake.

2 Methods

2.1 Epidemiological Population Model for Vaccine Refusal

We developed the model of measles transmission and vaccination (Eqs. 1–8), dividing population into two behavioral groups—vaccine skeptics and vaccine believers—depending on individual attitudes toward vaccination [20]. We define vaccine skeptics as individuals who may overestimate the risk of vaccines and/or underestimate the risk of infection, whereas vaccine believers would not have such misperceptions. Based on their perceptions of the benefits and risks of vaccination, parents decide whether to give measles vaccination to their children at the time of birth. Vaccine skeptics and vaccine believers are denoted by subscripts 1 and 2, respectively.

We define $\overline{\phi}_k$ as the average vaccination coverage of group k, while ϕ_k is defined as the vaccination strategy of a generic individual in behavioral group k ($k = 1, 2$). The overbar notation indicates the aggregate vaccination behavior in the population. The probability of vaccination among vaccine skeptics is assumed to be lower than that among vaccine believers ($\overline{\phi}_1 < \overline{\phi}_2$).

Within each behavioral group, individuals may be susceptible (S_1 and S_2), infected (I_1 and I_2), recovered (R_1 and R_2), or vaccinated (V_1 and V_2). We denote the population size (K) as N where $N = \Sigma_{k=1}^{2}(S_k + V_k + I_k + R_k) := K$. Children are born and enter the population at a constant rate per capita, μ. We also assume a constant natural mortality rate identical to the birth rate, μ, such that the population size is constant without disease-induced mortality. We denote the size of two groups, vaccine skeptics and vaccine believers, by $N_1 = S_1 + V_1 + I_1 + R_1 := K_1$ and $N_2 = S_2 + V_2 + I_2 + R_2 := K_2$, respectively. If the number of vaccine skeptics and vaccine believers is asymptotically constant, we can assume that $N_1 = q_1 N$ and $N_2 = q_2 N$, without loss of generality. Here, q_1 and q_2 represent relative sizes of vaccine skeptics and vaccine believers, respectively ($q_1 + q_2 = 1$). Furthermore we introduce the following variables: $s_j = S_j/K$, $i_j = I_j/K$, $r_j = R_j/K$, and $v_j = V_j/K$, denoting the epidemiological fractions in each behavioral group.

Given that two measles vaccine doses administered after twelve months of age are 95–100 % effective, we assume a perfectly efficacious vaccine against measles that confers lifelong immunity, as does recovery [17]. In addition, we define β and γ as the transmission rate and recovery rate, respectively. Given these assumptions, the epidemiological model of vaccination behavior can be expressed by the following deterministic system of ordinary differential equations:

$$ds_1/dt = \mu(1 - \overline{\phi}_1)q_1 - \beta(i_1 + i_2)s_1 - \mu s_1, \tag{1}$$

$$di_1/dt = \beta(i_1 + i_2)s_1 - (\gamma + \mu)i_1, \tag{2}$$

$$dr_1/dt = \gamma i_1 - \mu r_1, \tag{3}$$

$$dv_1/dt = \mu\overline{\phi}_1 q_1 - \mu v_1, \tag{4}$$

$$ds_2/dt = \mu(1-\overline{\phi}_2)q_2 - \beta(i_1+i_2)s_2 - \mu s_2, \tag{5}$$

$$di_2/dt = \beta(i_1+i_2)s_2 - (\gamma+\mu)i_2, \tag{6}$$

$$dr_2/dt = \gamma i_2 - \mu r_2, \tag{7}$$

$$dv_2/dt = \mu\overline{\phi}_2 q_2 - \mu v_2. \tag{8}$$

Using $s_j = q_j - i_j - r_j - v_j$ and the conditions for steady states, we can rewrite the equations, $i_1' = 0$ and $i_2' = 0$, as

$$\beta(i_1+i_2)(q_1 - i_1 - \overline{\phi}_1 q_1 - (\gamma/\mu)i_1) = (\gamma+\mu)i_1, \tag{9}$$

$$\beta(i_1+i_2)(q_2 - i_2 - \overline{\phi}_2 q_2 - (\gamma/\mu)i_2) = (\gamma+\mu)i_2. \tag{10}$$

By solving Eqs. (9) and (10) simultaneously, one can determine the stationary solutions to Eqs. (1)–(8). The disease-free steady state of Eqs. (1)–(8) always exists and it is given by

$$E_0 = (0,0,0,0,0,0,0,0), \tag{11}$$

and a non-uniform endemic steady state is

$$E_1 = (s_1^*, i_1^*, r_1^*, v_1^*, s_2^*, i_2^*, r_2^*, v_2^*), \tag{12}$$

where $s_k^* = \frac{(1-\overline{\phi}_k)q_k(\gamma+\mu)}{\beta(1-q_1\overline{\phi}_1-q_2\overline{\phi}_2)}$, $i_k^* = q_k(1-\overline{\phi}_k)\{\frac{\mu}{\gamma+\mu} - \frac{\mu}{\beta(1-q_1\overline{\phi}_1-q_2\overline{\phi}_2)}\}$, $r_k^* = q_k(1-\overline{\phi}_k)\{\frac{\gamma}{\gamma+\mu} - \frac{\gamma}{\beta(1-q_1\overline{\phi}_1-q_2\overline{\phi}_2)}\}$, and $v_k^* = \overline{\phi}_k q_k$ $(k=1,2)$, when $\Re_C > 1$. When calculating the cost of infection and vaccination, we assume the endemic steady state, Eq. (12).

The effective reproductive ratio of Eqs. (1)–(8) is $\Re_C = \frac{\beta(1-q_1\overline{\phi}_1-q_2\overline{\phi}_2)}{\gamma+\mu}$, whereas the basic reproductive ratio is given by $\Re_0 = \Re_C(\overline{\phi}_1 = \overline{\phi}_2 = 0) = \frac{\beta}{\gamma+\mu}$. For measles, the estimate of a basic reproductive ratio ranges between 15 and 17 [3], and we set $\Re_0 = 15$ as a baseline parameter.

2.2 *Utility Calculation for Measles Vaccination*

In our game-theoretic model of disease transmission and vaccination, vaccination behavior is modeled at the scales of both the population and the individual. We formulate our model as a population game, where the payoff of measles vaccination depends on both the individual's decision and the population's average behavior.

We define $n_k(t)$ as the distribution of individuals who belong to behavioral group k in each of the four possible epidemiological states $(k=1,2)$. The population-scale dynamics satisfy a system of ordinary differential equations G (Eqs. 1–8):

$$\frac{dn_k}{dt} = G(n_k, \overline{\phi}_k). \tag{13}$$

An individual-scale model is modeled as a Markov process with transition rates derived from the population-scale model, Eqs. (1)–(8). Here we define $x_k(t)$ as an individual's probability density over the life-history state space with a vaccination strategy, ϕ_k, at time t ($k = 1, 2$). Therefore, assuming that the population has reached the endemic steady-state distributions, n_k^*, the state of an individual is described by

$$\frac{dx_k}{dt} = Q_k(n_k, \phi_k)x_k, \tag{14}$$

where

$$Q_k(n^*, \phi_k) = \begin{pmatrix} -\lambda - \mu & 0 & 0 & 0 \\ \lambda & -\gamma - \mu & 0 & 0 \\ 0 & \gamma & -\mu & 0 \\ 0 & 0 & 0 & -\mu \end{pmatrix} \tag{15}$$

and $\lambda = \beta(i_1^* + i_2^*)$. All individuals enter the population as either susceptible or immunized newborns, depending on their parents' vaccination strategy (ϕ_k); thus the initial state of an individual in behavioral group k is given by $x_k(0) = [1 - \phi_k, 0, 0, \phi_k]^T$.

The instantaneous payoff gains for a Markov process can be represented in terms of a vector (f) of gains per unit of time for residents of each state and a vector (F) of instantaneous payoff gains associated with each transition. Using these definitions, it follows that $f_k = [0, -c_{I,k}, 0, 0]^T$ and $F_k = [0, 0, 0, -C_{V,k}]^T$. We define $c_{I,k}$ as the perceived cost per day of measles infection by an individual in group k, while $C_{V,k}$ is defined as the perceived cost of the measles vaccination, including possible adverse effects. The perceived costs of measles vaccination are likely to be greater for vaccine skeptics than for vaccine believers because of this group's perception of a greater risk of side effects ($C_{V,1} \geq C_{V,2}$).

By applying the Bellman equation for a continuous-time Markov process [2], we calculate the expected present values of each state, conditional on the measles vaccination strategy. The expected present value is calculated based on the probabilities of all future events and discounted future costs relative to immediate costs. Thus, the expected payoff is

$$U_k = F_k x_k(0) + \int_0^\infty e^{-\delta t} f_k^T x_k(t) dt, \tag{16}$$

$$= -\phi_k C_{V,k} - (1 - \phi_k) c_{I,k} \left(\frac{\lambda^*}{\delta + \lambda^* + \mu} \right) \left(\frac{1}{\delta + \gamma + \mu} \right), \tag{17}$$

where δ is a positive discount rate ($\delta = 0.03$/yr) and $\lambda = \beta(i_1^* + i_2^*)$. Unless otherwise specified, we used the following as a baseline parameter set for simulations: $q_1 = 0.3$, $q_2 = 0.7$, $\beta = 2.14$/day, $1/\gamma = 7$ days, $1/\mu = 25550$ days, $C_{V,1}/c_{I,1} = 4.8$, and $C_{V,2}/c_{I,2} = 2.4$ (Tables 1 and 2).

Table 1 Cost of measles vaccination

Variable	Value	Weighted average[a]	Reference
Price of MMR vaccine (per dose)	$18.64 (public)	$42.60	[5]
	$50.16 (private)		
Administrative cost (per dose)	$7.03 (public)[b]	$20.73	[23]
	$25.06 (private)[b]		
Travel cost for a round trip	$4.70		[23]
Two hours of time off from work to take the child for vaccination	$22.85[b]		[23]
Total vaccination cost for two doses		$181.76	

[a]We assumed that 76% of children obtain their measles vaccines from private health-care providers and 24% from public providers [23]
[b]2001 costs were inflated to 2011 costs

Table 2 Disease cost

Disease Costs	Average direct cost per case	Reference
Uncomplicated (85%)[a]	$150	[14]
Hospitalized (15%)[a]	$2,659	[14]
Weighted average	$526	
Average cost per day of infection	$75	

[a]1997 costs were inflated to 2011 costs

2.3 *Calculation of Optimal Measles Vaccination Strategy Driven by Self-interest*

In order to determine the Nash strategy for the population game, we first define a region of possible stationary incidence of measles (i_1^*, i_2^*) in Eq. (12) by varying resident strategies, $\overline{\phi}_k$ $(k = 1, 2)$ (Fig. 1) [19]. For each point in the reachable region of incidence, the force of infection exerted on the individuals in a behavioral group can be uniquely determined. In fact, the endemic prevalence of measles (i_1^*, i_2^*) decreases with an increase in the resident vaccination strategies, $\overline{\phi}_k$. We use this monotonicity of the endemic stationary solution to plot the prevalence of measles in behavioral groups 1 and 2 at the endemic equilibrium, Eq. (12). Specifically, the feasible domain of endemic equilibria can be drawn based on Eqs. (9) and (10) when $\overline{\phi}_1 = 0$ and $\overline{\phi}_2 = 0$, respectively.

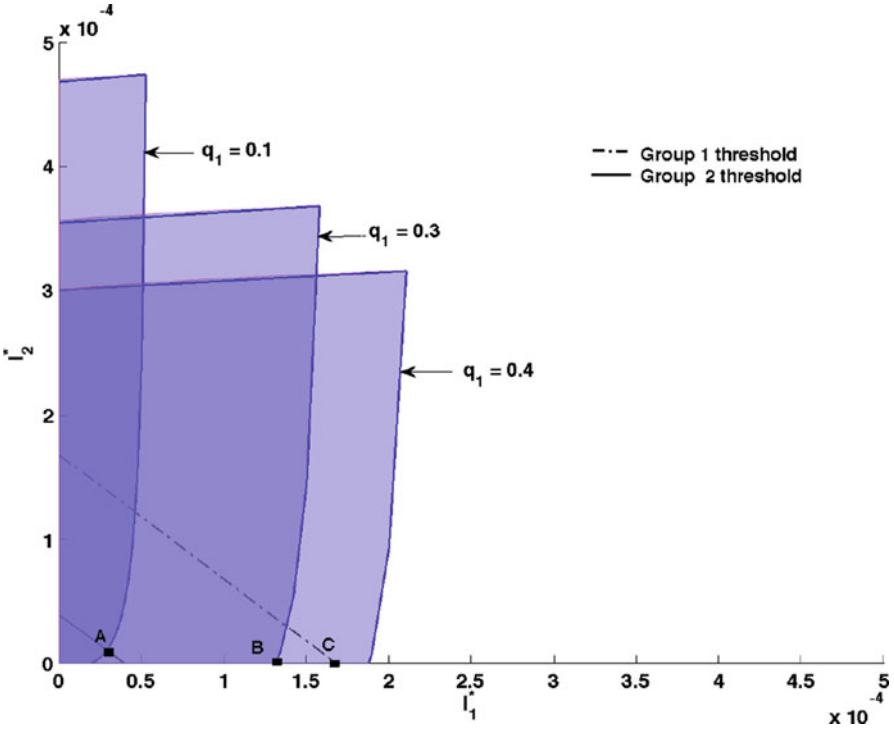

Fig. 1 Plots of the reachable region of disease incidence (i_1, i_2) and the threshold forces of infection under various resident strategies, ($\overline{\phi}_1$, $\overline{\phi}_2$). Each plot corresponds to the relative proportion of vaccine skeptics ($q_1 = 0.1$, 0.3, and 0.4). The *dotted* and *solid lines* indicate the threshold force of infection of behavioral groups 1 ($\lambda_1^+ = \beta(i_1^* + i_2^*)$) and 2 ($\lambda_2^+ = \beta(i_1^* + i_2^*)$), respectively. Dots A, B, and C indicate the Nash strategies when $q_1 = 0.1$, $q_1 = 0.3$, and $q_1 = 0.4$, respectively

In a game-theoretic context, individuals are strategists who strive to maximize their expected payoff. Thus, the Nash strategy for a population game described by Eqs. (1)–(8) is the best response that maximizes the expected payoff, Eq. (17). Differentiating U_k with respect to ϕ_k, we find that the Nash strategy is given by

$$argmax_{\phi_k} U_k(\phi_k, \overline{\phi}_1, \overline{\phi}_2) = \begin{cases} 0, & \text{if } \lambda < \lambda^+ \equiv \frac{C_{V,k}(\delta+\mu)(\delta+\gamma+\mu)}{c_{I,k} - C_{V,k}(\delta+\gamma+\mu)}, \\ [0,1], & \text{if } \lambda = \lambda^+, \\ 1, & \text{if } \lambda > \lambda^+. \end{cases} \tag{18}$$

The Nash strategy for the population game (Eqs. 1–8) can be determined by examining the threshold forces of infection (λ_k^+) over the reachable region (Fig. 1). Specifically, if the force of infection is below the threshold λ_k^+ in behavioral group k, the Nash strategy is to refuse vaccination ($\phi_k^* = 0$), as shown in Eq. (18).

For a special case, if the disease incidence at endemic steady states in the absence of vaccination is below both threshold forces of infection, i.e., $\lambda(\overline{\phi}_1 = \overline{\phi}_2 = 0) < \lambda_1^+$ and $\lambda(\overline{\phi}_1 = \overline{\phi}_2 = 0) < \lambda_2^+$ – then the resulting Nash strategy for both subpopulations will be to refuse vaccination ($\phi_1^* = \phi_2^* = 0$). On the other hand, individuals accept vaccination ($\phi_k^* = 1$) if the force of infection is above the threshold value λ_k^+ (see Eq. 34). Finally, if the force of infection is exactly at the threshold value, the individual payoff will be the same for all vaccination strategies. Therefore, the Nash strategy (ϕ_1^*, ϕ_2^*) can be obtained by solving for vaccination strategies (ϕ_k^*) at the intersection of $\lambda = \lambda_1^+$ and $\lambda = \lambda_2^+$ within the reachable region. In this case, one or both behavioral groups may prefer some intermediate vaccination level.

2.4 Calculation of Optimal Vaccination Strategy Driven by Group Interest

The average payoff for the population is defined as the total societal cost per individual, and the utilitarian strategy is calculated by maximizing the expected average payoff. Because the utilitarian strategy is the normatively optimal solution (often determined at a policy level), the best estimate of the parameters of infection and vaccination cost is used as a baseline parameter. The utilitarian strategy generates higher utilities for the community. Using endemic nonuniform steady-state distributions, we can calculate the average payoff:

$$\begin{aligned}\Omega &= -\phi C_V - \frac{(1-\phi)\Delta c_I}{(\Delta+\mu+\delta)(\gamma+\mu+\delta)} \\ &= -\phi C_V - \frac{(1-\phi)\mu c_I}{\gamma+\mu+\delta}\left\{\frac{(1-\phi)\beta-(\gamma+\mu)}{(1-\phi)\beta\mu+\delta(\gamma+\mu)}\right\},\end{aligned}$$

where $\Delta = \beta\mu\left(\frac{1-\phi}{\gamma+\mu} - \frac{1}{\beta}\right)$. Note that $\frac{\partial\Omega}{\partial\phi} = 0$ if and only if ϕ takes the values:

$$\phi_\pm = 1 + \frac{\delta(\gamma+\mu)}{\beta\mu} \pm \frac{(\gamma+\mu)\sqrt{c_I\delta(\mu+\delta)}}{\beta\mu\sqrt{c_I - C_V(\gamma+\mu+\delta)}}.$$

Using $\frac{\partial^2\Omega}{\partial\phi^2}|_{\phi=\phi_+}$ and $\frac{\partial^2\Omega}{\partial\phi^2}|_{\phi=\phi_-}$, we conclude that the optimal measles vaccine coverage for the population is achieved at ϕ_-, provided that $\phi_- \in [0,1]$.

3 Results

Our analysis shows how Nash vaccination levels change as the relative numbers of vaccine skeptics and vaccine believers vary. Specifically, if the proportion of vaccine skeptics is 10 % ($q_1 = 0.1$ and $q_2 = 0.9$), the Nash vaccination level among vaccine believers is less than complete, while the Nash strategy for vaccine skeptics is to reject measles vaccine, i.e., $\phi_1 = 0$ and $\phi_2 \in (0, 1)$ (marked as dot *A* in Fig. 1). Thus, when skeptics and believers are vaccinated according to the Nash strategy at this proportional ratio, the resulting measles vaccine coverage in the population does not exceed 86 % at baseline parameters, a value that is not sufficient to eliminate measles. On the other hand, when the proportion of vaccine skeptics increases to 40 % ($q_1 = 0.4$), the Nash strategy for vaccine believers will be to accept measles vaccination fully ($\phi_2 = 1$), although the Nash strategy of vaccine skeptics may lead to incomplete coverage, i.e., $\phi_1 \in (0, 1)$, or refusal of measles vaccination (marked as a dot *C* in Fig. 1). Under this scenario, the resulting overall measles vaccine coverage in the population would be 64 % (Figs. 2a and 2b). The expected incidence of measles is estimated at 168 cases per million individuals, and the probability of infection among the unvaccinated is 63 % (not shown).

In general, when both vaccine skeptics and believers are vaccinated according to the Nash strategy, the probability of infection among vaccine skeptics increases initially as the number of vaccine skeptics increases, but it decreases once the vaccine skeptics begin receiving the vaccination. This change of pattern occurs because the decline in herd immunity that resulted from the falling level of vaccination by vaccine skeptics generates a rebound in vaccine demand.

