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Interventions to Control Damage from Infectious Disease

Integrating Ecological, Evolutionary, and Economic Perspectives

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Abstract

Human infectious disease results from many factors (e.g., human behavior, disease organisms, institutions) that often interact as opposing agents in accordance to the investor–exploiter dichotomy. Directing interventions to influence these opposing roles may improve human health by differentially influencing the success of exploiters and investors. Alterations made on one level may change outcomes on other levels and affect the impact of disease on states of health. These interactions need to be incorporated into economic models to inform the assessments of interventions to improve health.

Introduction

Strategies that involve different interests among participants often involve roles that can be cast as investors and exploiters. Investors increase the presence of some resource whereas exploiters gain access to a resource without

Group photos (top left to bottom right) Paul Ewald, Frédéric Thomas, Markus Herrmann, Philipp Heeb, Benjamin Roche, Frédéric Thomas, Sam Brown, Paul Ewald, Arnon Lotem, Paul Ewald, Philipp Heeb, Markus Herrmann, Arnon Lotem, Frédéric Thomas, Sam Brown, Philipp Heeb, Paul Ewald, Arnon Lotem, Frédéric Thomas, Benjamin Roche, Markus Herrmann

increasing its presence. These roles can be applied to infectious diseases¹ and the medical activities used to control them. Assessments of these strategies encompass not only the infectious agents and their attributes, but immune function, human behavior, health care institutions, insurance companies, agriculture, the pharmaceutical industry, environmental conditions, and biological evolution. Understanding the interactions among these elements in the context of investors and exploiters may help inform decisions bearing on the control of infectious disease.

The success of interventions to control infectious disease is often quantified by measuring short-term reductions in incidence, prevalence, morbidity, and mortality. Any intervention, however, introduces a change in the environments of disease organisms. Target organisms may evolve in response to these environmental changes, altering variables such as virulence (i.e., harmfulness) and antibiotic resistance. Evaluations of control efforts, therefore, require an integration of ecological and evolutionary effects; influences on incidence, for example, need to be assessed in light of the evolutionary changes in resistance and virulence.

Assessments of alternative investments in disease control depend on the different interests of the affected participating entities as well as on the ways in which biological, social, and economic aspects interact. In a hospital setting, for instance, hospital administrators may benefit from making investments that reduce antibiotic resistance (e.g., restricted use of antibiotics and extra effort to maintain hygienic standards). These investments, however, may come at the cost of care for individual patients and revenue-enhancing activities. If knowledge about the dangers and rates of hospital-acquired infections are made available to the public, the threat of legal action and improvement in reputation of the hospital may make improved hygiene a higher priority. A pharmaceutical company, on the other hand, may benefit if the prevalence of infection is relatively high and resistance to its own antibiotic is low, especially if it is under patent.

From a public health perspective, the optimal outcome may not be associated with elimination of infection. Mild infections may help maintain an effective immune system; in addition, elimination of infection may be both costly and difficult to achieve. Alternative investments in hygiene may provide a more beneficial outcome and allow a substantial prevalence of benign infection, by inhibiting strains with elevated virulence and reducing the need for antibiotic use. Blocking transmission by hospital attendants, for example, may disfavor virulent, antibiotic-resistant hospital strains relative to mild antibiotic-sensitive, community strains, which are brought in by patients upon admission (Ewald 1994). In general, the best outcome for public health policy makers

¹ Infectious diseases are defined broadly here to include any disease caused by parasites, which, in turn, are defined broadly to encompass multicellular, unicellular, and subcellular replicating agents that live in or on hosts and cause harm to them.

would be reduced prevalence, virulence, and antibiotic resistance. Categories of interventions that need to be considered in economic models include the introduction of microorganisms (e.g., probiotic bacteria), administration of antimicrobials (i.e., anti-infectives used against microorganisms) or other therapeutic agents, vaccination programs, and environmental changes that influence pathogen transmission. In this chapter we integrate these considerations to illustrate various levels at which the investor–exploiter dichotomy may be relevant to assessments of interventions to control infectious disease.