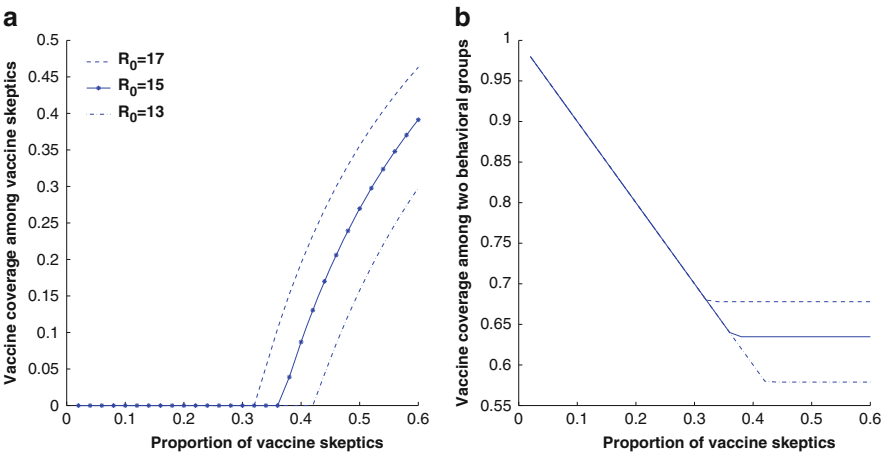

Fig. 2 Effects of the proportion of vaccine skeptics on the demand for measles vaccine and on the resulting measles incidence, based on the Nash strategy. (**a**) The coverage of measles vaccine among vaccine skeptics increases with the proportion of vaccine skeptics and with a basic reproductive ratio. (**b**) Overall measles vaccine coverage in the population, combining both vaccine skeptics and vaccine believers, decreases with the proportion of vaccine skeptics

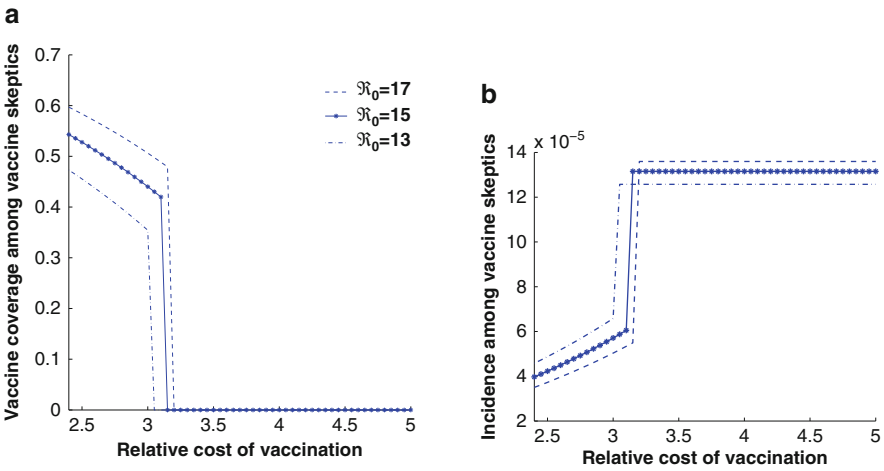

Fig. 3 Sensitivity analysis of the vaccination decision among vaccine skeptics when the cost of vaccination relative to the daily cost of infection ($C_{V,1}/c_{I,1}$) varies. A basic reproductive ratio is varied from 13 to 17, and it is assumed that $q_1 = 0.3$ for illustration purpose. (**a**) The Nash strategy dictates whether to get a vaccination or not, depending on the relative cost of vaccination. With an increasing cost of vaccination, vaccine skeptics are less likely to vaccinate. (**b**) The incidence of measles under the Nash vaccination strategy increases with the relative cost of vaccination

Nash vaccination of vaccine skeptics reveals the trade-off between the risk of infection and vaccine cost (Fig. 3a). Here the vaccine cost is a function of perceived severity of the disease and probability of all potential costs and risks. That is, the calculation of vaccine cost includes perceived risk of measles infection and medical costs associated with the infection. At low vaccine costs, even vaccine skeptics are likely to seek vaccination. However, at higher vaccine costs, the demand for vaccination among vaccine skeptics drops dramatically, resulting in increased incidence of measles (Fig. 3b). The threshold cost of vaccination at which the demand for vaccine starts to drop is increasing with the basic reproductive ratio (Fig. 3a), i.e., the more transmissible a disease is, the lower the barrier to vaccination among vaccine skeptics.

When both behavioral groups are vaccinated according to the utilitarian strategy, levels of measles incidence are significantly lower than they are when vaccination adheres to the Nash strategy (Figs. 3 and 4). For the current vaccine cost (value of 2.4 on the x-axis of Figs. 3b and 4b), the incidence of measles with the utilitarian strategy was estimated to be 40 lower per million individuals than the resulting incidence when vaccination is guided by the Nash strategy (Figs. 3b and 4b). The gap between the incidence of measles under the Nash and utilitarian strategies becomes wider as the perceived cost of vaccination increases among vaccine skeptics (Fig. 4a). This is because utilitarian vaccination level is less elastic to increasing vaccine cost than the Nash vaccination level over the wide range of $\Re_0$ examined (Figs. 3a and 4a).

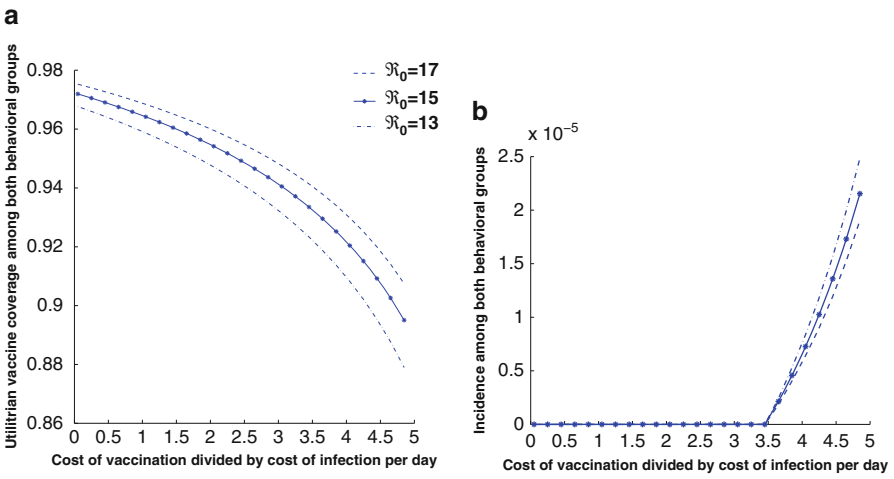

Fig. 4 Utilitarian measles vaccination strategy and its impact on the incidence of measles. (**a**) The measles vaccine coverage level dictated by the utilitarian strategy decreases as the cost of vaccination rises and the basic reproductive ratio falls. (**b**) Measles is likely to become epidemic when the relative cost of vaccination compared to that of infection ($\frac{C_V}{c_I}$) is over 3.5, at the range of basic reproductive ratios considered (i.e., 13–17)

4 Discussion

Our results show that the pursuit of self-interest is likely to lead to suboptimal implementations of vaccination policies and increased risk of measles resurgence, especially in the presence of vaccine skeptics. Compared to the utilitarian vaccination strategy, the vaccine coverage determined by the Nash strategy is generally lower. Furthermore, the discrepancy between the Nash strategy and the utilitarian strategy increases with an increasing proportion of vaccine skeptics.

Measles immunization has stopped measles circulation in the USA, so the memory of measles has faded from the public consciousness. Without the memory of the damage the disease can do, the perceived risks of vaccination among some parents have begun to outweigh their perceived benefits of vaccination [16]. Parents who choose not to vaccinate their own children increase the risk of infection not only for their children but also for the whole community, including vulnerable newborns who are too young to have received vaccines [16]. According to a survey of fellows of the American Academy of Pediatrics (AAP) on immunization-administration practices, MMR vaccine was listed as the most frequently refused vaccine [7]. Major reasons for vaccine refusal were found to be a low perceived risk of infection, parental concerns about effectiveness of vaccine, as well as its safety [16], all of which may reduce the perceived benefits of vaccination. Media messages about even a single adverse vaccine event can quickly change behavior, leading to major declines in vaccine coverage.

The game-theoretic epidemiological analysis we performed can yield insights into the interplay between anti-vaccine behavior, vaccine coverage, and disease dynamics. An individual's vaccination decision depends on the perception of the benefits of vaccination, and these decisions affect the degree of population-level immunity and the force of infection in the population. Our study demonstrates that if the enormous benefits to society from measles vaccination are to be maintained, the public will need to be educated about those benefits in order to increase public confidence.

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References

1. Bauch, C.T. Bhattacharyya, S., Ball, R.F.: PLoS ONE **5**(9), e12594 (2010)
2. Bellman, R.: Dynamic Programming. Princeton University Press, Princeton (1957)
3. Berger, B.E., Omer, S.B.: Hum. Vaccin. **6**, 1016 (2010)
4. Bhattacharyya, S., Bauch, C.T.: J. Theor. Biol. **267**, 276 (2010)
5. Centers for Disease Control and Prevention: Measles–United States, January 1-April 25, 2008. MMWR **57**, 494–498 (2008)
6. Centers for Disease Control and Prevention: Increased transmission and outbreaks of measles–European Region, 2011. MMWR **60**, 1605–1610 (2011)
7. Diekema, D.S.: Pediatrics **115**, 1428 (2005)
8. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **264**, 2, 237 (2010)
9. d'Onofrio, A., Manfredi, P., Poletti, P.: J. Theor. Biol. **273**(1), 63 (2011)
10. Fine, P.E.M., Clarkson, J.A.: Amer. J. Epidemiol. **124**, 1012 (1986)
11. Godlee, F., Smith, J., Marcovitch, H.: Wakefield's article linking MMR vaccine and autism was fraudulent. Br. Med. J. **342**, c7452 (2011)
12. Gust, D.A., Strine, T.W., Maurice, E., Smith, P., Yusuf, H., Wilkinson, M., Battaglia, M., Wright, R., Schwartz, B.: Pediatrics **114**, e16 (2004)
13. Manfredi, P., Posta, P.D., d'Onofrio, A., Salinelli, E., Centrone, F., Meo, C., Poletti, P.: Vaccine **28**, 98 (2009)
14. Miller, M.A., Redd, S., Hadler, S., Hinman, A.: Vaccine **16**(20), 1917 (1998)
15. Nash, J.F.: Proc. Natl. Acad. Sci. USA **36**(1), 48 (1950)
16. Omer, S.B., Salmon, D.A., Orenstein, W.A., deHart, M.P., Halsey, N.: N. Engl. J. Med. **360** 1981 (2009)
17. Parker Fiebelkorn, A., Redd, S.B., Gallagher, K., Rota, P.A., Rota, J., Bellini, W., Seward, J.: J. Infect. Dis. **202**, 1520 (2010)
18. Poland, G.A., Jacobson, R. M.: Vaccine **30**(2), 103 (2012)
19. Reluga, T.: J. Biol. Dyn. **3**, 515 (2009)
20. Shim, E., Grefenstette, J.J., Albert, S.M., Cakouros, B.E., Burke, D.S.: J. Theor. Biol. **295** 194 (2012)
21. Shim, E., Kochin, B., Galvani, A.P.: Math. Biosci. Eng. **6**, 841 (2009)
22. Shim, E., Meyers, L.A., Galvani, A.P.: BMC Public Health. **11**, Suppl 1, S4 (2011)
23. Zhou, F., Reef, S., Massoudi, M., Papania, M.J., Yusuf, H.R., Bardenheier, B., Zimmerman, L., McCauley, M.M.: J. Infect. Dis. **189**, Suppl 1, S131 (2004)

Vaccinating Behaviour and the Dynamics of Vaccine Preventable Infections

Alberto d'Onofrio, Piero Manfredi, and Ernesto Salinelli

Abstract A main research area in the behavioural epidemiology (BE) of infectious diseases deals with the modelling of vaccinating behaviour under voluntary immunisation. We attempt to provide a broad overview of our research work on the subject, by separately analysing a general prevalence-based framework, where vaccine uptake is taken as a function of the relevant information used by parents to immunise their children, such as the prevalence (or incidence) of infection, of serious disease, or of vaccine associated side effects, and an imitation-based framework where behaviour perceived as optimal spreads through spontaneous communication between individuals about the benefits and cost of vaccination. We also discuss the relationships between the two modelling framework. Finally, we supply new results concerning the impact of realistic information kernels and the appearance of chaotic oscillations due to the interplay of periodic contact patterns and vaccinating behaviour.

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1 Introduction

As documented in the historical overview [2], a main research area in the behavioural epidemiology (BE) of infectious diseases deals with the modelling of vaccinating behaviour under voluntary immunisation for vaccine preventable infections, as measles or pertussis, and the related implication for infection transmission and control. In the last years we have investigated the implications of vaccinating behaviour and the underlying pattern of information for the dynamics of simple deterministic transmission models (e.g. SIR models). In particular, we have considered both *prevalence-based* [14] models, where behaviour is represented through some phenomenological functions relating, e.g. vaccine uptake to infection prevalence [7–10], and *imitation-based* models [11], where vaccinating behaviour perceived as optimal spreads through an imitation process, as originally investigated by [3]. In this chapter we depart from our past work on the area to provide a broad overview of modelling vaccinating behaviour and its dynamic consequences, and to also introduce some new results. We first introduce a general prevalence-based framework developed in [7] where vaccine uptake is taken as an appropriate function of the relevant information used by parents to immunise their children, such as the prevalence (or incidence) of infection, of serious disease, or of vaccine associated side effects. We subsequently focus on the central case where vaccine uptake depends on infection prevalence alone, originally considered in [16] and separately developed in [7] and [23]. We report a general proof of the main results of this literature, i.e. the impossibility to eliminate infection when vaccine behaviour is prevalence dependent, and show that sustained oscillations are the rule when realistic patterns of information, including not only the current but also past information according to plausible mechanisms, are considered. We also report new results showing chaotic oscillations arising from the interplay between realistic, i.e. periodic, patterns of transmission, and prevalence-based vaccination behaviour. Then we move to the other critical case, i.e. a highly vaccinated population where vaccine uptake depends on the burden of vaccine side effects (VSE) alone [10]. This case is perhaps the most relevant in modern industrialised countries where, due to decades of sustained immunisation, the perceived risk of infection is steadily low, and therefore the perceived risk of VSE might become the central determinant of vaccine uptake. We indeed show, by appropriately modelling, that the transmission dynamics is fully determined in this case by the feedback between vaccine uptake and the burden of VSE. Finally, we critically review the imitation-based model in [11]. Thanks to the formulation adopted therein, we are able to unravel the relationship between prevalence-based and imitation-based models.

As our focus is on substantive matters, we almost never report mathematical details, unless required for model building or for presenting new results.

This chapter is organised as follows. In Sect. 2 we present our general prevalence-dependent framework. Sections 3 and 4 are respectively devoted to the case where vaccine uptake depends on infection prevalence alone and on the VSE burden alone. The imitation-based model is reported in Sect. 5. Concluding remarks follow.

2 A Family of Information-Based Models for Vaccinating Behavior

In the standard SIR model for childhood immunisation, vaccine uptake is just constant [1]. Under voluntary vaccination parents will decide whether to immunise or not their children depending primarily on available information about perceived costs and benefits of that immunisation. Our framework for information-related immunisation [7–10] considers the following SIR model for a non-fatal paediatric infection in a stationary homogeneously mixing population:

$$S' = \mu\,(1 - p(M)) - \mu S - \beta(t)SI, \tag{1}$$

$$I' = I(\beta\,(t)\,S - (\mu + \nu)), \tag{2}$$

where S and I respectively denote the fractions of susceptible and infectious individuals, $\mu > 0$ denotes the birth and death rates, which are assumed identical, $\nu > 0$ the rate of recovery from infection, $\beta(t) > 0$ the transmission rate, which is taken either constant or periodically varying with minimal period θ equal to one year [1]. As the population is constant, the recovered fraction R is simply given by $R = 1 - S - I$.

The novelty of Eqs. (1)–(2) is the vaccine uptake at birth (based for simplicity on a perfect vaccine), which is assumed to be a function p of a suitable variable M summarising the information on benefits and costs of immunisation used by parents to take their vaccination decisions. Thus M might be any function of the *current*, or *past*, infection prevalence (or incidence), taken as measures of the perceived cost of acquiring infection or some serious sequelae of it, or of the prevalence (or incidence) of vaccine adverse events (VAE), taken as measures of the perceived cost of suffering some VAE or even of both. We will analyse in a later section the case where M measures the perceived risk of VAE, and focus here on the perceived risk of disease as the driving force of immunisation decisions. Noteworthy examples measures of perceived risk based on current incidence, or prevalence, are respectively $M = h\beta(t)SI$ $(h > 0)$ or $M = kI$ $(k > 0)$. For example, the latter expression defines the perceived risk of disease as the product of the perceived risk of infection, given by some linear function of prevalence, times the perceived risk of serious disease given infection, taken as constant. Generalising these examples above, we can assume that M is given by a continuous function g of S and I, which is increasing in the I variable. For simplicity, here we shall deal with functions g depending on I alone.

More realistically M also depends on past values of state variables, as for many infections information becomes available only after long procedures (laboratory confirmations, reporting to public health authorities, etc.), and moreover spreading among the population requires time. In this case M also includes past values of the function g, supplying a third equation to system (1)–(2):

$$M(t) = \int_{-\infty}^{t} g(I(\tau))K(t-\tau)d\tau, \tag{3}$$

where K is a probability density function called the *delaying kernel* [20].

Here, besides the trivial kernel $K(t) = \delta(t)$, where δ is the Dirac function, yielding the unlagged case, we consider two main types of delaying kernels, i.e. the well-known *exponentially fading memory* kernel $K(t) = a\exp(-at)$, with expectation given by the fading timescale $T = 1/a$ [20], and the kernel

$$K(t) = \frac{1}{T_1 - T_2}\left(e^{-t/T_1} - e^{-t/T_2}\right). \tag{4}$$

This kernel, which is used here for the first time, in the context of BE, may take into account two sub-processes occurring at different timescales: *(i)* formation and acquisition of information, with time-scale T_1, and *(ii)* memory fading, with timescale T_2. Note that if the first process is much faster than the second, i.e. $T_1 \approx 0$ then $K(t) \approx (1/T_2)e^{-t/T_2}$, i.e. the memory fades exponentially with timescale T_2. This kernel has expectation $T_1 + T_2$ and variance $T_1^2 + T_2^2$. Compared to the exponentially fading memory, which assigns maximum weight to the current information—usually unavailable—this kernel satisfies $K(0) = 0$, mirroring unavailability of current information, as in the commonly used Erlangian kernels [20], and it is still reducible to ordinary differential equations (ODE). Compared to Erlangian kernels which consider sub-process having the same timescale, this kernel is obviously much flexible. We will call it the *acquisition-fading* kernel.

The vaccine uptake function p is defined as

$$p(M) = p_0 + p_1(M) \quad , 0 < p_0 < 1, \tag{5}$$

i.e. it is the sum of a fixed baseline component p_0, meaning that a fraction of the population vaccinates independently of the state of information M and of an increasing—usually sigmoidal—function $p_1(M)$, mirroring the parents' reaction to the changing perceived risk of the disease. For example, taking M to be the current infection prevalence, our formulation means that when infection prevalence increases, parents in the group influenced by information react by increasing the vaccine uptake of their children and vice versa. In particular, for large levels of M, we assume p_1 to saturate to some level $p_1^{\text{sat}} \leq 1 - p_0$. We assume that $0 \leq p_1(M) \leq 1 - p_0 \; \forall M > 0$, with $p_1(0) = 0$, and that p_1 is continuous and differentiable, except at a finite number of points.

Many sub-models can derived by the general formulation (1)–(3). Under the trivial kernel, we recover the unlagged case $M = g(I)$, obtaining

$$\begin{aligned} S' &= \mu(1 - p_0 - p_1(g(I)) - \mu S - \beta(t)SI, \\ I' &= I(\beta(t)S - (\mu + \nu)). \end{aligned} \tag{6}$$

Under the exponentially fading memory Eq. (3) reduces to the single ODE:

$$M' = a(g(I) - M). \tag{7}$$

Finally, under the kernel (4) Eq. (3) reduces to the pair of ODEs:

$$M_1' = a_1 (g(I) - M_1), \tag{8}$$

$$M_2' = a_2 (M_1 - M_2), \tag{9}$$

where $a_1 = 1/T_1$, $a_2 = 1/T_2$, $M(t) = M_2(t)$.

Following the review in [14], we remark that the framework considered here is *prevalence-based*, as opposite to belief-based, with *global* information, i.e. (homogeneously) available to everyone. Prevalence-based vaccinating behaviour has been documented in the literature [22].

3 Properties of the General Model

Investigating the model properties, through mathematics and simulation, gives insight about the interplay between information and vaccinating behaviour on the one hand and infection transmission and control on the other. There are two main substantive questions here, i.e. whether elimination is possible under prevalence-dependent vaccination and how behaviour might affect the dynamical pattern of infection, e.g. by triggering oscillations.

3.1 Elimination Is an Unfeasible Target

As for the first question we have some fairly general results [7]. Note that model (1)–(3) always admits the disease-free equilibrium (DFE):

$$DFE = (1 - p_0, 0, 0). \tag{10}$$

The stability properties of the DFE are provided by the following theorem.

Theorem 1. *Both under θ-periodic or constant β, the DFE (10) of Eqs. (1)–(3) is globally asymptotically stable (GAS) if*

$$\frac{1 - p_0}{\mu + \nu} \frac{1}{\theta} \int_0^\theta \beta(u) du \leq 1. \tag{11}$$

Note that if β is constant, then condition (11) becomes the well-known one $R_0(1-p_0) \leq 1$, where $R_0 = \beta/(\mu+\nu)$ is the basic reproduction number of the infection of the well-known SIR model for endemic infections [1,6].

The previous result shows that if the steady component p_0 of vaccine uptake lies below the appropriate elimination threshold (given by $p_c = 1 - 1/R_0$ in the constant β case), elimination can never be achieved even if the overall uptake could reach values as high as 100 % during epochs of high prevalence. We called this result *elimination: mission impossible* [7,9,10].

Moreover, if β is constant and the following condition holds:

$$(1-p_0)\,R_0 > 1 \tag{12}$$

there exists a unique endemic equilibrium $\mathrm{EE} = (S_e, I_e, M_e)$ for (1)–(2)–(3) [7,9,10]. Note that the location of the EE is not affected by the delays.

For the unlagged case Eq. (6), and under the assumption that β is constant and p_1 is differentiable, we could prove the following global result [7]:

Theorem 2. *Let $R_0(1-p_0) > 1$. Then the unique endemic state EE of system (6) is GAS in the positively invariant set:*

$$\Omega^{**} = \{(S,I) \mid S \geq 0,\ I > 0,\ S+I \leq 1,\ S \leq 1-p_0\}\,. \tag{13}$$

3.2 Onset of Stable Oscillations Under Delayed Responses

The previous global result indicates that information delays are necessary to have oscillations, as first conjectured in [16]. Next result shows that stable oscillations appear by Hopf bifurcation of the endemic state, under the simplest pattern of delay, i.e. the exponentially fading memory. Assuming for simplicity $g(I) = kI$, the following result shows how the local stability of EE and onset of oscillations depend on the delay parameter $a = 1/T$ [7]:

Theorem 3. *If and only if*

$$(\beta I_e + \mu)^2 - \beta I_e \mu k p_1'(M_e) + 2(\beta I_e + \mu)\sqrt{\beta I_e(\nu+\mu)} < 0 \tag{14}$$

there exist two Hopf bifurcations points a_1, a_2 with $0 < a_1 < a_2$ of parameter a such that EE is LAS for $a \notin [a_1, a_2]$ and unstable for $a \in (a_1, a_2)$, where global Yacubovich oscillations occur [13].

The previous result shows that oscillations, which arise in an intermediate window of the range of the average information delay, require the presence of a strong (delayed) behavioural response to changing prevalence. Further details are reported in [7]. Under the more realistic kernel (4), computations are more involved.

Anyhow, from the Jacobian matrix at the endemic equilibrium, one can symbolically calculate the characteristic polynomial, in the form

$$\sum_{i=0}^{4} b_i(a_1, a_2)\lambda^i = 0, \tag{15}$$

where each coefficient is taken as a function of the two delay parameters a_1, a_2. By the Routh–Hurwitz condition one can then seek in the positive quadrant of the (a_1, a_2) plane the regions of local stability. A numerical example is reported in the next section.

3.3 Some Illustrations and Numerical Simulations

In this section we report illustrations for some selected sub-cases, relying on the following parameter constellation, roughly mimicking measles in developed countries, [7,9,11]: $\mu = (1/L)\text{days}^{-1}$ where $L = 75 \cdot 365$ days is the life expectancy at birth, $\nu = (1/\mathscr{D})\text{days}^{-1}$ where $\mathscr{D} = 7$ days is the average duration of infection, and $R_0 = 10$ or $R_0 = 15$ ($\beta \approx 1.43\,\text{days}^{-1}$). For simplicity we set $g(S,I) = I$. As for the vaccine uptake function we set the baseline component p_0 at $p_0 = 0.75$, while for p_1 we follow the functional forms adopted in [7]. A first possibility is the piecewise linear coverage:

$$p_1(M) = \min\{cM,\ 1 - p_0\},$$

where c is a positive constant. In this case the information-dependent component of vaccine uptake reacts linearly to increasing prevalence until the point when it jumps to its upper bound $1 - p_0$. A more realistic case is given by the following Michaelis–Menten function:

$$p_1(M) = (1 - p_0 - \varepsilon)\,\frac{DM}{DM + 1}. \tag{16}$$

This parametrisation implies a maximal overall coverage of $= 1 - \varepsilon$ for very large M values. Here we choose $\varepsilon = 0.01$. Keeping constant the maximal coverage the reactivity of p_1 to changes in M is tuned by D.

3.3.1 Stability Regions Under the *Acquisition-Fading* kernel

Under linear p_1 it is possible to obtain sufficiently simple forms for the coefficients $b_i(a_1, a_2)$ for the characteristic polynomial (15):

$$b_0(a_1,a_2) = a_1a_2\beta\mu(p_{cr}-p_0),$$

$$b_1(a_1,a_2) = \frac{\mu(\mu(1+c)+\nu+\beta(p_{cr}-p_0))}{\mu+\nu+\mu c}a_1a_2 - \frac{\beta\mu(\mu+\nu)(p_0-p_{cr})}{\mu+\nu+\mu c}(a_1+a_2),$$

$$b_2(a_1,a_2) = a_1a_2 + \frac{\mu(\mu(1+c)+\nu+\beta(p_{cr}-p_0))}{\mu+\nu+\mu c}(a_1+a_2) - \frac{\beta\mu(\mu+\nu)(p_0-p_{cr})}{\mu+\nu+\mu c}$$

$$b_3(a_1,a_2) = (a_1+a_2)+\mu+\frac{\beta\mu(p_{cr}-p_0)}{\mu+\nu+\mu c}.$$

In Fig. 1 we show the corresponding local stability regions (in grey), in the space (T_1,T_2) for increasing values of the parameter c. Notably, the area of the instability region increases with the sensitivity c of vaccine uptake to changing prevalence, up to the point where any however small delay in information acquisition yields oscillations. This shows the intrinsically oscillating nature of the system: an increasing prevalence raises the *demand* for vaccines, whose increase will reduce prevalence, and eventually the vaccine demand, as first noted in [16].

3.3.2 Dynamic Patterns in the Oscillating Regime

We illustrate some dynamic effects of vaccinating behaviour by simulating (1)–(3) under *exponentially fading* kernel and Michaelis–Menten response in a situation where the infection is endemic with constant vaccine uptake at the baseline level p_0, and prevalence-dependent behaviour abruptly arises at time $t = 0$. We assume $g(S,I) = I$, $T = 4$ months, $D = 15000$ and $R_0 = 15$, implying that the systems is in its "cyclic zone"(see [7]). Figure 2 reports the transient (left-hand side) and long-term (right-hand side) time paths of the effective reproduction number $R_E(t) = R_0S(t)$ (top), of the infective proportion (medium), and of the overall vaccine uptake $p(M) = p_0 + p_1(M)$ (bottom), jointly with its time average. All state variables converge to a stable limit cycle. Note that in the long-term the inter-epidemic period stabilises around 12 years, i.e. about 2.5 times the value of the pseudo-period of the SIR model with constant baseline vaccination ($p_0 = 0.75$). Moreover though $p(M)$ reaches levels as high as 97 % during epochs of high perceived risk, i.e. in correspondence of the epidemic phases, the average long-term coverage does not exceed 79 % over time. This supplies further intuition on why elimination is impossible.

3.4 The Effects of Seasonal Fluctuations in the Contact Rate

Since the seminal work in [21], the seasonal oscillations of the contact rate $\beta(t)$ are considered the main route to complex behaviour in simple models for infectious diseases. In the context of vaccination models, they may have a deep impact,

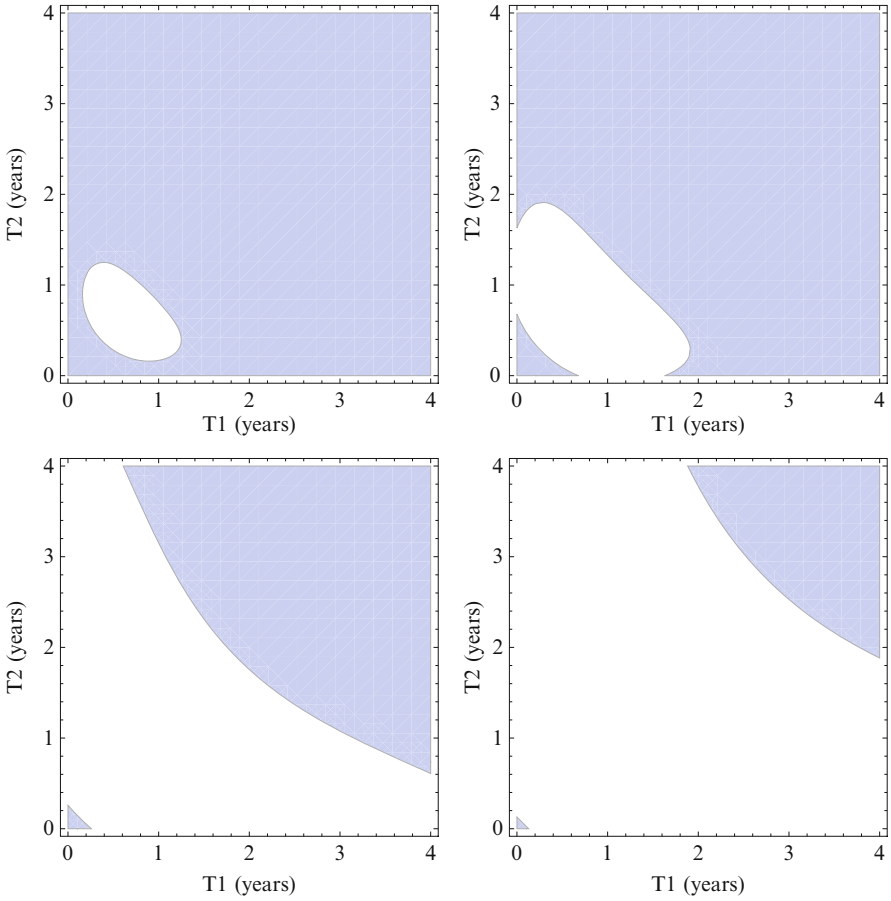

Fig. 1 Local stability region *(grey)* under the *information-fading* kernel and piecewise linear vaccination response $p_1(M) = Min(1 - p_0, cM)$ with $g(I) = I$ for various values of c. *Upper-left panel*: $c = 0.20(1 - p_0)/I_{SIR}$; *upper-right panel*:$c = 0.25(1 - p_0)/I_{SIR}$; *lower-left panel*: $c = 0.5(1 - p_0)/I_{SIR}$; *lower-right panel*: $c = (1 - p_0)/I_{SIR}$

see the exhaustive study by **choisy** [5] in the framework of pulse vaccination strategies. As regards the interplay of behaviour and seasonality, we already found chaotic oscillations in a periodically forced SIR model with a prevalence-dependent contact rate [12]. Seasonal patterns of prevalence are especially interesting for vaccinating behaviour as might strength prevalence-based vaccinating responses [22]. Here we just illustrate (Figs. 3 and 4) the possibility of complex behaviour triggered by a periodic contact rate $\beta(t) = \beta_*(1 + Asin(2\pi t/T))$ ($A \in [0, 1]$) under the *acquisition-fading* kernel and Michaelis-Menten-type $p_1(M)$. Note that in such a case in absence of oscillations of β the damped or sustained periodic fluctuations of the state variables exhibit a, respectively, pseudo-period or period that is far

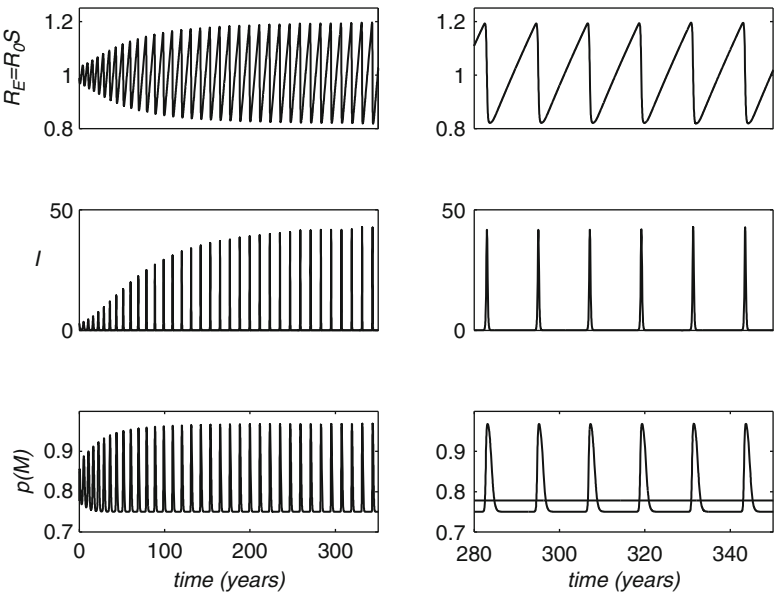

Fig. 2 Dynamics of model (1)–(2)–(3) for $g(S,I) = I$ under *exponentially fading* kernel ($T =$ 4 months) and Michaelis–Menten response ($D = 500$). Transient (*left-hand side*) and long-term (*righ-hand side*) paths of (**a**) effective reproduction number $R_E = R_0 S$, (**b**) infective proportion I (normalised to its equilibrium value), and (**c**) overall vaccine uptake p_M (compared to its time average given by the flat line in the right-bottom graph). R_0 is equal to 15. Figure adapted from reference [7] (C) Elsevier Science Ltd

larger than one year, which might suggest impossibility of observing nonlinear resonances. These were, instead, observed in our simulations. In the baseline case of damped oscillations in absence of fluctuations in β (Fig. 4), already small amplitude seasonal fluctuations ($A = 0.1$, upper left panels in Figs. 3 and 4) yield irregular oscillations with a strongly variable inter-epidemic period and distribution of peak amplitudes. The inter-epidemic period increases with A, and maximum observed peak increases more than linearly with A. Moreover, in a background of behaviour-induced oscillations (Fig. 4) the variance of the distribution of peaks seems decreasing in A.

3.5 Inclusion of Disease-Related Mortality

If infection may cause death, as is still the case for measles and pertussis, then the perceived cost associated with infection is essentially described by the probability of suffering death as a consequence of infection. Modelling vaccinating behaviour requires in this case to include in the model disease-related mortality, e.g. as a

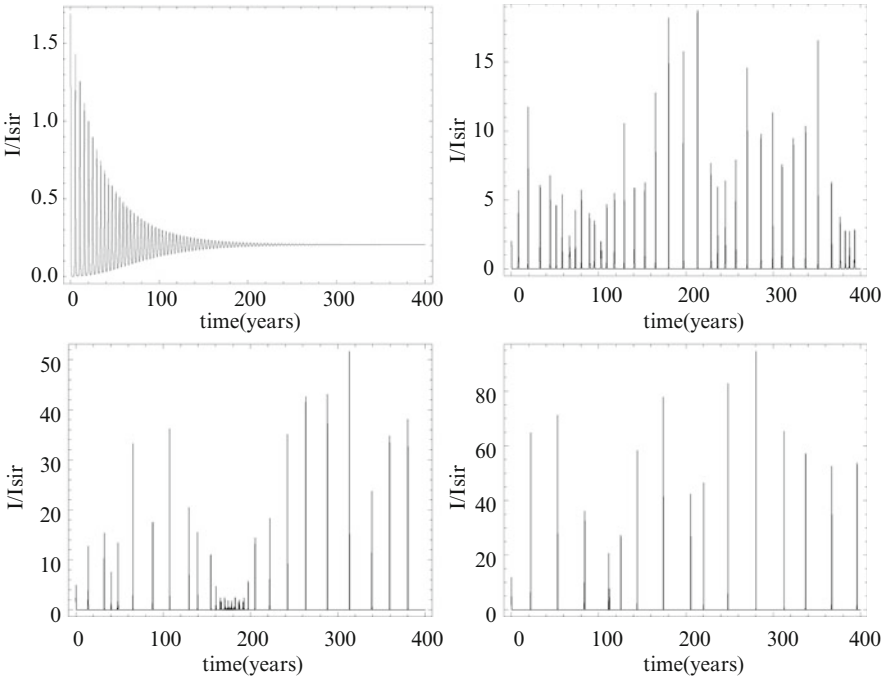

Fig. 3 Prevalence dynamics of periodic contact rate $\beta(t) = \beta_*(1 + A sin(2\pi t/T))$, *acquisition-fading* delay kernel ($T_1 = 1\,year$, $T_2 = 7\,days$), and Michaelis–Menten p_1 reaction with $D = 500$ (no information-induced oscillations). *Upper-left panel*: baseline case of constant contact rate ($A = 0$); *upper-right panel*: $A = 0.1$; *lower-left panel*: $A = 0.25$; *lower-right panel*: $A = 0.5$. Parameters: $\beta_* = 20(\mu + \nu)$, $T = 1\,year$

constant proportion δ of those who are infectious. As well known this prevents the possibility of an endemic equilibrium with positive population in the basic model SIR with stationary population [15] and therefore a more general framework for the dynamics of the population is required. Common candidates for this are density-dependent or exponential population dynamics [24]. In the former case, whose most natural example is the classical logistic law for population growth, the birth and death rates are replaced by appropriate functions $B(N)$ and $D(N)$, of the total population size. In the latter case the birth and death rates are taken as distinct constants b, μ, thereby promoting—in absence of the infection—either exponential population growth ($b > \mu$) or decay ($b < \mu$).

In [9] we amended the basic model Eqs. (1)–(3) by making the information index M dependent on the incidence δI of disease-related mortality, within a fully consistent framework. The results we obtained are fairly consistent with those of model Eqs. (1)–(3).