Microbes as Investors or Exploiters

Parasites can cause disease by using host resources and generating compounds that damage host tissues. In economic terminology, damaging compounds can be considered “goods.” The ways in which these goods influence members of the microbial community within a host and between hosts (during pathogen transmission) determines whether the goods are categorized as public, congested, private, or club (see Figure 9.1 and Burton-Chellew et al., this volume). Public goods are available to all parasites in the environment (i.e., they are not “excludable”), and their use does not deplete the use by others in the environment (i.e., there is no “rivalry” for a secreted compound). These concepts can be applied to the population of a parasite species within a host. For example, if consideration is restricted to the within-host environment, the toxin secreted by

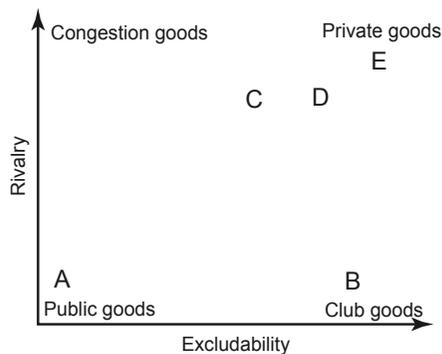


Figure 9.1 Diagrammatic representation of the categorization of microbial goods according to the presence of rivalry (use of good reduces its availability to others) and excludability (benefits of good are not shared). These categorizations can be used to assess expected effects of interventions on pathogens and the diseases they cause. A: Cholera toxin is a public good for the *Vibrio cholerae* within the host. B: Cholera toxin released within a host is not available to the *V. cholerae* in other hosts, so it is a club good when its use is considered among hosts. C: Diphtheria toxin within a host benefits the toxin producers and other *Corynebacterium diphtheriae* in the immediate vicinity and so has an intermediate position in the goods space. D: Diphtheria toxin considered among hosts. E: Compounds that are not secreted, such as those used for cell invasion by *Shigella*, are not shared and hence are private goods.

Vibrio cholerae (the bacterium that causes cholera) is a public good: the toxin released from the bacterium causes cells that line the intestinal tract to generate a diarrheal response, which in turn flushes competing species of bacteria out of the intestinal tract. This effect on competing species allows *V. cholerae* to avoid running through a gauntlet of competitors as they travel through the intestine to the external environment to initiate transmission to other hosts. This transmission benefit is shared with the other *V. cholerae* within the intestinal tract (i.e., the benefit is not excludable), and its use by one *V. cholerae* bacterium does not reduce its use by other *V. cholerae* in the intestinal tract (i.e., there is no rivalry). Consideration of the action of toxin within a host, therefore, leads to its categorization as a public good (location A in Figure 9.1). If, however, the scope of the analysis is broadened to consider the entire cycle of transmission, excludability is present because the transmission benefit is restricted to the group of *V. cholerae* within the host. The toxin is therefore labeled a club good (location B, Figure 9.1). Terminology can be confusing because evolutionary biologists, who consider how levels of selection act on virulence, define goods according to the within-host scale (e.g., Buckling and Brockhurst 2008; Leggett et al. 2014; Zhou et al. 2014). The reason for doing this is that arguments for selection of public goods within hosts must invoke indirect benefits through genetic relatedness of the pathogen population within hosts. Virtually all of the examples of public goods that are discussed in the context of the evolution of virulence, however, correspond to club goods when the analysis is expanded to the population of hosts, because the virulence mechanisms shared by the population of a pathogen within one host (i.e., the “club” of pathogens) are not shared with the pathogens in other hosts.