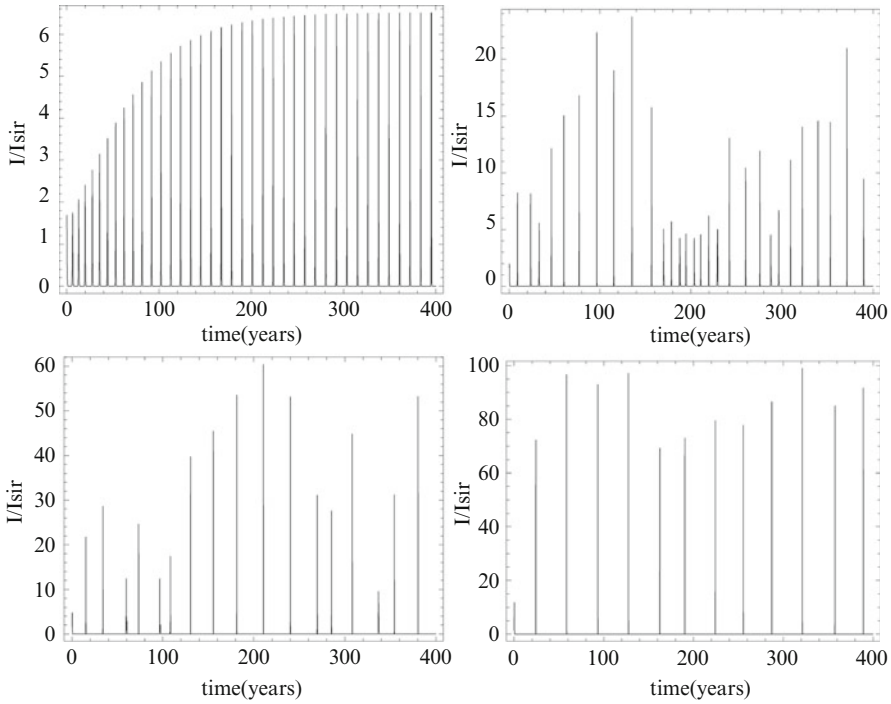

Fig. 4 As in Fig. 3 but Michaelis–Menten p_1 reaction with $D = 5000$ (presence of behaviour-induced oscillations). *Upper-left panel*: $A = 0$; *upper-right panel*: $A = 0.1$; *lower-left panel*: $A = 0.25$; *lower-right panel*: $A = 0.5$

4 Vaccine Demand Driven by Vaccine Side Effects

Due to the herd immunity allowed by decades of mass immunisation, in modern industrialised countries the current perceived risk of serious disease from many infections is steadily very low. At the same time the large number of yearly immunisations unavoidably yields, despite the safety of current vaccines [25], a steady flow of VAE [26]. For example, in the USA the yearly reported number of VAE is about 30,000, with 10–15 % causing disability, hospitalisation, life-threatening illness, or death [4]. The VAE burden might make the perceived risk of suffering VSE much higher than the perceived risk of serious infection. This has been the case for polio immunisation: for instance in Italy during 1979–1999 the number of vaccine-induced poliomyelitis cases exceeded natural Polio cases by a factor 3 [19]. In these situations the perceived risk of VSE might become the driving force of the vaccine demand.

We therefore present a model [10], complementary to that of Sect. 2 in which the vaccine uptake $p(M)$ is determined by the perceived risk M of suffering VSE alone, according to a decreasing function of the (current or past) prevalence of

VSE. After having developed a framework for describing VSE, we show that in this case the burden of VSE becomes the main determinant on infection transmission and report some noteworthy general results and predictions about the evolution of immunisation programmes.

4.1 Modelling the Prevalence of Individuals Hit by VSE

We consider an infection for which the perceived risk of serious disease is negligible, because, e.g. the disease is mild or the incidence of infection is steadily low, which is controllable by a perfect vaccine having a constant probability of severe, non-lethal, VSE. If M now represents the perceived risk of VSE, then the vaccine uptake $p(M)$ is decreasing in M: $p'(M) < 0$. Let $C(t)$ and $H(t)$ denote the current prevalence and incidence of individuals hit by VSE. If parents make their vaccination choices by using information on current prevalence only, then $M = F(C)$, where F is a continuous increasing function. For the sake of simplicity we take $M = C$.

Under these assumptions the dynamics of $C(t)$ is determined by the balance between the outflow of natural mortality (on the assumption that having suffered a VSE does not affect mortality) and the inflow H represented by the current incidence of VSE:

$$C'(t) = H(t) - \mu C. \tag{17}$$

Let us now seek an appropriate relation for the incidence H of VSE. Consistently with the WHO definition, we assume that the hazard of VSE is a function $\psi(\tau)$ of the time τ elapsed since vaccination. By introducing the age-since-vaccination density $W(t,\tau)$, representing the distribution (at any time t) of vaccinated individuals at risk of VSE according to the time τ elapsed since vaccination, $W(t,\tau)$ obeys the PDE:

$$\begin{aligned} \frac{\partial W}{\partial t} + \frac{\partial W}{\partial \tau} &= -\psi(\tau)W - \mu W, \\ W(0,\tau) &= W_o(\tau), \\ W(t,0) &= \mu p(M(t)). \end{aligned} \tag{18}$$

The PDE (18) states that vaccinated individuals at risk of VSE can be removed either by the onset of a VSE, at rate $\psi(\tau)$, or by mortality. The boundary condition $W(t,0)$ is given by the per capita incidence $\mu p(M(t))$ of new immunisations per unit of time. In particular the overall fraction V of individuals at risk of VSE is

$$V(t) = \int_0^{+\infty} W(t,\tau)d\tau \tag{19}$$

while the incidence H of VSE is given by

$$H(t) = \int_0^{+\infty} \psi(\tau) W(t,\tau) d\tau. \tag{20}$$

By solving Eq. (18) [18] the incidence of VSE can be expressed as

$$H(t) = f(t) + \mu \int_0^t p\left(M(t-\tau)\right) \psi(\tau) K_o(\tau) d\tau, \tag{21}$$

where the function $f(t)$ depends on the initial age distribution of W and tends to zero for large t; moreover

$$K_0(\tau) = \exp\left(-\mu\tau - \int_0^\tau \psi(x) dx\right). \tag{22}$$

Plugging (21) in Eq. (17) on the assumption that $M = C$, we obtain the following distributed-delay differential equation for C:

$$C'(t) = -\mu C + f(t) + \mu \int_0^t p\left(C(t-\tau)\right) \psi(\tau) K_o(\tau) d\tau \tag{23}$$

with convolution kernel $K_D(\tau) = \psi(\tau) K_0(\tau)$. A similar equation can be derived for H. Note that the equation for C (H) is independent of the epidemiological variables S, I, so one can first study the dynamics of C (H) from Eq. (23) and then use the relation $p = p(C)$ as an input for the system in S and I. The interpretation is that under our hypotheses the burden of VSE is the unique determinant of vaccine uptake and consequently the trigger of the transmission dynamics of the infection. Note finally that if M depends on past rather than current prevalence parents then the same arguments used in Sect. 2 apply [10].

4.2 Equilibria and Stability of the Prevalence of VSE

As the mechanisms governing the onset of VSE and the related hazard $\psi(\tau)$ are poorly understood (especially under multi-vaccine), it is of interest to analyse the properties of Eq. (23) for a generic $\psi(\tau)$. Let us introduce the following useful function:

$$B_\psi(\mu) = \int_0^{+\infty} \psi(\tau) K_o(\tau) d\tau = \int_0^{+\infty} \exp(-\mu\tau) \exp\left(-\int_0^\tau \psi(z) dz\right) \psi(\tau) d\tau. \tag{24}$$

The function $B_\psi(\mu)$ is positive and decreasing with $B_\psi(0) = 1$.

We start by observing that Eq. (23) always has a unique epidemiologically meaningful steady state C_∞, which fulfils:

$$C_\infty = B_\psi(\mu) p(C_\infty). \tag{25}$$

Note that $C_\infty < \widetilde{C}$, where $\widetilde{C}$ fulfils: $\widetilde{C} = p\left(\widetilde{C}\right)$.

The local stability properties of C_∞ are determined by linearising Eq. (23) at C_∞ and Laplace-transforming, getting

$$\lambda + \mu = \mu p'(C_\infty) B_\psi(\mu + \lambda). \tag{26}$$

The analysis of Eq. (26) for a generic hazard of VSE yields the following easily interpretable stability condition:

Theorem 4. *If the following constraint*

$$|p'(C_\infty)|B_\psi(\mu) < 1 \tag{27}$$

holds then the equilibrium point C_∞ is locally and globally asymptotically stable.

In simple words, C_∞ is globally stable—independently of the age mechanism which generates VSE—as far as the demand for vaccines $p(C)$ (at C_∞) is not too sensitive to changing perceived risks of VSE.

In [10] deeper analyses are carried out for noteworthy sub-cases of the hazard of VSE $\psi(\tau)$, namely, *(i)* $\psi(\tau) = \bar{\psi}\delta(\tau)$, i.e. the hazard of VSE is concentrated during vaccination; *(ii)* $\psi(\tau) = \psi \ \ \forall \tau > 0$, i.e. VSE arise at constant rate $\psi > 0$ independent of the age τ since vaccination; *(iii)* $\psi(\tau) = \bar{\psi}\delta(\tau - T)$, i.e. VSE arise with a fixed delay. We have shown that global stability always holds in sub-cases *(i)-(ii)*, whereas Hopf bifurcations of the steady state can occur under *(iii)*. Obviously, considering lagged information allows the onset of oscillations even in cases that are globally stable in absence of the delay. Results on the impact of the vaccine uptake $p(M)$ dynamics for the epidemiological variables S and I are available in [10].

4.3 Numerical Simulations

Even in simple cases vaccination choices informed by the perceived risk of VSE have interesting effects on infection dynamics. We illustrate this by simulation of the base case $M(t) = C(t)$, where M is given by the current VSE prevalence, under an age-independent VSE hazard (case *(ii)* above). In this case the dynamics of prevalence is given by the 2-dimensional ODE system in the variables (V, C):

$$\begin{aligned} V'(t) &= \mu p(C) - (\mu + \psi)V \\ C'(t) &= \psi V - \mu C \end{aligned} \tag{28}$$

having a unique equilibrium point $E_{VC} = (V_\infty, C_\infty)$ where $V_\infty = (\mu/\psi)C_\infty$, which is always GAS independently of $p'(C_\infty)$ [10]. For the simulation we use the following form for $p(M)$:

$$p(M) = p_0 + (1 - p_0 - \varepsilon) \cdot p_1(M),$$

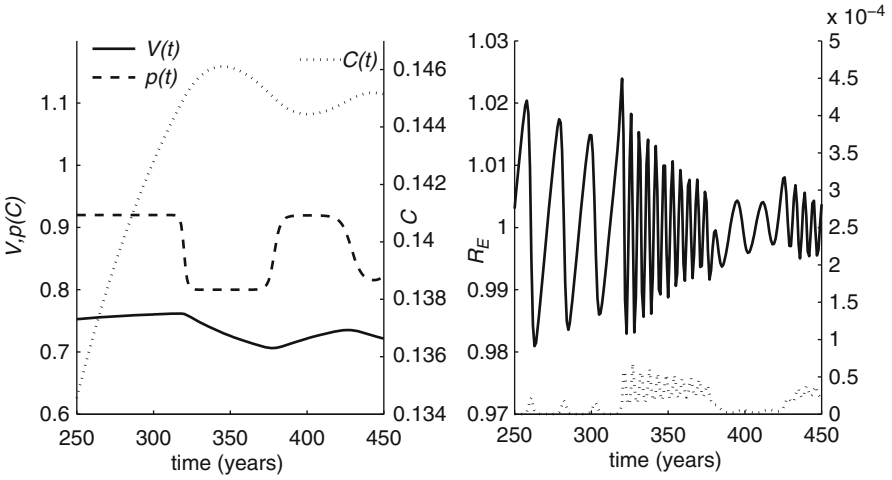

Fig. 5 Switch between different transmission epochs in the base case model with $M(t) = C(t)$, and age-independent VSE hazard. The figure reports long-term behaviour (250 years after the initiation of the programme). *Left panel*: time paths of VSE prevalence C, vaccine uptake $p(C)$, and exposed to risk of VSE, V. *Right panel*: effective reproduction number R_E and infective prevalence I. The system is initialised at time $t = 0$ from the pre-vaccination equilibrium of S, I, and with $p = 0.92$. Parameter values are reported in the main text. Figure taken from [10] (C) Elsevier Science Ltd

where

$$p_1(M) = p_{\min} + \frac{(p_{\max} - p_{\min})}{1 + \exp(-\sigma(M - M^*))}$$

with $p_0 = 0.80$, $\varepsilon = 0.08$, $\psi = \mu/5$, $M^* = .145$,$\sigma = 10,000$, and $R_0 = 15$ (other parameters as in Sect. 2). Under this parameter constellation the infection cannot be eliminated because the maximal coverage in absence of VSE is 92 %, which is below the critical threshold. However, Eq. (28) shows (damped) oscillations. As the vaccine uptake function $p(M)$ is very steep about the steady state C_∞, even very mild changes in C might cause substantial changes in vaccine uptake, thereby substantially affecting the dynamic regime of infection. This is illustrated in Fig. 5 where the long-term path following a new immunisation programme with coverage equal to the maximal one (92 %) is initiated at time $t = 0$. There is long uninteresting transient phase lasting about 250 years (not reported in the figure), during which nothing happens to transmission because the prevalence of VSE, which is slowly increasing toward its steady state, is too low to affect $p(M)$ significantly. However as C, V approach their steady state, they start oscillating. These oscillations of C bring large oscillations in vaccine uptake, due to the steepness of $p(M)$ about the steady state. These oscillations in vaccine uptake have a long pseudo-period (about 40 years) thereby yielding remarkable changes in the dynamics. Indeed, while for the long initial adjustment epoch the infection oscillates with long pseudo-period induced by the slow recruitment of susceptibles due to the high coverage, as soon as C approaches its equilibrium (about 330 years after the initiation of the

programme) the vaccine uptake $p(M)$ experiences a big drop, falling to about p_0, where a different epidemiological regime prevails. This new regime is characterised by a much shorter inter-epidemic period, due to the lower uptake, and lasts about 45 years, i.e. until when vaccine uptake restarts increasing, yielding a new regime with high coverage and long-inter-epidemic period, and so on. This example is suggestive of the fact that strong behavioural responses perceptions about vaccine side effects might strongly affect vaccine uptake and therefore infection trends.

5 An imitation-Based Model of Vaccine Uptake Process and Vaccine Side Effects

Unlike previous sections, we now consider a more behaviour-explicit model where vaccine uptake is determined by an *imitation process*, as in the seminal paper [3], with however a more general formulation, including a different specification of the perceived cost of VSE [11]. This alternative formulation will prove useful to link the class of imitation-based models with the prevalence-based models of previous sections and supplies some further noteworthy insight.

5.1 Imitation-Based Models for Vaccine Uptake: Some General Remarks

Let us consider the model

$$S' = \mu(1-p) - \mu S - \beta SI, \tag{29}$$

$$I' = \beta SI - (\mu + \nu)I, \tag{30}$$

$$p' = k_1 \Delta E p(1-p), \tag{31}$$

where the vaccinated proportion at birth p now is a state variable obeying an imitation process [17] with "imitation" coefficient k_1 and $\Delta E(t)$ is the *perceived pay-off gain* which governs switches between the decisions to vaccinate or not to vaccinate. The latter can be defined by the difference between the perceived cost $-\rho_I(t)$ of suffering serious disease as a consequence of infection, and the perceived cost $-\rho_V(t)$ of vaccination. In the review [14] this type of model has been classified as *belief-based*, as different from the prevalence-based models of previous sections. However, it is easy to understand that as soon as perceived costs are evaluated from prevalences, e.g. of infection and VSE, the two classes of models are intimately related.

Note that, irrespective of the specific forms of $\Delta E(t)$, Eqs. (29)–(31) always has the following three equilibria: (i) an unstable disease-free state with no vaccinators

$A = (1,0,0)$; (ii) a *pure-vaccinator* disease-free equilibrium $B = (0,0,1)$; (iii) the pre-vaccination endemic equilibrium $C = \left(S_{SIR}, I_{SIR}\right) = \left(R_0^{-1}, \mu(1-R_0^{-1})/(\mu+\nu), 0\right)$.

The stability of B and C as well as the existence of further equilibria depend on chosen form of the pay-off gain.

In [3] $\rho_I(t)$ is taken proportional to the infective prevalence $I(t)$: $\rho_I(t) = r_I m I(t)$, where $mI(t)$ is the current perceived risk of infection, and r_I the perceived conditional risk of serious disease given infection while $\rho_V(t)$ is constant:$\rho_V = r_V$, representing the perceived risk of suffering VSE from vaccination. Hence

$$\Delta E(t) = r_I m I(t) - r_V = r_V\left(\vartheta I(t) - 1\right),$$

where $\vartheta = m r_I / r_V$ is the *relative cost* of disease. On these hypotheses [3] has shown that the B equilibrium is unstable and that there is a post-vaccination equilibrium $D = \left(R_0^{-1}, \vartheta^{-1}, \widehat{p}\right)$, where $\widehat{p} = (1+\nu/\mu)\left(I_{SIR} - \vartheta^{-1}\right)$. At $\vartheta = \vartheta_0 = I_{SIR}^{-1}$, there is a transcritical bifurcation between C and D. In turn, the stability of D depends on $k_1(\vartheta - \vartheta_0)$.

5.2 A Model with Myopic Perception of the Cost of VSE

Here, we reconsider the assumption of [3] of constant perceived cost of vaccination $\rho_V(t)$. This can be justified if the public correctly evaluates this risk, e.g. as the ratio between total reported VSEs for a given infection, and the total number of immunisations for that infection per unit of time. In this case the perceived risk would actually be proportional to α_I ($\alpha_I \in (0,1)$), the per capita probability of VSE during a single immunisation. We instead suppose [11] that the public *myopically* evaluates the risk of VSEs by available information on the total number of VSE, given by $\alpha_I(\mu N)\, p(t)$, where N is the total population size. In this case, given that μ and N are constant, the perceived cost of VSE would become a function of the proportion actually immunised p. We therefore set

$$\rho_V(t) = \alpha p(t). \tag{32}$$

The previous expression defines the perceived risk of vaccination, as the product of the (perceived) probability of being immunised, times the conditional probability of VSE given immunisation. An implication of Eq. (32) is that periods of high vaccine uptake negatively feedback, through an increase in the incidence of VSEs, into the perceived cost of vaccination.

For reasons that will become clear later on, we model the perceived cost of infection as an increasing function of infection prevalence

$$\rho_I(t) = h_1(I(t)), \tag{33}$$

where $h_1'(\cdot) > 0$ and $h_1(\cdot) \geq 0$. The case $h_1(0) > 0$ accounts for a scenario of local elimination where re-emergence (e.g. by importation) is feared. Using Eqs. (32) and (33) we eventually obtain the following formulation for $p(t)$:

$$p' = k\,(h(I) - p)\,p\,(1-p)\,, \tag{34}$$

where $k = k_1\alpha$ and $h_1(\cdot) = h(\cdot)/\alpha$.

5.2.1 Relationship Between Imitation-Based and Prevalence-Based Models

Note that if $h(0) \geq 1$ then $p(t) \to 1$. On the other hand, if $h(0) < 1$ then for large t $p(t) \geq h(0)$. If imitation dynamics is fast compared to infection dynamics, i.e. the respective timescale obey $k >> (\mu + \nu)$, then

$$p(t) \approx \min\left(h\left(I(t)\right), 1\right), \tag{35}$$

which is the phenomenological relationship for vaccine uptake introduced in the prevalence-based model [7] of the first section. In simple words this shows that the prevalence-based dynamic of vaccine uptake can be considered as a special case of an imitation-based dynamic when the imitation process is fast.

5.3 Dynamic Implications and Further Comparison Between Imitation and Prevalence-Based Models

Comparing the present model to [3], Eqs. (29)–(34) has the equilibria A (unstable), B (unstable) and C, which, unlike [3], is always unstable. Moreover, two further equilibria are induced by our formulation: (i) a disease-free equilibrium with positive vaccine uptake $E_{dfe} = (1 - h(0), 0, h(0))$; (ii) a new endemic equilibrium

$$E_{beh} = \left(R_0^{-1}, I_e, h\left(I_e\right)\right),$$

where $R_0 = \beta/(\mu + \nu)$ is the basic reproduction number of the infection and I_e is the unique solution of the equation:

$$h(I) = 1 - R_0^{-1} - \frac{\mu + \nu}{\mu} I. \tag{36}$$

As all equilibria are independent of k, it is natural to choose k as a bifurcation parameter. Our main results are as follows:

(A) If

$$\beta I_e \mu h'(I_e) < (\mu + \beta I_e)\left((\mu + \beta I_e) + 2\sqrt{\beta I_e(\mu + \nu)}\right), \tag{37}$$

then E_{beh} is locally asymptotically stable (LAS) irrespective of the imitation speed k.