Other disease-producing compounds lie at intermediate places in the goods space of Figure 9.1. The toxin secreted by *Corynebacterium diphtheriae*, for instance, kills nearby host cells in the respiratory tract, releasing nutrients which can benefit the bacterium that secreted the toxin, but also, to a lesser extent, nearby *C. diphtheriae* (some excludability), and the toxin is consumed in the process (some rivalry). On the basis of within-host effects, the toxin is therefore intermediate between a public good and a private good (location C, Figure 9.1). As is the case with *V. cholerae*, when consideration is expanded to include the *C. diphtheriae* in different hosts, excludability is greater; thus the diphtheria toxin is best considered to have a stronger private goods character (location D, Figure 9.1).

The toxins of *V. cholerae* and *C. diphtheriae* are secreted from these bacteria. Nonsecreted virulence factors are typically private goods. For example, the compounds that *Shigella* bacteria use to invade the intestinal cells are not shared with other bacteria in the intestinal tract (they are excludable); they provide resources that are used solely by the invading bacteria (i.e., they are associated with rivalry) (location E, Figure 9.1). A nonsecreted virulence mechanism could, however, be shareable if it alters the biology of the host

systemically in a way that benefits the population of parasites in the host (e.g., an alteration of host behavior that facilitates transmission).

“Public goods” and “private goods” are typically used more broadly in evolutionary ecology than in contemporary economics (e.g., Buckling and Brockhurst 2008; Taylor et al. 2013; Leggett et al. 2014; Zhou et al. 2014). In evolutionary ecology, excludability has been emphasized and variation in rivalry has not been a focus of interest, nor has excludability of effects between hosts. Consequently, the literature of evolutionary ecology generally contrasts public goods with provide goods, with little (if any) reference to congested and club goods. In this chapter we adjust our usage to conform with contemporary usage in economics as illustrated in Figure 9.1.

Interventions to Control Infectious Disease

The health sciences have relied mainly on three categories of interventions to control infectious disease: use of anti-infectives, vaccines, and hygienic improvements. Anti-infectives include antibiotics, used against bacteria; anti-protozoals, used against single-celled eukaryotic parasites; anthelmintics, used against wormy parasites; and, increasingly, antivirals. Vaccines rely on inoculation of parasite molecules that stimulate antibody-mediated or cell-mediated immunity. Vaccines can be prophylactic (i.e., preventive) if administered prior to infection or therapeutic if administered after the onset of infection. Hygienic interventions alter the transmission process. For instance, they can involve disinfecting the skin or environmental surfaces, screening of blood supply, filtration of water or air, or introducing organisms into the host (e.g., probiotic bacteria) that compete with pathogenic organisms or influence immune responses.

Interventions to control infectious diseases alter the selective pressures that act upon causal parasites. In turn, the parasites may evolve to be less controlled by the intervention. This may occur, for example, through increased resistance to anti-infectives or via vaccine escape (i.e., an evolutionary change in the target pathogen characterized by reduced sensitivity to the control by the vaccine).

Evolutionary effects of anti-infectives have been considered most extensively for bacterial resistance to antibiotics for several reasons:

- Antibiotics have been widely used to control bacterial infections for three-quarters of a century, whereas bacteria can evolve noticeably increased resistance within a few years or even a few months after the introduction of treatment.
- Antibiotic resistance is apparent because it diminishes the effectiveness of treatment, which is the focus of medical attention.
- Antibiotic resistance is relatively easy to document *in vitro*.
- Mechanisms of antibiotic resistance are amenable to study.

Most of the attention given to antibiotic resistance within the medical community focuses on evolutionary processes, as the cause of the problem, rather than part of the solution (Chadwick and Goode 1997; Choffnes et al. 2010). The focus, therefore, has been on how to reduce the strength of selection for resistance in bacteria and ways to develop new antibiotics (Choffnes et al. 2010). Guidelines encompass methods to make use of surveillance for resistant organisms, infection control to reduce the use of antibiotics, and prudent use of antibiotics (e.g., by restricting use in agriculture, reliance on narrow spectrum antibiotics, and curtailing inappropriate use of antibiotics) (Stein 2005; Ferri et al. 2015).