(B) On the contrary, if

$$\beta I_e \mu h'(I_e) > (\mu + \beta I_e)\left((\mu + \beta I_e) + 2\sqrt{\beta I_e(\mu + \nu)}\right) \tag{38}$$

holds then there are two positive values k_1 and $k_2 > k_1$ such that

1. If $0 < k < k_1$ or $k > k_2$ then E_{beh} is LAS.
2. At $k = k_1$ and at $k = k_2$ there are Hopf bifurcations.
3. If $k \in (k_1, k_2)$ then E_{beh} is unstable and the system's orbits $x(t) = (S(t), I(t), p(t))$ are oscillatory in the sense of Yabucovich [13].

(C) If $h_0 > p_c$ then E_{dfe} is GAS; if $h_0 < p_c$ then E_{dfe} is unstable.

Property **C** shows that, unlike [3], elimination is possible but only if the perceived cost of disease due to infection re-emergence is so large to yield a vaccine uptake in excess of the elimination threshold. Moreover, in [3], large values of $k(\vartheta - \vartheta_0)$ induce sustained oscillations around the endemic state, whereas in our model oscillations are possible in an intermediate window of values of the imitation coefficient k. This suggests that both slow and fast imitation might be stabilising forces. More important, one can note that result **A**-**B** is very similar to Theorem 3 for the delayed prevalence-based model under exponentially fading memory. This suggests that the dynamic similarity between the two classes of models extend beyond the case of fast imitation dynamics. Indeed, as discussed in [11], imitation induces a simple delay mechanism that under appropriate conditions is essentially equivalent to the fading memory adopted in the first section of the paper. Further analyses, simulation results, and insight about the natural history of vaccination programmes can be found in [11].

6 Discussion

This chapter has focused on the effects of vaccinating behaviour on the dynamical properties of simple SIR models for vaccine preventable infectious diseases under voluntary vaccination. In free immunisation regimes, vaccination choices are governed by the perceived costs of the disease and of vaccine adverse events. We have considered both prevalence-based, and imitation-based, models of vaccinating behaviour. We have shown two main substantive, predictions about the effects of behaviour on dynamics. The first one is that when information is globally [14] available, then it becomes impossible to eliminate the infection. The second is that complex oscillating patterns of vaccine uptake and the infection will arise when

delayed information is used to evaluate perceived risks. These predictions hold for both approaches and allow to unfold the relationship between them. Finally, we have reported new results for prevalence-based models, concerning the impact of realistic patterns of delayed information and the way information-driven vaccinating behaviour amplifies the seasonal oscillations in the contact rate. Overall, these results show the importance of simple models in suggesting how complex the interplay between infection transmission and vaccinating behaviour might be. This in turn makes it critically important to develop more realistic and better parametrised transmission models. The search of appropriate field data is therefore a critically urgent need if we want to allow behavioural epidemiology models to also become useful policy assisting tools.

References

1. Anderson, R.M., May, R.M.: Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford (1998)
2. Bauch, C., d'Onofrio, A., Manfredi, P.: Behavioral epidemiology of infectious diseases: an overview. In: Manfredi, P., d'Onofrio, A. (eds.) Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases, Springer (in press)
3. Bauch, C.T.: Proc. R. Soc. Lond. B **272**, 1669 (2005)
4. Center for Disease Control, Vaccine safety, http://www.cdc.gov/vaccinesafety/vaers/.
5. choisy, M., Guegan, J.F., Rohani P.: Physica D **223**, 26 (2006)
6. Diekmann, O., Heesterbeek, J.A.P.: Mathematical Epidemiology of Infectious Diseases Springer (2000)
7. d'Onofrio, A., Manfredi, P., Salinelli, E.: Th. Pop. Biol. **71**, 301 (2007)
8. d'Onofrio, A., Manfredi, P., Salinelli, E.: Math. Mod. Nat. Phen. **2**, 23 (2007)
9. d'Onofrio, A., Manfredi, P., Salinelli, E.: Math. Med. Biol. **25**, 337 (2008)
10. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **264**, 237 (2010)
11. d'Onofrio, A., Manfredi, P., Poletti. J. Theor. Biol. **273**, 63 (2011)
12. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **256**, 473 (2009)
13. Efimov, D.V., Fradkov A.L.: Math. biosc. **216**, 187–191 (2008)
14. Funk, S., Salathe, M., Jansen, V.A.A.: J. R. Soc. Interface **7**, 1247 (2010)
15. Gao, L., Hethcote, H. W. J.: Math. Biol. **30**, 717 (1992)
16. Geoffard, P.-Y., Philipson, T.: Am. Econ. Rev. **87**, 222 (1997)
17. Hofbauer, J., Sigmund K.: Evolutionary Games and Population Dynamics. Cambridge University Press, Cambridge (1998)
18. Iannelli, M., Martcheva, M., Li, W.: Math. Biosci. **211**, 23 (2005)
19. Istituto Superiore di Sanità, Surveillance of adverse events, http://www.iss.it/sorveglianza/
20. MacDonald, N.: Biological Delay Systems: Linear Stability Theory. Cambridge University Press, Cambridge (1989)
21. Olsen, L.F., Truty, G.L., Schaffer, W.M.: Theor. Pop. Biol. **33**(3), 344 (1986)
22. Philipson, T.J.: Human. Res. **31**(3), 611 (1996)
23. Reluga, T.C., Bauch, C.T., Galvani, A.P.: Math. Biosci **204**, 185 (2006)
24. Thieme, H.: Mathematics in Population Biology. Princeton University Press, Princeton (2003)
25. WHO. Immunization safety. hhttp://www.who.int/immunization_safety/aefi/en/i (2009)
26. WHO (1999). Guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization (WPRO/EPI/99.01.). Manila: WHO, Regional Office for the Western Pacific

The Geometric Approach to Global Stability in Behavioral Epidemiology

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Abstract Three behavioral-epidemic models (i.e., epidemic systems including feedbacks (FB) that the information about an infectious disease has on its spreading) are introduced. Two relevant FB are explicitly considered: the pseudo-rational exemption to vaccination and the information-related changes in contact patterns by healthy subjects. The global stability analysis of the endemic states is performed by means of the geometric approach to stability, with particular focus on a model of vaccination of adult susceptible subjects. Biological implications of the results are discussed.

1 Introduction

Feedbacks (FB) and global stability are among the most important features of all mathematical models in biology [15, 35]. In mathematical epidemiology (ME) the vast majority of efforts have been devoted to the study of global stability. Indeed, determining under which conditions a disease, independently from the initial burden, either remain endemic or get extinct is probably the most important topic.

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Recently, however, it is increasingly becoming clear that a realistic epidemic model must include the FB that the information about an infectious disease has on its spreading [3, 16, 17, 36, 38].

A first type of FB is the *pseudo-rational exemption* which is defined as the family's decision to not vaccinate children because of a pseudo-rational comparison between the perceived risk of infection and the perceived risk of side effects caused by the vaccine. This type of FB has a paramount relevance in nonmandatory vaccinations. Indeed, the progress toward increasing degrees of disease control is intermixed by temporal trends of declining vaccination coverage [37]. Especially modern societies (where the vaccinations are increasingly voluntary) face the challenging paradox of pseudo-rational exemption. The paradox stems in the fact that the vaccination success makes very low the perceived risk of infection, so that the risk of side effects appears erroneously huge.

This peculiar unbalance of perceptions, particularly large in transient period of low disease incidence, induces dynamics that cannot be captured by traditional mathematical models of infectious diseases spreading and vaccinations.

A second type of FB is the one given by the influence of the information on the behavior of healthy subjects. For example, in [16] the authors consider simple epidemic models in which the social contact rate is described as a decreasing function of the available information on the present and the past disease prevalence. It is shown that social behavior change alone may trigger sustained oscillations that, in case of seasonal fluctuation in the contact rate, can degenerate and become chaotic. This indicates that human behavior might be a critical explaining factor of oscillations in time series of endemic diseases.

The role of human behavior and also misbehaviors (as the above-mentioned pseudo-rational exemption) has thus to be included in some manner in the modeling of infectious disease spreading, which is triggering a large corpus of scientific research (see, just to name a few contributors [1–3, 6, 21, 23, 36]) which is the subject of this book.

For example, in [17, 18], the dynamic implications of rational exemption were investigated by using a simple extension of the standard susceptible-infectious-removed (SIR) model, where the information-dependent vaccination is modeled by means of a simple information index mostly based on the publicly available information on the disease, as reviewed and extended in the contribution by d'Onofrio and Manfredi in this book. In this simple framework, the vaccination coverage is modeled as a phenomenological function of the current and past state of the disease (see also the game-funded function employed in [36]), defined as the sum of a constant component plus a variable one, increasing with the perceived risk of infection.

In [17, 18] it was shown that if the baseline rate of vaccination does not exceed the so-called May–Anderson threshold, then a globally or also only locally stable eradication is impossible, and there is an endemic equilibrium, whose stability was studied only from the local point of view.

However, a global analysis of stability is of the outmost importance from an epidemiological point of view. Indeed, if the endemic equilibrium is GAS, then, also in case of infinitesimal initial prevalence, the disease will permanently be present in the population.

From a mathematical point of view, the analysis of the GAS of the endemic equilibria of bidimensional epidemic systems may be usefully approached by means of the Poincaré–Bendixson trichotomy. Less simple is the study in dimensions $n \geq 3$. A major progress was achieved in the 1990s, when Li and Muldowney developed a generalization of the Poincaré–Bendixson criterion for systems of n ordinary differential equations (ODEs), with $n \geq 3$ [28, 30] the so-called *geometric approach to global stability*. Since its development [29], their approach has been (and currently is being) extensively applied to the study of the global behavior of mathematical models arising in ME and in several other different biomathematical contexts, such as toxicant–population interaction models [10, 11], Lotka–Volterra models including delay [4, 5], and ME-like models of dynamics of HIV in a human host [14, 39]. As far as ME is concerned, the majority of applications of this method refer SIR models including the *exposed* class, i.e., SEIR, SEIS, and SEIRS models (see, e.g., [27, 29–31]). The SEIR-like models are represented by a system of four ODEs. Its dynamics can be usually deduced by studying a reduced three ODEs system in the variables, say, x, y, and z. Usually, the only nonlinearity is given by the incidence rate of the infectious disease. When it is postulated that the spread of the disease occurs according to the principle of mass action, then the corresponding incidence rate is bilinear with respect to the susceptibles and infective populations [15]. In this case such a bilinearity represents the only nonlinearity of the model. The bilinearity is of kind "xz" and is included in the balance equations of the variables x and y. Generally speaking, the structure of SEIR-like systems appears to be particularly suitable for the applications of the geometric method for global stability [12, 13]. However, several well-known models present a different bilinearity. That is, the balance equations of the variables x and y contain a bilinearity of kind "xy" instead of "xz." A simple example is the classical SIRS model with temporary immunity [24]:

$$\begin{cases} \dot{x} = k_0 - k_1 xy - k_2 x + k_3 z \\ \dot{y} = k_1 xy - k_4 y \\ \dot{z} = k_5 y - k_6 z, \end{cases} \tag{1}$$

where the upper dot denotes the time derivative, $d \cdot / dt$, and the k_i's are all positive parameters. Sometimes, systems like Eq. (1) may be reduced to a planar system. However, if no reduction is available, the stability analysis for system (1), or systems with a similar structure (which we call *SIR-like models*), may become quite involved. In such cases, the geometric approach to global stability may be a powerful tool [26]. Nevertheless, applications of the method to SIR-like models are not very common in the literature. We want to illustrate, by means of a new example and by means of the brief review of some previously published results, the utility of the geometric approach to global stability in the framework of the information-dependent epidemic models of behavioral epidemiology.

We start by giving a complete global analysis of a model of vaccinations at all ages, which was defined but incompletely studied in [17]. This model is particularly interesting since in it the vaccinations are distributed in all ages. We provide here for the first time its complete global analytical study.

2 Information-Dependent Vaccinations on All Ages

In [17] the following information-dependent vaccination model was introduced:

$$\begin{cases} \dot{S} = \mu - \mu S - \varphi(M)S - \beta SI \\ M(t) = \int_{-\infty}^{t} g(I(\tau))K_a(t-\tau)d\tau \\ \dot{I} = \beta SI - (\mu + \nu)I. \end{cases} \tag{2}$$

The state variables S and I denote, respectively, the fraction of the susceptible individuals and the fraction of the infectious and infective individuals at time t. The variable M is addressed to be the *information variable* and summarizes information about the past values of the disease. All the parameters in Eq. (2) are strictly positive constants. The function $\varphi(M)$ models the information-dependent rate of vaccinations, and it may be, for ease of biological interpretation, split as follows:

$$\varphi(M) = \varphi_0 + \varphi_1(M).$$

Here, φ_0 is a positive constant representing the fraction of susceptibles that are vaccinated independently on the available current and historical information on the prevalence level of the disease in the population and $\varphi_1(M)$ models the fraction of susceptibles that are vaccinated in dependence of the social alarm caused by the disease.

The function g describes the role played by the infectious size in the information dynamics.

We assume that (1) $\varphi_1(M)$ and $g(I)$ are continuous and differentiable, except in some cases, at finite number points; (2) $\varphi_1(M) \geq 0$, for all M, and $g(I) \geq 0$, for all I; (3) $\varphi_1(0) = 0$, and $g(0) = 0$; and (4) $0 < \varphi_1'(M) < \Phi$, $0 < g'(I) < \Gamma$, and for some constants Φ and Γ.

Specific functional forms of $\varphi_1(M)$ turn out to be relevant for the applications, as the linear function,

$$\varphi_1(M) = bM,$$

where b is a positive constant or the Hill Order n function

$$\varphi_1(M) = \frac{CM^n}{1 + DM^n},\ n = 0, 1, \ldots$$

where $C > 0$, $D > 0$. Similar functions may be chosen for g.

The information variable M is a function of the past values of I for two main reasons. From one hand, the information regarding the spread of a disease is seldom instantaneous, since it is generally subject to delays of technical nature due to the presence of time-consuming processes (clinical tests, notification of cases, the collecting and propagation of information and/or rumors, etc.). On the other hand, in some cases there can be a memory of the previous epidemics.

An important case of kernel $K_a(t)$ is the *weak exponential delay kernel* [32], $K_a(t) = ae^{-at}$, where the parameter a assumes the biological meaning of inverse of the average delay of the collected information on the disease, as well as the average length of the historical memory concerning the disease in study. With this particular choice of the kernel, by applying the *linear chain trick* [32], the (infinite dimensional) nonlinear integro-differential system (2) is equivalent to the following set of (finite dimensional) nonlinear ODEs:

$$\begin{cases} \dot{S} = \mu - \mu S - \varphi(M)S - \beta SI \\ \dot{M} = a\,[g(I) - M] \\ \dot{I} = \beta SI - (\mu + \nu)I. \end{cases} \tag{3}$$

2.1 Basic Properties

It is easy to check that model (3) admits the disease-free equilibrium $E_0 = (A, 0, 0)$, where $A = \mu/(\mu + \varphi_0)$. Note that if it were $\varphi_0 \geq \nu$, then this inequality would imply that $A < \mu/(\mu + \nu) << 1$. Indeed, the average duration of a disease (ν^{-1}) is much smaller than the average lifespan ($L = \mu^{-1}$). In other words, if we considered baseline vaccination rates φ_0 equal or larger than the recovery rate ν, then at the disease-free equilibrium, the fraction of residual susceptible subjects would be so small to make rather pleonastic the study of the influence of information feedback. For these reasons, the analysis of model (3) will be performed under the realistic assumption

$$\varphi_0 < \nu \tag{4}$$

First we show that it exists an invariant adsorbing set in the state space.

Proposition 1. *The set*

$$\Omega = \left\{(S, M, I) \in R^3_+ | 0 \leq M \leq g(A),\ 0 \leq S + I \leq A\right\}$$

is positively invariant and absorbing and, as a consequence, the orbits of Eq. (3) are bounded, provided that $(S(0), M(0), I(0)) \geq (0, 0, 0)$.

Proof. Defining $\sigma = S + I$, one has that

$$\dot{\sigma} < \mu\,(1 - \sigma) - \varphi_0 S - \nu I;$$

thus,

$$\dot{\sigma} < \mu \left(1 - (1 + \varphi_0 \mu^{-1})\sigma\right).$$

As a consequence

$$\limsup_{t \to +\infty} (S(t) + I(t)) \leq A.$$

From the following inequality

$$\dot{M} \leq a\,(g(A) - M),$$

it follows that

$$\limsup_{t \to +\infty} M(t) \leq g(A),$$

and our claim is demonstrated. □

Let us now denote $R_0 = \beta/(\mu + \nu)$ the basic reproduction number in absence of vaccinations. It follows that

Proposition 2. *if*

$$R_0 A \leq 1 \tag{5}$$

then E_0 is GAS in Ω; otherwise, E_0 is unstable.

Proof. The first claim easily follows from the following differential inequality:

$$\dot{I} \leq I\,(\beta(A - I) - (\mu + \nu)).$$

The second claim follows from the linearized equation at E_0. Indeed, the equation for I reads as follows:

$$\dot{I} = I(\beta A - (\mu + \nu)).$$

□

Note that if $R_0 A > 1$, then system (3) admits another equilibrium point, the *endemic* equilibrium $E = (S^*, M^*, I^*) = (1/R_0, g(I^*), I^*)$, where $I^* \in (0,1)$ is the unique solution of

$$\mu \left(1 - \frac{1}{R_0 A}\right) - (\mu + \nu) I = \frac{\varphi(g(I))}{R_0}.$$

We also remark that due to Eq. (4), the condition $R_0 A > 1$ reads $\varphi_0 < (R_0 - 1)\mu$. In order to better appreciate this inequality, and since in absence of infection, the term $1/(\varphi_0 + \mu)$ is the average time of permanence in the susceptibility class, it is convenient to express φ_0^{-1} as a fraction of the average lifespan: $\varphi_0^{-1} = f_0 L$, where $L = \mu^{-1}$ is the average lifespan and $f_0 \in (0,1)$. This allows to further rewrite the instability condition as $f_0 > 1/(R_0 - 1)$.

The local stability analysis of the endemic equilibrium E may be performed by using the same procedure of Proposition 12 in [17]. System (3) may admit oscillatory solutions (in the sense of Yacubovitch [8, 19, 20]) as stated by the following theorem [8]:

Theorem 1. *If and only if*

$$\mu^2 R_0^2 + 2\mu\beta R_0\sqrt{I^*S^*} - \beta\, g'(I^*)\varphi'(M^*)I^*S^* < 0, \tag{6}$$

there exist two values a_1 and a_2, with $0 < a_1 < a_2$, for the parameter a, such that E is locally asymptotically stable (LAS) for $a \notin [a_1, a_2]$. On the contrary, if $a \in (a_1, a_2)$, then E is unstable, and the solutions of system (1) exhibit Yacubovitch oscillations. At the points a_1 and a_2, Hopf bifurcations occur. If the reverse of Eq. (6) holds, then E is LAS.

2.2 Global Stability of the Endemic Equilibrium

Global stability analysis for the endemic equilibrium E will be performed through the approach due to Li and Muldowney [30].

When $R_0 A > 1$, the disease-free equilibrium, which is located on the boundary $\partial\Omega$, is unstable, and this implies that system (3) is uniformly persistent [22], i.e., there exists a constant $c > 0$ such that any solution $(S(t), M(t), I(t))$ with $(S(0), M(0), I(0))$ in the interior of Ω, satisfies

$$\min\{\liminf_{t\to\infty} S(t), \liminf_{t\to\infty} M(t), \liminf_{t\to\infty} I(t)\} > c.$$

The uniform persistence together with boundedness of Ω is equivalent to the existence of a compact set in the interior of Ω which is absorbing for Eq. (3), see [25]. This condition is required by the Li–Muldowney approach, together with a specific Bendixson criterion (inequality (34) in the Appendix) which will be the goal of the next theorem.