The introduction of benign bacteria can alter the community of bacteria in a patient, as is the case with most probiotic treatments. If benign variants of conspecifics (naturally occurring or engineered) are introduced, the intervention lowers the frequency of harmful variants and thus causes at least a short-term evolutionary change. Studies need to be conducted to determine how the persistence of the benign variants can be encouraged. Continual reintroduction or changes in environmental conditions to favor the benign strains are two possibilities. Suppressing harmful organisms through such introductions may be akin to biological control programs in which new species are introduced to control undesirable pest species.

Parasite Goods Involved in Virulence

The effectiveness of an intervention may depend on whether virulence-enhancing compounds are secreted. As suggested above for cholera toxin, expansion of the scope of analysis to consider transmission between hosts in time and space has the general effect of shifting the categorization of the cholera toxin from a public good toward a club good, because fitness benefits of the toxin to other *V. cholerae* are not excludable within hosts but are excludable between hosts. These fitness benefits include the elimination of competing bacteria from the intestinal tract through toxin-induced diarrhea, as mentioned above, and the spread of *V. cholerae* in the external environment, which also results from the diarrhea. Because high toxin production can make a person extremely ill, this latter benefit of high toxin production occurs particularly (a) when water supplies can be contaminated by the fecal material of cholera patients, (b) when sewerage systems are inadequate, and (c) through the movement of the water itself. Within each host, *V. cholerae* variants that produce no toxin should be favored over those that produce high amounts of toxin, because the benefits of toxin production are shared among all vibrios in the intestinal tract (no excludability and no rivalry) and variants that produce little if any toxin are more efficient because they expend fewer resources on toxin production (Baselski et al. 1978, 1979; Sigel et al. 1980; Ewald 1994). In this case, the toxin producers are investors and the toxin-less variants are exploiters. Blockage of waterborne

transmission, however, changes these relationships because it changes the relative importance of different transmission routes (i.e., relatively healthy hosts are required for transmission). Where water supplies are protected, lower levels of toxin production are favored evolutionarily (i.e., production of the club good is disfavored), and cholera illness is controlled, even though *V. cholerae* may still be present (Ewald 2002).

Vaccines can provide effective protection by targeting toxins secreted from pathogens. The diphtheria vaccine, for example, controls diphtheria by stimulating antibodies against the diphtheria toxin, which is the most important cause of pathology in diphtheria. The toxin, however, is not produced by all strains of *C. diphtheriae*. If transmitted to a vaccinated host, a toxin-producing strain of *C. diphtheriae* wastes nutrients, making a toxin that is impotent (because the vaccine-induced immune response neutralizes the toxin). Nontoxigenic *C. diphtheriae* do not pay this cost of toxin production. Within vaccinated hosts, they can therefore convert a greater portion of the available nutrients acquired into their own reproduction. The overall consequence is that diphtheria vaccination has led to an evolutionary reduction in virulence of *C. diphtheriae*. The control of diphtheria by this vaccine has thus been extraordinarily successful, not by eliminating *C. diphtheriae* from populations but rather by favoring toxin-less *C. diphtheriae*, which cause little harm to humans while stimulating acquired immunity against both toxigenic and nontoxigenic strains (Ewald 1994, 2002). This vaccination approach, termed the “virulence antigen strategy,” illustrates how targeting of virulence antigens can lead to particularly effective control of disease because vaccination favors evolutionary reductions in virulence in addition to reductions in disease incidence.