Theorem 2. *If $R_0 A > 1$ and*

$$\nu - \varphi_0 < a(1 - \Gamma), \tag{7}$$

$$(\beta + \Phi)A < a, \tag{8}$$

then the endemic equilibrium E of system (3) is globally asymptotically stable with respect to solutions of Eq. (3) initiating in the interior of Ω.

Proof. We first observe that the second additive compound matrix $J^{[2]}(S, M, I)$ is given by

$$J^{[2]} = \begin{pmatrix} -\mu - \beta I - \varphi(M) - a & a\,g'(I) & \beta S \\ 0 & -\mu - \beta I + \beta S - (\mu + \nu) - \varphi(M) & -\varphi'(M)\,S \\ -\beta I & 0 & \beta S - (\mu + \nu) - a \end{pmatrix}.$$

Now we take the function,

$$P = P(S,M,I) = diag\left\{\frac{S}{I}, \frac{S}{I}, \frac{S}{I}\right\}. \tag{9}$$

It follows,

$$P_f P^{-1} = \text{diag}\left\{\frac{\dot{S}}{S} - \frac{\dot{I}}{I}, \frac{\dot{S}}{S} - \frac{\dot{I}}{I}, \frac{\dot{S}}{S} - \frac{\dot{I}}{I}\right\},$$

and $PJ^{[2]}P^{-1} = J^{[2]}$ so that

$$B = P_f P^{-1} + PJ^{[2]}P^{-1} = \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix},$$

where $B_{11} = \frac{\dot{S}}{S} - \frac{\dot{I}}{I} - \mu - \beta I - \varphi(M) - a$, $B_{12} = [a g'(I),\ \beta S]$, $B_{21} = [0,\ -\beta I]^T$, and

$$B_{22} = \begin{bmatrix} \dfrac{\dot{S}}{S} - \dfrac{\dot{I}}{I} - \mu - \beta I - \varphi(M) + \beta S - (\mu + \nu) & -\varphi'(M)S \\ 0 & \dfrac{\dot{S}}{S} - \dfrac{\dot{I}}{I} + \beta S - (\mu + \nu) - a \end{bmatrix}.$$

Consider now the norm in $\mathbf{R}^3$ as

$$|(u,v,w)| = \max\{|u|, |v| + |w|\}, \tag{10}$$

where (u,v,w) denotes the vector in $\mathbf{R}^3$ and denote by $\mathscr{L}$ the Lozinskiĭ measure with respect to this norm. It follows [33]

$$\mathscr{L}(B) \le \sup\{g_1, g_2\} \equiv \sup\{\mathscr{L}_1(B_{11}) + |B_{12}|,\ \mathscr{L}_1(B_{22}) + |B_{21}|\}, \tag{11}$$

where $|B_{21}|$, $|B_{12}|$ are matrix norms with respect to the L^1 vector norm and $\mathscr{L}_1$ denotes the Lozinskiĭ measure with respect to the L^1 norm.[1]

$$\mathscr{L}_1(B_{11}) = \tfrac{\dot{S}}{S} - \tfrac{\dot{I}}{I} - \mu - \beta I - \varphi(M) - a, \tag{12}$$

$$|B_{12}| = \max\{a g'(I), \beta S\}, \tag{13}$$

$$|B_{21}| = \beta I, \tag{14}$$

$$\mathscr{L}_1(B_{22}) = \frac{\dot{S}}{S} - \frac{\dot{I}}{I} + \beta S - (\mu + \nu) + \max\{-\mu - \beta I - \varphi(M); -a + \left|-\varphi'(M)S\right|\}. \tag{15}$$

[1] That is, for the generic matrix $A = (a_{ij})$, $|A| = \max_{1\le k\le n} \sum_{j=1}^{n} |a_{jk}|$ and $\mathscr{L}(A) = \max_{1\le k\le n}(a_{kk} + \sum_{j=1(j\ne k)}^{n} |a_{jk}|)$.

Taking into account of Eqs. (11) and (12)–(15), the general expressions of g_1 and g_2 for system (3) are thus

$$g_1 = \frac{\dot{S}}{S} - \frac{\dot{I}}{I} - \mu - \beta I - \varphi(M) - a + \max\left\{a\,g'(I);\ \beta S\right\}, \tag{16}$$

and

$$g_2 = \frac{\dot{S}}{S} - \frac{\dot{I}}{I} + \beta S - (\mu + \nu) + \beta I + \max\{-\mu - \beta I - \varphi(M);\ -a + \varphi'(M)S\}. \tag{17}$$

Observe that system (3) provides the following equality:

$$\frac{\dot{I}}{I} = \beta S - (\mu + \nu); \tag{18}$$

hence, from Eq. (16) one gets

$$g_1 = \frac{\dot{S}}{S} - \beta S + \nu - \beta I - \varphi(M) - a + \max\left\{a\,g'(I);\ \beta S\right\}, \tag{19}$$

and from Eq. (17),

$$g_2 = \frac{\dot{S}}{S} + \beta I + \max\{-\mu - \varphi(M);\ \beta I - a + \varphi'(M)S\}.$$

It follows

$$g_1 = \frac{\dot{S}}{S} + \max\left\{-\beta S + \nu - \beta I - \varphi(M) - a + a\,g'(I);\ \ \nu - \beta I - \varphi(M) - a\right\},$$

and

$$g_2 = \frac{\dot{S}}{S} + \max\left\{-\mu - \varphi(M);\ \ \beta I + \varphi'(M)\,S - a\right\}.$$

Hence, from Eq. (11),

$$\begin{aligned}\mathscr{L}(B) &\le \sup\{g_1, g_2\}\\ &= \frac{\dot{S}}{S} + \max\{-\beta S + \nu - \beta I - \varphi(M) - a + a\,g'(I),\ \ \nu - \beta I - \varphi(M) - a,\\ &\quad -\mu;\ \ \beta I + \varphi'(M)S - a\},\end{aligned}$$

i.e.,

$$\begin{aligned}\mathscr{L}(B) \le \frac{\dot{S}}{S} + \max\{&-\beta c + \nu - \varphi_0 - \beta c - a + a\Gamma,\ \ \nu - \varphi_0 - \beta c - a,\\ &-\mu;\ \ \beta A + \Phi A - a\},\end{aligned}$$

where c is the constant of uniform persistence.

Now, impose that

$$\begin{aligned} \nu - \varphi_0 + a\Gamma &< a + 2\beta c, \\ \nu - \varphi_0 &< a + \beta c, \\ (\beta + \Phi)A &< a. \end{aligned} \tag{20}$$

This allows to conclude that

$$\mathscr{L}(B) \leq \frac{\dot{S}}{S} - \omega,$$

where

$$\omega = \min\{a(1-\Gamma) + 2\beta c - \nu + \varphi_0,\ a + \beta c - \nu + \varphi_0,\ \mu,\ a - A(\beta + \Phi)\},$$

and $\omega > 0$. Hence

$$\frac{1}{t}\int_0^t \mathscr{L}(B)ds \leq \frac{1}{t}\log\frac{S(t)}{S(0)} - \omega,$$

and the Bendixson criterion given in [30] is thus verified. Finally, because of $c > 0$, conditions (20) are fulfilled if the inequalities (7)–(8) hold true. □

Note that in the important case where $g(I) = kI$, the fulfillment of the assumptions that are needed by the above theorem implies a restriction for k in the range $k \in (0, 1)$.

2.3 Information-Dependent Vaccinations of Newborns

In [17] the problem of information-driven vaccination of newborns was thoroughly analyzed both numerically and analytically, focusing, however, only on the local properties of the endemic equilibrium. In [7], we performed a global analysis, which we shall summarize here, for the important case $g(I) = kI$. The model is the following:

$$\begin{cases} \dot{S} = \mu(1 - p(M)) - \mu S - \beta SI \\ \dot{M} = akI - aM \\ \dot{I} = \beta SI - (\mu + \nu)I, \end{cases} \tag{21}$$

where the nondecreasing positive function $p(M)$ models the proportion of vaccinated newborns, and it may be split as follows: $p(M) = p_0 + p_1(M)$. Here, p_0 models the fraction of newborns that are in any case vaccinated, whereas $p_1(M)$ models the fraction of newborns that are vaccinated in dependence of the social alarm caused by the disease. Note that p_0 is lower than the minimum vaccination rate to obtain the eradication. Assume the following properties to hold: (1) $0 \leq p_1(M) \leq 1 - p_0$, for all M; (2) $p_1(0) = 0$; (3) $p_1(M)$ is continuous and differentiable, except in some cases, at finite number points; and (4) $0 < p_1'(M) < \Pi$, for some constant Π.

Proposition 3. *The set*

$$\Gamma = \left\{(S,M,I) \in R^3_+ | 0 \leq M \leq k,\ 0 \leq S+I \leq 1-p_0\right\},$$

is positively invariant and absorbing, and as a consequence, the orbits of Eq. (21) are bounded, provided that $(S(0),M(0),I(0)) \geq (0,0,0)$.

Theorem 3. *System (21) admits the disease-free equilibrium* $E_0(1-p_0,0,0)$. *If*

$$(1-p_0)R_0 > 1, \tag{22}$$

then the equilibrium E_0 *is unstable, and Eq. (21) admits also a unique endemic equilibrium with positive components,* $E = (S^*,M^*,I^*)$, *where* $S^* = (\mu+\nu)/\beta$, $M^* = kI^*$, *and* I^* *is the unique positive solution of*

$$\mu(1-p_0) - \mu p_1(kI^*) - \left(\frac{\mu+\nu}{\beta}\right)[\mu+\beta I^*] = 0.$$

Moreover, if and only if

$$(\beta I^*+\mu)^2 - \beta\mu k I^* p'(M^*) + 2(\beta I^*+\mu)\sqrt{\beta(\nu+\mu)I^*} < 0, \tag{23}$$

there exist two values a_1 *and* a_2 *for the parameter a, with* $0 < a_1 < a_2$, *such that E is unstable for* $a \in (a_1,a_2)$ *and the solutions of the system exhibit Yacubovitch oscillations, whereas it is locally asymptotically stable (LAS) for* $a \notin [a_1,a_2]$. *At the points* a_1 *and* a_2, *Hopf bifurcations occur. If the reverse of Eq. (23) holds, then E is LAS. Finally, if the reverse of Eq. (22) holds, then* E_0 *is globally asymptotically stable in* Γ.

Reasoning as in Sect. 2.2, it can be shown that system (21), under the assumption (22), is uniformly persistent. Thus, in order to satisfy the Li–Muldowney theorem, it remains to find conditions for which the Bendixson criterion given by Eq. (34) is verified.

Theorem 4. *Under the assumptions (22) and*

$$\nu + ak < a,\ \beta(1-p_0) + \mu\Pi < a, \tag{24}$$

the endemic *equilibrium E of system (21) exists and is globally asymptotically stable with respect to solutions of Eq. (21) initiating in the interior of* Γ.

The proof of the above theorem, which is reported in [7], is obtained by means of the same function P and the same vector norm used for the proof of Theorem 2.

We remark that also here that the fulfilling of GAS conditions implies the restriction $k \in (0,1)$, as in the previous section. In view of this remark, the parameter k may play an interesting role on the stability properties of the endemic equilibrium. To elucidate this aspect, we will show, numerically, how the global stability properties of the endemic equilibrium E critically depend on the interplay between the parameters a and k.

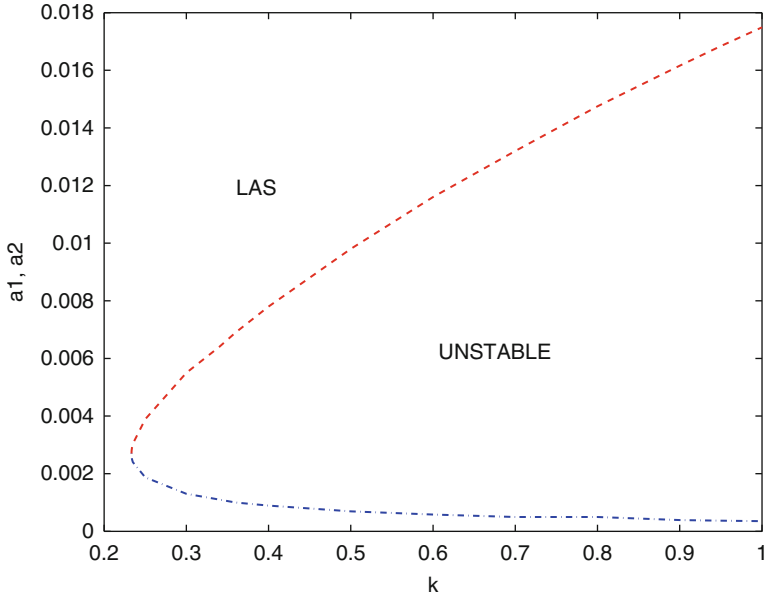

Fig. 1 The local stability properties of the endemic equilibrium E, varying a and k. The numerical values for the other parameters are chosen as in [17]. Bifurcation diagram in the (k,a) plane: the *dashed-dot* branch (-.) is the a_1's branch, and the *dashed* branch (- -) is the a_2's branch. a_1 and a_2 are defined in Theorem 3. Figure from [7]: © Elsevier Science Ltd

As in [17], we choose $p_1(M) = (1-p_0-\varepsilon)DM/(1+DM)$, where ε and D are positive constants and ε is arbitrarily small.

Condition (23) can be rewritten as $B_1^2 - 4\beta I^*(\nu+\mu)(\beta I^*+\mu)^2 > 0$, where,

$$B_1 = (\beta I^*+\mu)^2 - \beta I^* \mu k p_1'(M^*).$$

Our purpose is to show that some set of parameter values exist such that hypotheses of Theorem 4 are verified.

We fix the parameter values as in [17]: $\mu = 1/27375\ \text{days}^{-1}$, $\nu = 0.1429\ \text{days}^{-1}$, $R_0 = 10$, $\beta = 1.4289\ \text{days}^{-1}$, $p_0 = 0.75$, $D = 5000$, $\varepsilon = 0.01$. Furthermore, in the present case, $\Pi \approx (1-p_0-\varepsilon)D$.

We observe that conditions (22) and (24) can be combined. It follows that, to apply Theorem 4, the bifurcation parameter a has to be chosen in the range $a > a_{min}$, where

$$a_{min} = \max\{\nu(1-k)^{-1}; \beta(1-p_0) + \mu(1-p_0-\varepsilon)D\}. \tag{25}$$

As it can be seen in Fig. 1, values of k exist such that the endemic equilibrium is LAS, independently of the delay (e.g., $k = 0.1$ and $k = 0.2$). For these choices of k, global stability properties of E are solely determined by condition $a > a_{min}$.

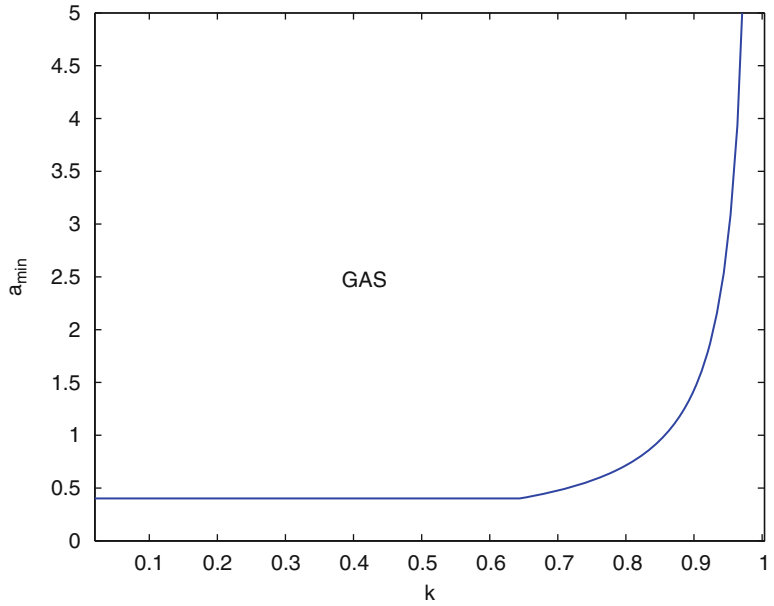

Fig. 2 The global stability region in the (a,k) plane for the endemic equilibrium E, i.e., Eq. (26). The numerical values for the other parameters are chosen as in [17]. Figure from [7]: © Elsevier Science Ltd

From Eq. (25), it follows that the region where a_{min} is independent on k is $(0, k_c)$, with

$$k_c = 1 - \frac{\nu}{\beta(1-p_0) + \mu(1-p_0-\varepsilon)D}.$$

For the selected numerical values, $k_c \approx 0.6437$ and

$$a_{min} = \begin{cases} 0.4016, & if \quad 0 < k < k_c, \\ 0.1429(1-k)^{-1}, & if \quad k_c < k < 1. \end{cases} \tag{26}$$

The function $a_{min}(k)$ is plotted in Fig. 2, where it is shown the GAS region in the (a,k) plane for the endemic equilibrium E. We can observe that, especially for medium–low values of k, $0 < k < k_c$, the GAS of E is always verified by both medium or high values of a, progressively increasing the value of k to approach 1; the values of a for which condition $a > a_{min}$ may be verified become progressively larger.

Thus, if $k <\approx 0.65$, according to our result, the GAS of the endemic equilibrium is guaranteed for values of the information delay up to ≈ 2.5 days. Only for $k >\approx 0.855$, the GAS is guaranteed for delays that are less long than a single day.

The values of the parameter a, ensuring the local and the global stability of the equilibrium E, for different values of k, are summarized in Table 1. For $a \in (0, a_1) \cup (a_2, a_{min})$, the global stability for the endemic equilibrium may be only guessed.

Table 1 Different values of the parameter k are chosen and the related ranges of the parameter a are shown, for which local (LAS) and global (GAS) stability of the endemic equilibrium E is obtained

k	a_1	a_2	LAS	GAS ($a > a_{min}$)
0.95	0.00037	0.01684	$0 < a < a_1, a > a_2$	$a > 2.8580$
0.9	0.00039	0.01616	$0 < a < a_1, a > a_2$	$a > 1.4290$
0.8	0.00043	0.01475	$0 < a < a_1, a > a_2$	$a > 0.7145$
0.7	0.00049	0.01323	$0 < a < a_1, a > a_2$	$a > 0.47633$
0.6	0.00058	0.01159	$0 < a < a_1, a > a_2$	$a > 0.40106$
0.5	0.00069	0.0098	$0 < a < a_1, a > a_2$	Idem
0.4	0.00089	0.0078	$0 < a < a_1, a > a_2$	Idem
0.3	0.00130	0.0055	$0 < a < a_1, a > a_2$	Idem
0.2	–	–	$\forall a$	Idem
0.1	–	–	$\forall a$	Idem
0.02	–	–	$\forall a$	Idem

The numerical values for the other parameters are chosen as in [17]. a_1 and a_2 are defined in Theorem 3

3 FB on Behavior of Susceptible Subjects

In [16] the dynamics of interactions between susceptibles, infectious, and the information index is described by the following model:

$$\begin{cases} \dot{S} = \mu(1-S) - \beta(M)IS \\ \dot{I} = \beta(M)IS - (\mu+\nu)I \\ \dot{M} = a\,g(I) - aM, \end{cases} \tag{27}$$

where the function β is required to be a positive decreasing function and g such that $g(0) = 0$, and $g'(I) > 0$. We will prove the global stability result of the endemic equilibrium for g satisfying

$$g'(I)I \leq g(I). \tag{28}$$

Both the previously mentioned functions $g(I) = kI$ and $g(I) = I/(1+qI)$ fulfill the constraint (28).

In [16] it has been shown that the set

$$\Omega = \{(S,I,M) : S \geq 0,\ I \geq 0,\ S+I \leq 1,\ 0 \leq M \leq g(1)\}$$

is positively invariant for model (27). Moreover the disease-free equilibrium $E_0 = (1,0,0)$ is on $\partial\Omega$, as well as its stable manifold, which is the set $\{(S,I,M) \in \Omega : I = 0\}$. As a consequence, the state variables are strongly persistent. Furthermore, model (27) admits a unique endemic equilibrium, $E = (S^*, I^*, M^*)$, where $S^* = (\mu+\nu)/\beta(g(I^*))$, $M^* = g(I^*)$ and I^* is the unique solution of

$$\mu\left(\frac{\mu+\nu}{\beta(g(I))}\right) - (\mu+\nu)I = 0.$$

Let us introduce the basic reproduction number

$$R_0 = \frac{\beta(0)}{(\mu+\nu)}. \tag{29}$$

The following stability result holds [16]:

Theorem 5. *If $R_0 \leq 1$, then the disease-free equilibrium E_0 is globally asymptotically stable. If $R_0 > 1$, then E_0 is unstable, and the endemic equilibrium E is locally asymptotically stable.*

As far as the global stability of E is concerned, in [9] the following theorem has been proven:

Theorem 6. *Assume that g satisfies the inequality (28). If $R_0 > 1$ and*

$$\nu > 2\beta(\varepsilon_0), \tag{30}$$

where ε_0 is the constant of uniform persistence, then the endemic *equilibrium E of system (27) exists and is globally asymptotically stable with respect to solutions of Eq. (27) initiating in the interior of Ω.*

The proof of the above theorem, which is reported in [9], is obtained by means of the same vector norm used for the proof of Theorem 2, but the following different P function is employed: $P = diag\,(1, I/M, I/M)$.

3.1 A SIS Case

In this section we briefly analyze the impact of the information-driven behavior of susceptible subjects on the transmission of a SIS communicable disease.

By including the variable contact rate $\beta(M)$ in the classical SIS model, we obtain the following system:

$$\begin{cases} \dot{S} = \mu(1-S) - \beta(M)IS + \gamma I \\ \dot{I} = \beta(M)IS - (\mu+\gamma)I \\ \dot{M} = a\,g(I) - aM. \end{cases} \tag{31}$$

We can study the model on the plane (limit set) $S + I = 1$. Model (31) reduces to

$$\begin{cases} \dot{I} = \beta(M)I(1-I) - (\mu+\gamma)I \\ \dot{M} = a(g(I) - M). \end{cases} \tag{32}$$

System (32) has two equilibrium points: a disease-free one, $E_0 = (0,0)$, and an endemic equilibrium $E = (I_e, g(I_e))$, where I_e is the solution of the following equation:

$$\beta(kI) = \frac{\mu + \gamma}{1 - I}.$$

The equilibrium E exists only if $R_0 > 1$, where R_0 is given by Eq. (29).

Stability properties are given in the following:

Theorem 7. *If $R_0 \leq 1$, then the disease-free equilibrium E_0 is globally asymptotically stable. If $R_0 > 1$, then E_0 is unstable, and the endemic equilibrium E is globally asymptotically stable.*

4 Conclusions

In this work, we consider three SIR epidemic models with information-dependent feedback. Our main goals are (1) to obtain (sufficient) conditions, expressed in terms of the parameters of the system, ensuring the global asymptotic stability of the unique endemic equilibrium, and (2) apply the geometric approach to global stability analysis, due to Li and Muldowney. This gives an example of the application of the method to a class of SIR-like models including peculiar nonlinearities, modeling new types of biological feedback mechanisms: the influence that the available information has on either vaccinating behaviors or on the contact behavior of the population.

We have obtained that imposing the conditions required by the Li–Muldowney approach (see $(H1)$–$(H2)$ and Eq. (34) in the Appendix) leads to parameter restrictions in all the three considered cases.

We stress that the approach to stability applied in this chapter is based on two crucial choices: the entries of the matrix P and the vector norm in $\mathbf{R}^3$. Clearly, different choices of the matrix P and of the vector norm may lead, in principle, to better sufficient conditions than the ones we found here, in the sense that the restrictions on the parameters may be weakened.

For example in the two cases involving vaccination (models (3) and (21)), when $g(I) = kI$, the range of variability of the parameter k is restricted to the interval $(0, 1)$. This restriction may be discussed as follows. The parameter k may be seen as a "summary" of two contrasting phenomena:

- The phenomenon of disease underreporting: for mainly technical reasons, the number of reported cases of an infectious disease is in any case smaller than the real number, leading to an underestimate of the infectious fraction I.
- The level of media and rumors coverage of the state of a disease, which tends to amplify the social alarm.

Thus, we could decompose k as follows: $k = k_{underreporting} \times k_{media}$, where in all cases $0 < k_{underreporting} \leq 1$ and where generally $k_{media} > 1$, although one may depict a realistic scenario where, in order to avoid extreme social alarm, or because of lack of mediatic "appeal" of the disease, media would lower the focus on the disease,

implying that $0 < k_{media} < 1$. Finally, of course, there is the case of totally objective press: $k_{media} = 1$. Consequently,

- The cases of objective and of alarm-avoiding media are fully described by the constraint $k \in (0, 1)$.
- The case of "amplifying" media may be well modeled provided that $k_{media} < k_{underreporting}^{-1}$.

These considerations suggested that, in the case of vaccination of newborns, the role of the parameter k was worth further investigations via a numerical bifurcation analysis. We obtained that if k exceeds a threshold depending on a, $k^*(a)$, limit cycles arise through Hopf bifurcations at $k = k^*(a)$. We may read this phenomenon as follows:

- If the media coverage is low, then the "rational exemption" leads to a globally stable endemic state.
- On the contrary, if the "media exposure" exceeds a threshold that interestingly depends on a, then a destabilization appears and oscillations arise.

Finally, in the case of information feedback on contact behavior for SIS epidemic diseases, we obtained that the endemic equilibrium is GAS in a way independent from any constraints on the epidemic, information, and delay parameters.

5 Appendix

Here, we will shortly describe the general method developed in Li and Muldowney, [30]. Consider the autonomous dynamical system:

$$\dot{x} = f(x), \tag{33}$$

where $f : D \to \mathbf{R}^n$, $D \subset \mathbf{R}^n$ open set and simply connected and $f \in C^1(D)$. Let x^* be an equilibrium of Eq. (33), i.e., $f(x^*) = 0$. We recall that x^* is said to be *globally stable* in D if it is locally stable and all trajectories in D converge to x^*.

Assume that the following hypotheses hold:

($H1$) There exists a compact absorbing set $K \subset D$.
($H2$) Equation (33) has a unique equilibrium x^* in D.

The basic idea of this method is that if the equilibrium x^* is (locally) stable, then the global stability is assured provided that $(H1)$–$(H2)$ hold and no nonconstant periodic solution of Eq. (33) exists. Therefore, sufficient conditions on f capable to preclude the existence of such solutions have to be detected.

Li and Muldowney showed that if $(H1)$–$(H2)$ hold and Eq. (33) satisfies a Bendixson criterion that is robust under C^1 local ε-perturbations[2] of f at all nonequilibrium non-wandering[3] points for Eq. (33), then x^* is globally stable in D provided it is stable. Then, a new Bendixson criterion robust under C^1 local ε-perturbation and based on the use of the Lozinskiĭ measure is introduced.

Let $P(x)$ be a $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 on D and consider

$$B = P_f P^{-1} + P J^{[2]} P^{-1},$$

where the matrix P_f is

$$(p_{ij}(x))_f = (\partial p_{ij}(x)/\partial x)^T \cdot f(x) = \nabla p_{ij} \cdot f(x),$$

and the matrix $J^{[2]}$ is the second additive compound matrix of the Jacobian matrix J, i.e., $J(x) = Df(x)$. Generally speaking, for an $n \times n$ matrix $J = (J_{ij})$, $J^{[2]}$ is a $\binom{n}{2} \times \binom{n}{2}$ matrix (for a survey on compound matrices and their relations to differential equations, see [34]) and in the special case $n = 3$, one has

$$J^{[2]} = \begin{bmatrix} J_{11} + J_{22} & J_{23} & -J_{13} \\ J_{32} & J_{11} + J_{33} & J_{12} \\ -J_{31} & J_{21} & J_{22} + J_{33} \end{bmatrix}.$$

Consider the Lozinskiĭ measure $\mathscr{L}$ of B with respect to a vector norm $|\cdot|$ in $\mathbf{R}^N$, $N = \binom{n}{2}$ (see [33])

$$\mathscr{L}(B) = \lim_{h \to 0^+} \frac{|I + hB| - 1}{h}.$$

It is proved in [30] that if $(H1)$ and $(H2)$ hold, condition

$$\limsup_{t \to \infty} \sup_{x_0 \in \Gamma} \frac{1}{t} \int_0^t \mathscr{L}(B(x(s, x_0)))ds < 0, \tag{34}$$

guarantees that there are no orbits giving rise to a simple closed rectifiable curve in D which is invariant for Eq. (33), i.e., periodic orbits, homoclinic orbits, and

[2] A function $g \in C^1(D \to \mathbf{R}^n)$ is called a C^1 local ε-perturbation of f at $x_0 \in D$ if there exists an open neighborhood U of x_0 in D such that the support $\mathrm{supp}(f - g) \subset U$ and $|f - g|_{C^1} < \varepsilon$, where $|f - g|_{C^1} = \sup\{|f(x) - g(x)| + |f_x(x) - g_x(x)| : x \in D\}$.

[3] A point $x_0 \in D$ is said to be non-wandering for Eq. (33) if for any neighborhood U of x_0 in D and there exists arbitrarily large t such that $U \cap x(t, U) \neq \emptyset$. For example, any equilibrium, alpha limit point or omega limit point, is non-wandering.

heteroclinic cycles. In particular, condition (34) is proved to be a robust Bendixson criterion for Eq. (33). Besides, it is remarked that under the assumptions $(H1)$–$(H2)$, condition (34) also implies the local stability of x^*.

As a consequence, the following theorem holds [30]:

Theorem 8. *Assume that conditions (H1)–(H2) hold. Then x^* is globally asymptotically stable in D provided that a function P(x) and a Lozinskiĭ measure $\mathscr{L}$ exist such that condition* (34) *is satisfied.*

References

1. Auld, C.: J. Health Econ. **22**, 361–377 (2003)
2. Bauch, C.T.: Proc. Royal Soc. London B **272**, 1669–1675 (2005)
3. Bauch, C.T., Earn, D.: PNAS **101**, 13391–13394 (2004)
4. Beretta, E., Kon, R., Takeuchi, Y.: Nonlinear Anal. RWA **3**, 107–129 (2002)
5. Beretta, E., Solimano, F., Takeuchi, Y.: Nonlinear Anal. TMA **50**, 941–966 (2002)
6. Brito, D.L., Sheshinski, E., Intriligator, M.D.: J. Public Econ. **45**, 69–90 (1991)
7. Buonomo, B., d'Onofrio, A., Lacitignola, D.: Math. Biosci. **216**, 9–16 (2008)
8. Buonomo, B., d'Onofrio, A., Lacitignola, D.: Math. Biosci. Eng. **7**, 561–578 (2010)
9. Buonomo, B., d'Onofrio, A., Lacitignola, D.: Appl. Math. Lett. **25**, 1056–1060 (2012)
10. Buonomo, B., Lacitignola, D.: Nonlinear Anal. RWA **5**, 749–762 (2004)
11. Buonomo, B., Lacitignola, D.: Proc. Dyn. Syst. Appl. **4**, 53–57 (2004)
12. Buonomo, B., Lacitignola, D.: J. Math. Anal. Appl. **348**, 255–266 (2008)
13. Buonomo, B., Lacitignola, D.: In: Manganaro, N., et al. (eds.) Proceedings of Waves and Stability in Continuous Media, Scicli, Italy, June 2007, pp 78–83. World Scientific, Hackensack (2008)
14. Buonomo, B., Vargas De-León, C.: J. Math. Anal. Appl. **385**, 709–720 (2012)
15. Capasso, V.: Mathematical structures of epidemic systems. In: Lecture Notes in Biomathematics. Springer, Berlin (2008)
16. d'Onofrio, A., Manfredi, P.: J. Theor. Biol. **256**, 473–478 (2009)
17. d'Onofrio, A., Manfredi, P., Salinelli, E.: Theor. Pop. Biol. **71**, 301–317 (2007)
18. d'Onofrio, A., Manfredi, P., Salinelli, E.: Math. Med. Biol. **25**, 337–357 (2008)
19. Efimov, D.V., Fradkov, A.L.: Math. Biosc. **216**, 187–191 (2008)
20. Efimov, D.V., Fradkov, A.L.: Siam J. Contr. Optim. **48**, 618–640 (2009)
21. Fine, P., Clarkson, J.: Am. J. Epidemiol. **124**, 1012–1020 (1986)
22. Freedman, H.I., Ruan, S., Tang, M.: J. Diff. Eq. **6**, 583–600 (1994)
23. Geoffard, P.Y., Philipson, T.: Am. Econ. Rev. **87**, 222–230 (1997)
24. Hethcote, H.W.: Math. Biosci. **28**, 335–356 (1976)
25. Hutson, V., Schmitt, K.: Math. Biosci. **111**, 1–71 (1992)
26. Iwami, S., Takeuchi, Y., Liu, X.: Math. Biosci. **207**, 1–25 (2007)
27. Li, M.Y., Graef, J.R., Wang, L., Karsai, J.: Math. Biosci. **160**, 191–213 (1999)
28. Li, M.Y., Muldowney, J.S.: J. Diff. Eq. **106**, 27–39 (1993)
29. Li, M.Y., Muldowney, J.S.: Math. Biosci. **125**, 155–164 (1995)
30. Li, M.Y., Muldowney, J.S.: SIAM J. Math. Anal. **27**, 1070–1083 (1996)
31. Li, G., Wang, W., Jin, Z.: Chaos Soliton. Fract. **30**, 1012–1019 (2006)
32. MacDonald, N.: Biological Delay Systems: Linear Stability Theory. Cambridge University Press, Cambridge (1989)
33. Martin Jr, R.H.: J. Math. Anal. Appl. **45**, 432–454 (1974)
34. Muldowney, J.S.: Rocky Mount. J. Math. **20**, 857–872 (1990)

35. Murray, J.D.: Mathematical Biology. Interdisciplinary Applied Mathematics, vol. 17. Springer, Heidelberg (2002)
36. Reluga, T.C., Bauch, C.T., Galvani, A.P.: Math. Biosci. **204**, 185–198 (2006)
37. Salmon, D.A., Teret, S.P., Raina MacIntyre, C., et al.: Lancet **367**, 436–442 (2006)
38. Vardavas, R., Breban, R., Blower, S.: PLoS Comp. Biol. **3**, e85 (2007)
39. Wang, L., Li, M.Y.: Math. Biosci. **200**, 44–57 (2006)

Part IV
Concluding Overview

Capturing Human Behaviour: Is It Possible to Bridge the Gap Between Data and Models?

W. John Edmunds, Ken Eames, and Marcus Keogh-Brown

Abstract Do people respond to changes in perceived risk of disease? The answer to this is surely yes, but how? And will we ever be able to reliably predict how individuals will react to a given situation? In this chapter we examine the evidence for changes in behaviour as a result of changing epidemiological situations and the practical implications of this research. We show that, with a few notable exceptions, empirical support for recent theoretical advances is generally weak. We highlight the areas where further observational data are needed, and suggest ways to collect this information.

1 Background

In his diary on the 21st of June 1665, Samuel Pepys wrote, 'I find all the towne almost going out of towne, the coaches and waggons being all full of people going into the country'. This was no holiday: the plague had arrived in London. The King and his court moved to Oxford, as did Parliament, and many people with the means to do so—doctors, priests, lawyers, and merchants—fled from the dangers of pestilential London. Pepys sent his mother out of town on the 22nd, though he himself stayed (and survived). The following spring, in the village of Eyam in the county of Derbyshire, plague cases began to rise. Rather than running, the villagers of Eyam chose to stay put, severing all direct contact with surrounding villages, to prevent the spread of infection. Perhaps they had nowhere else to go; perhaps livelihoods were too tied to farmsteads, livestock, and mining claims to permit easy relocation; perhaps they were simply doing what they believed to

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be right. In any case, faced with the horrors of the plague, different people and different communities changed their behaviour in a variety of different, perhaps unpredictable, ways.

People continue to respond to changes in perceived risk of disease. The scenes of empty airports and people wearing facemasks during the SARS and H1N1pdm epidemics are all too familiar. How might they react to the next outbreak of a novel infection? Do fluctuations in the prevalence of endemic diseases alter the demand for preventative actions, such as immunisation? This chapter examines the empirical evidence for changes in behaviour as a result of a changing epidemiological situation and discusses the practical implications of this research.

2 Motivating Questions

Does a change in epidemiology influence behaviour, and does this change in behaviour influence epidemiology? Put another way, is there feedback between the prevalence or incidence of an infectious disease and protective behaviours taken by individuals? And do these protective behaviours actually lower individual's risk of disease? What is the empirical evidence for this? Can we improve the predictive ability of dynamic transmission models by encapsulating these potential feedbacks? And finally, can public health authorities make use of this information to tailor their responses to changing epidemiological circumstances?

3 Narrowing the Field

Before addressing these questions, we need to define what we are looking at. There are many behaviours that are stimulated or imposed as a result of the actions of public health officials. Closing schools or other public meeting places during an outbreak being examples. Under these circumstances individuals must adapt their behaviours. Likewise, illness itself may induce an alteration in the daily routine [1]. These behavioural changes are not the primary subject of this volume. Instead, we are interested in individual's choices: whether they react to a change in epidemiological circumstances in order to modify their own risk. This implies that the individuals concerned must have some information on the risk of disease (however inaccurate), a choice between actions, and the belief that their actions will reduce their risk (or that of a loved one). The epidemiological circumstances could include an outbreak, where the risk of infection is presumably changing relatively quickly, or an endemic disease, against which protective behaviours such as vaccination might be effective. We focus here exclusively on infectious diseases, although it should be noted that a number of 'lifestyle' diseases, such as drug use or smoking, share elements with infectious diseases (an increase in prevalence amongst peers leading to increasing use), and so many of the findings from this book may well have implications for a wider range of diseases.

4 Practical Considerations

Before the epidemiological circumstances arise that might prompt behavioural modification, a range of a priori possibilities can be envisaged. Some of these can be seen as a response to a present risk (e.g. self-isolation, moving away from areas with high incidence, avoiding public transport, children being kept away from school by their parents). Others could be carried out either in response to current circumstances or in expectation of future risk (e.g. seeking protective vaccination or stocking up on medicines).

Some behavioural changes involve a one-off action (e.g. vaccination), whereas others would be expected to continue over longer periods of time (e.g. social distancing). The former would be expected to be at a low cost to the individual, as might those that are essentially changes in habit (e.g. condom use, hand-washing); other changes could have large impacts on quality of life and would be highly inconvenient if carried on indefinitely.

When considering possible behavioural change in response to infectious disease risk, it is necessary to consider the practical implications for individuals attempting to implement such changes. Not everyone will be free to alter their behaviour in ways that they might want to, and certainly it will be hard to sustain these changes for long periods of time. In many cases we would expect behaviour to eventually revert to normal. In such circumstances, the benefit of behavioural change may not be a sustained reduction in risk but a delay in risk. At a population level this could be beneficial, providing extra time to plan a response, but this benefit may be strongly dependent on the change in behaviour taking place at an appropriate time—social distancing will be ineffective if people are bored of it before the epidemic arrives.

5 Perverse Outcomes

Not all changes in behaviour are likely to be beneficial, and some may be harmful. When plague gripped Europe in the centuries after 1347, the general response from those citizens with the means to do so was to flee affected cities. Although this may have reduced their personal risk, the increased movement of people might well have seeded infection in distant communities, hastening the spread of the epidemic across the continent. Similarly, a rush for treatment during an outbreak could result in high concentrations of the sick and the worried well at health-care facilities, resulting in additional transmission, diverting resources from other roles, and hindering the effective delivery of treatments to those most in need.

The consequences of large-scale behavioural change on the delivery of key services and on the smooth functioning of a nation's infrastructure are potentially vast. The need for health-care workers, food, and fuel delivery personnel, for example, to continue to work might come into conflict with a desire from individuals for social distancing. Reduction in public transport use, shopping, and use of bars

and restaurants may have a significant effect on these aspects of the economy [2, 3]. There are therefore likely to be trade-offs between the individual and society. To what extent this can be controlled, guided, or influenced by government in the event of a large-scale epidemiological event is a moot point.

6 Epidemiological Models of Behavioural Change

Most epidemiological models assume that behaviour is static, unaffected by the incidence of disease. Those that have attempted to model how behaviour changes during an epidemic have tended to perform 'what-if' analyses, in which the effect of a certain behavioural change is examined. For instance, Del Valle et al. (in this volume) [4] assume that individuals isolate themselves at home due to the fear of being infected. Their model then shows the potential impact of such behaviour. Whilst this can give useful insight, the quantitative details of the results are driven by the assumptions used, not by an empirical examination of whether such behaviour is likely to occur and under what circumstances.

There have been very few attempts to quantify how behaviour might change in the event of an epidemic. One such example is that of Sadique et al. [5] who asked individuals in eight different countries (5 in Europe and 3 SARS-affected Asian countries) which settings (e.g. public transport, places of entertainment, shops, work) they thought were most risky and whether they would change behaviour in the event of an influenza pandemic. The results suggested that potentially large numbers of individuals would take precautionary behaviours. Over 70% reported that they would avoid public transport, and large numbers reported that they would avoid places of entertainment, would be absent from work, would limit shopping to the essentials, and keep children from school [5]. If these results are combined with data on usual contact patterns (available from the large population-based survey POLYMOD [6]), then it is possible to infer the impact of these behavioural changes. If people behaved as reported, then the reproduction number of the epidemic would fall to approximately two thirds of its original value, with reduced contacts at school, at work, and during leisure activities contributing approximately equally to this fall. Because public transport accounts for such a small fraction of social contacts, it is unlikely that avoiding it would have a noticeable impact on transmission. That is, the most commonly reported avoidance behaviour may play a very limited role in reducing risk.

This analysis does not include any information about how the strength of social contacts might be influential and might change. The riskiness of an encounter could be reduced for instance by avoiding physical contact such as shaking hands, wearing face masks, or increasing physical separation during conversation. Weighting social contacts by their likely risk of transmission would further reduce the impact of changes in public transport use and shopping as a means of limiting epidemic spread.

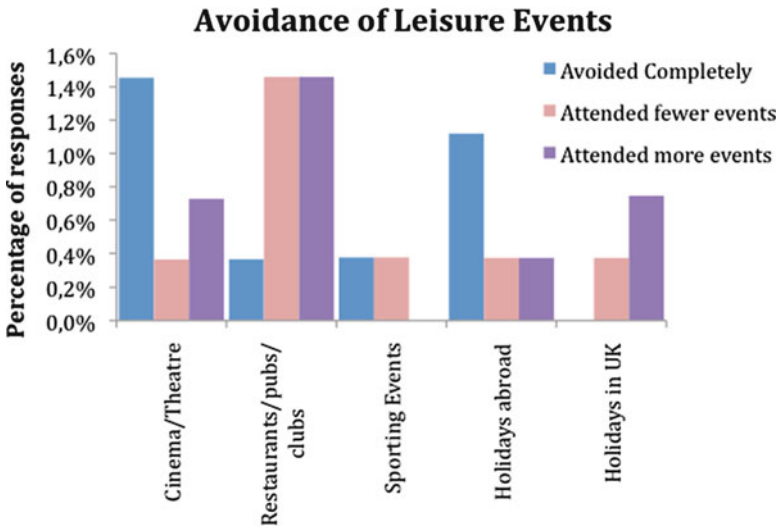

Fig. 1 Avoidance of leisure events during the H1N1pdm influenza pandemics in UK

The problem with surveys of hypothetical situations is that respondents may not react in the way they expect when faced with a real epidemic. The responsibilities and necessities of normal life may restrict behavioural changes in ways that are not possible to pick up adequately in surveys. It is interesting to note, for instance, that in the survey of Sadique et al. [5] those who were employed were less likely to report that they would avoid public transport, perhaps because of the constraints of getting to work.

In an attempt to collect data during a real epidemic, we included a survey on risk behaviour as part of our ongoing Internet-based surveillance of influenza like illness (www.flusurvey.org.uk) [7,8]. The survey was completed by 279 respondents between 14th December 2009 and 10th February 2010. Respondents were asked questions concerning changes in their behaviour as a direct result of the H1N1pdm influenza pandemic during the previous week. We asked about changes in work-related travel, time off work due to school closures, changes in shopping behaviour, and changes in leisure activities.

For each of these questions, more than 98% of respondents submitted a response, and more than 96% of respondents reported no change in behaviour. Given the mildness of the pandemic and rapidly declining risk of infection at the time that many respondents completed the survey, these results are not surprising, but a small number of respondents indicated that they had undertaken risk averse behaviour change (shifting to exclusive or increased online shopping or avoiding leisure events (see Fig. 1) in all response categories.

A telephone-based survey performed at the outset of the 2009 H1N1pdm influenza epidemic in the UK (early May 2009) showed a similar lack of action to avoid 'risky' scenarios [9]. Only about 1% of over 900 respondents reported

cancelling or postponing a social event, 3% reported a reduction in the use of public transport, and 2% reported a reduction in shopping. The major behaviours that were adopted were in relation to personal hygiene with 17% reporting an increase in cleaning and disinfecting and 28% reporting an increase in hand washing. Thus, although the number of social contacts was almost unchanged, the riskiness of encounters may have been reduced somewhat. Although, again, we do not know the efficacy of such measures (increased from what baseline level, by how much, and in what settings?) and how well these behaviours were maintained.

In contrast a telephone-based survey in the USA conducted at the outset of the epidemic (April to June 2009) found that almost two thirds had washed their hands or used hand sanitisers more frequently, and around a half had taken steps to prepare to stay at home to care for themselves or others who may be sick [10]. By June 20% reported taking measures to reduce contact with others outside the home, even though such measures were not recommended at the time. As in the survey of Sadique et al. [5], avoiding public transport and shopping malls were the most likely behaviours to be adopted, though the fraction of individuals reporting having undertaken these behaviours (around 10–15% for each) was far lower than the anticipated reaction to a hypothetical influenza pandemic. The contrast between the UK and US results is marked, reflecting cultural and context-specific factors.

The risk of acquiring influenza was probably roughly similar at the time all three surveys were performed (both telephone surveys were performed at the outset of the epidemic, the Internet-based UK survey at the end). The objective risk of disease is clearly then not the only driver of behavioural change—in fact it may be relatively unimportant—and other factors, such as media reports and peer influence play a role in shaping how individuals respond to a given situation. As can be seen in the differences between the UK surveys, with somewhat higher levels of avoidance behaviour at the outset of the epidemic, it is clear that the epidemiological triggers for action may be unrelated to the recent incidence. It is worth noting that the few epidemiological models that do try and incorporate behavioural change tend to exclude the influence of these other factors.

Surveys of behaviour during outbreaks give an invaluable insight into what may occur. However, these situations are rare, and it is difficult to perform these studies in real-time due to the rapidly changing epidemiological picture and the inevitable delays inherent in designing a survey, securing permissions, and obtaining a sample. A further problem is that we rarely know the baseline—how frequently do people normally wash their hands or travel by public transport? Do individuals take preventative measures against seasonal flu, for instance, and if not, why not? We need to start to collect this information now, and simple online tools such as the flusurvey [7, 8] may be a convenient way to do this and link with self-reported illness simultaneously. Surveys performed during outbreaks can also be enhanced by studies of hypothetical situations that can be performed in ‘peace time’. Such data can give an indication of which behaviours are likely to be most affected—public transport and entertainment, for instance—but are probably quantitatively unreliable due to the restrictions on behaviour that are likely to arise in real life. Both hypothetical surveys and studies of behaviour during an epidemic are unlikely

to be able to accurately quantify what may occur during future events as the scenarios studied are highly unlikely to be similar to any given future epidemic in all relevant respects. Mechanistic explanations of behaviour change are required to help generalise these results to other contexts.

7 Economic Models of Behavioural Change

The economic approach makes incentives for behavioural change explicit. Typically these models assume that the prevalence of disease induces a change in behaviour to reduce individual's risk of acquisition. Rational individuals try to maximise expected utility. In the absence of disease this is maximised by adopting a certain behaviour (such as engaging in unprotected sex), and as the disease prevalence increases, a change to protective behaviour is induced. Other behaviours can be adopted to reduce the risk of disease, such as accepting vaccination. The risk of a vaccine-preventable disease declines with increasing uptake, whereas the per-dose risk from the vaccine remains unaltered. Eventually there is a point at which individuals decide that the risk from the vaccine exceeds the risk of disease and choose not to vaccinate. This in turn can lead to an increase in incidence and so on. Typically, this rational epidemic behaviour leads to levels of vaccine coverage below that necessary for elimination (the herd immunity threshold) [11, 12], even when the vaccine in subsidised [12], although in a structured population network effects can allow elimination to be achieved [13].

Empirical support for these theories is generally reliant on ecological analyses. For instance, Bauch and Bhattacharyya [14] fit a series of models to overall uptake data for MMR and pertussis vaccines using aggregate data on measles cases and pertussis notifications (see later). There are a few studies that have used individual-level data. Philipson [15] analysed data on MMR vaccine uptake from the 1991 US National Health Interview Survey and state-level data on measles incidence, in two time periods: just before and during a major outbreak of measles. He found that during the period of the epidemic residents of states with high incidence were vaccinated more quickly than residents of states with low incidence, but there had been no difference prior to the measles outbreak. The suggestion being that individuals were responding to this higher incidence, although many other factors may also have played a role, including the role of health-care workers in ensuring that children are promptly immunised during an outbreak. One of the more convincing studies of behavioural responses to an emerging epidemic threat is the analysis of sexual behaviour in gay men in San Francisco during the 1980s. The prevalence of HIV in this population increased from around zero in the late 1970s to around 50% by 1984, after which it stabilised. Auld [16] examined individual-level longitudinal data on sexual behaviour and HIV prevalence and found that a 10% increase in prevalence reduced the sexual partner change rate by about 5%. Importantly, however, he also showed that this average elasticity masked significant variability. Men in the lowest risk group were much more likely to further reduce

their risk, whereas those in the highest risk group were largely unresponsive. That is, a similar stimulus (prevalence) can lead to differing behaviours in different population subgroups: something that would be impossible to pick up using an ecological analysis of aggregate data.

8 Environments, Peer Networks, and Behavioural Change

Other studies have postulated that an individual's environment helps shape decisions to take preventative actions. For example an individual's peer network may play a role in influencing whether they accept vaccination [14, 17, 18]. This can be because the risk of infection is determined by others close to a given individual in the contact network, and/or because attitudes towards vaccination (or other preventative measures) can be spread along a network of influence. Eames [18] showed that if there is significant overlap between these two networks (the networks of contacts of children and the opinion networks for their carers), then clusters of susceptibles may build up. This can allow outbreaks to occur even in a population with high overall vaccine coverage. The empirical basis for these interesting findings is again rather weak. A number of studies of vaccination behaviour have shown that peers can be influential. For instance, Kraut and others [19] surveyed the attitudes of health-care workers to the seasonal and pandemic flu vaccines and found that co-workers were the most important source of influence for both those who accepted the pandemic flu vaccine and those that did not.

Bauch and Bhattacharyya [14] present one of the very few attempts to parameterise an epidemiological model that incorporates the influence of others in the population as well as the feedback that may occur from the incidence of diseases. They go beyond a theoretical exposition and attempt to fit their model to data. The authors used aggregate data on MMR and pertussis vaccine coverage and measles and pertussis incidence data from England and Wales during periods of vaccine scares (1970s and 1980s for pertussis, and 1990s and beyond for MMR). They include a social learning component (the decision to (not) vaccinate being passed on from person to person) as well as a feedback component (as incidence increases demand for vaccination increases) and tested whether these two mechanisms operated by comparing models with/without them using Akaike information criteria methods. They compared their model to both vaccine coverage and disease incidence data and even validated their findings by fitting to the early part of the time series and comparing their predications to the remaining data. Interestingly they found that both the social learning and feedback components appear to be necessary to adequately explain the observed trends.

So social learning may play a role, but how in practice does this come about? Individuals receive information from a wide range of sources, including personal contacts, media reports, and official announcements. Different sources may have different levels of accuracy, perceived accuracy, and trustworthiness, and two individuals may be given the same information but respond in different

ways. Understanding how different sources are perceived and the societal, socio-economic, and social factors that influence the eventual action are extremely complex problems: how does one measure the degree of encouragement towards a behavioural change from different individuals or institutions and the sensitivity of the decision to a change in this level of encouragement?

9 Psychological Theories of Behavioural Change

The economic and epidemiological approaches almost certainly oversimplify the complex psychological processes that feed into decision-making. A number of different psychological theories exist that attempt to explain and predict behavioural change in response to health threats [20]. These include rational models, such as the theory of planned behaviour, and lay theories which may include irrational beliefs, and motivations (e.g. that diseases are a result of divine judgement, and so there is little that can be done to prevent them), and emotions. Within this broad field, amongst the most common rational models of health behaviours are the health belief model and the related protection motivation theory. These models suggest that individuals weigh up the potential perceived benefits of a change against the perceived costs. They assume that there are a number of factors (constructs) that affect behaviour change. These vary between different version of the models, but typically include: susceptibility (whether the individual is at risk), perceived severity, perceived benefits, and perceived costs of the change in behaviour. These factors then feed into a decision about whether to adopt a new behaviour (such as stopping smoking) or not.

There is a large literature on the use of these theories to help frame analyses of decisions about the uptake of preventative and therapeutic health interventions. To pick just one example, Regan and Morisky [21] recently examined perceptions about HIV and the uptake of condoms in the clients of female sex workers in the Philippines. They found that more educated men were significantly more likely to consistently use condoms. They also found that two factors taken from protection motivation theory were significantly associated with consistent condom use, namely, higher perception of the severity of AIDS and a higher score for the response efficacy of condoms. Many other examples exist, drawn from all areas of public health, including decisions to vaccinate [22], accept screening [23], and reduce risk of exposure to infectious diseases [24].

There is only one example, as far as we are aware, of an epidemiological model being parameterised explicitly by a psychological model. Durham and Casman [25] embedded a health belief model within an individual-based epidemic model of SARS in Hong Kong. Sub-models were developed and parameterised for each of the major constructs of the health belief model: perceived susceptibility, which was assumed to be related to recent or cumulative prevalence of disease; perceived severity, which was assumed to be related to either estimated case-fatality ratios or news coverage; perceived benefits of face-mask wearing (assumed to remain

constant over the course of the epidemic); and perceived barriers of mask wearing, which was assumed to be related to the number of others who were wearing masks. The model was then calibrated by fitting to data on mask wearing, which increased dramatically during the outbreak. Their empirical analysis suggested that perceived susceptibility was the most influential parameter and that it was related to cumulative rather than the instantaneous number of cases. This study represents an important first step, although the authors themselves point out that far more work is needed on the factors associated with decisions to take preventative behaviours and the functional forms that should be adopted in a parametric description. It should also be noted that the risk of disease was assumed to be exogenous in this analysis—that is, there was no feedback resulting from the uptake of these measures on the incidence of disease.

10 Conclusions

Simple epidemic models have proved to be very useful in providing qualitative and quantitative insight into the spread of infectious diseases and their control via public health measures [26], despite the vast majority assuming that host behaviour does not respond to the epidemiological situation. Nevertheless it has become increasingly obvious that individuals may adapt their behaviours according to their perceived risk or because of what others are doing and that these changes may alter projections of the future incidence of disease and effectiveness of alternative policies. This book outlines some of the recent advances in this field. However, it is evident from this volume that this is an area of research in which the development of theory and its illustration using simulation has outstripped empirical evidence. Accurately parameterising these models and selecting and validating models by confrontation with data will be the next major challenge.

As this chapter has attempted to show, there are different approaches that have been taken ranging from simple assumptions that behaviour will change to an exploration of the factors underlying these changes. It is tempting to think that as more psychological detail is included in the model, the more accurate will be the predictions. This is potentially misguided. Increased complexity does not necessarily lead to increased precision or qualitative insight. There is almost certainly a need for multiple approaches to be taken forward. Observational studies are extremely useful but are limited in their generalisability. Mechanistic models can help with this, but there is no clear theory that can be used to guide model structure. The existence of multiple theories of behavioural change illustrate the problem, and it seems likely that there is an element of truth in each. Understanding which of these are most applicable and in what circumstances will be a significant undertaking for which high-quality empirical information will be essential if these models are to be used to guide future decision-making in this challenging and fascinating field.

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References

1. Eames, K.T., Tilston, N.L., White, P.J., Adams, E., Edmunds, W.J.: Health Technol Assess **14**, 267–312 (2010)
2. Beutels, P., Edmunds, W.J., Smith, R.D.: Health Econ. **17**, 1317–1322 (2008)
3. Keogh-Brown, M.R., Smith, R.D.: Health Policy **88**, 110–120 (2008)
4. Del Valle, S.Y., Mniszwewski, S.M., Hyman, J.M.: Modelling the impact of behaviour changes on the spread of pandemic influenza. In: Manfredi, P., d'Onofrio, A. (eds.) Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases. Springer, New York (2012)
5. Sadique, M.Z., Edmunds, W.J., Smith, R.D., Meerding, W.J., de Zwart, O., Brug, J., Beutels, P.: Emerg. Infect. Dis. **13**, 1307–13 (2007)
6. Mossong, J., Hens, N., Jit, M., Beutels, P., Auranen, K., Mikolajczyk, R., Massari, M., Salmaso, S., Tomba, G.S., Wallinga, J., Heijne, J., Sadkowska-Todys, M., Rosinska, M., Edmunds, W.J.: PLoS Med. **5**(3), e74 (2008)
7. Tilston, N.L., Eames, K.T., Paolotti, D., Ealden, T., Edmunds, W.J.: BMC Public Health **10**, 650 (2010)
8. Brooks-Pollock, E., Tilston, N., Edmunds, W.J., Eames, K.T.: BMC Infect. Dis. **11**, 68 (2011)
9. Rubin, G.J., Amlt, R., Page, L., Wessely S.: BMJ **339**, b2651 (2009)
10. SteelFisher, G.K., Blendon, R.J., Bekheit, M.M., Lubell, K.: N. Engl. J. Med. **362**, e65 (2010)
11. Fine, P.E., Clarkson, J.A.: Am. J. Epidemiol **124**, 1012–1020 (1986)
12. Geoffard, P-Y., Philipson, T.: Am. Econ. Rev. **87**, 222–230 (1997)
13. Perisic, A., Bauch, C.T.: PLoS Comput. Biol. **5**, e1000280 (2009)
14. Bauch, C.T., Bhattacharyya, S.: PLoS Comput. Biol. **8**, e1002452 (2012)
15. Philipson, T.: J. Hum. Resour. **31**, 611–630 (1996)
16. Auld, M.C.: Contrib. Econ. Analy. Policy **5**, 1–27 (2006)
17. Salath, M., Bonhoeffer, S.: J. R. Soc. Interface **5**, 1505–1508 (2008)
18. Eames, K.T.: J. R. Soc. Interface. **6**, 811–814 (2009)
19. Kraut, A., Graff, L., McLean, D.: Vaccine **29**, 8357–8363 (2011)
20. Weinstein, N.D.: Health Psychol. **12**(4),324–33 (1993)
21. Regan, R., Morisky, D.E.: Health Educ. Behav. (2012) (in press)
22. Bennett, K.K., Buchanan, J.A., Adams, A.D.: J. Soc. Psychol. **152**, 480–492 (2012)
23. Gu, C., Chan, C.W., He, G.P,, Choi, K.C., Yang, S.B.: Eur. J. Oncol. Nurs. (2012) (in press)
24. Teasdale, E., Yardley, L., Schlotz, W., Michie, S.: Br. J. Health Psychol **17**, 44–59 (2012)
25. Durham, D.P., Casman, E.A.: J. R. Soc. Interface **9**, 562–70 (2012)
26. Anderson, R.M., May, R.M.: Infectious Diseases of Humans: Dynamics and Control. Oxford University Press, Oxford (1991)

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