The cholera and diphtheria examples illustrate how disease can be controlled by a hygienic intervention and by vaccination, respectively, when the virulence mechanism is based on a secreted toxin: a club good in the case of cholera and a toxin that is intermediate between all four categories of goods in the case of diphtheria (see Figure 9.1). Secreted goods may be particularly amenable to evolutionary control because the benefits they provide are often shared within hosts, generating opportunities for less virulent parasites (exploiters) to exploit the benefits of the good that is secreted by the more virulent parasites (investors). Both categories of parasites can therefore be maintained by frequency-dependent selection. If so, the benign strains will already be present in a pathogen population prior to an intervention that favors benign strains. The result can be a rapid evolutionary reduction in virulence, as has occurred in response to diphtheria vaccination. The production of virulence compounds may often be graded rather than categorized as all or none, in which case selection is expected to lead to a graded lowering of virulence rather than a lack of virulence. Evidence indicates that a graded reduction of toxin production occurred in *V. cholerae* in response to protection of water supplies, whereas elimination of toxin production occurred in *C. diphtheriae* in response to diphtheria vaccination (Ewald 2002).

When virulence molecules are private goods, similar evolutionary effects can occur. *Shigella* species, for example, have evolved toward benignity in association with water purification (Ewald 1994). When virulence compounds are not secreted, however, mild strains may be more difficult to maintain by frequency-dependent selection because options for exploiters of the virulence mechanism are more restricted for private goods than they are for shared secreted products. Evolutionary responses to interventions that target virulent variants may therefore be delayed because benign variants (i.e., the exploiters) are not already present at the time of the intervention. When mild variants are present, however, the evolutionary response may be even more rapid than with secreted goods: an immune response to a private good (e.g., a toxin that is physically attached to, rather than secreted from, the pathogen) may directly destroy the virulent pathogen rather than just impose a drain on the investor's fitness (e.g., by neutralizing a toxin).

Evolutionary Stability of Interventions

Medical activities can change the selective pressure acting on target pathogens. Antibiotic treatment, for example, can favor the evolution of antibiotic resistance, and vaccination can lead to the evolution of vaccine escape. The more extensive the activity, the greater the selection pressure for resistance or escape, and hence the greater the loss in the effectiveness of the activity (Figure 9.2). The history of antibiotic use is also the history of resistance to the antibiotics in use (Hede 2014). This linkage is a source of concern because the

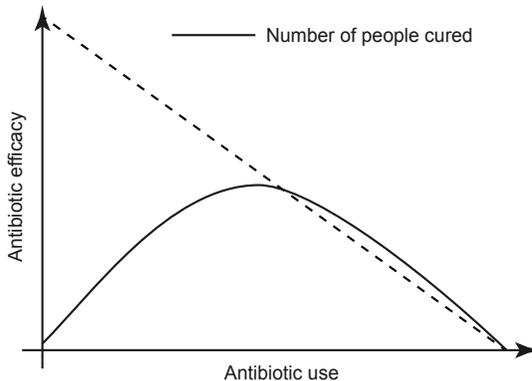


Figure 9.2 Expected relationships between antibiotic use, antibiotic efficacy, and cure rate. As antibiotic use increases, so does the selection for antibiotic resistance. Greater use of antibiotics is thus predicted to be associated with a rise in cure rates that peaks when the positive effect of antibiotic treatment on cure rate equals the negative effect of antibiotic resistance (dashed line). Thereafter higher rates of antibiotic use are associated with decreasing cure rates because of further increases in antibiotic resistance.

generation of new classes of antibiotics has declined as antibiotics have lost effectiveness (Figure 9.3).

The loss of efficacy for antibiotics and vaccines due to evolutionary responses of target pathogens highlights the need to assess whether there are intervention strategies that are more stable evolutionarily. If so, it would be important to specify whether the stability results from limited existing variation in the pathogen population or restrictions on any feasible variation that could arise through genetic changes (as mentioned above for virulence mechanisms that are private goods). New genetic changes hold potential for unforeseen mechanisms that counter an intervention.

Therapies against *Plasmodium falciparum*, the most severe agent of human malaria, provide an illustration. Resistance to antimalarials has increased over the past half century. In response, combinations of antimalarial drugs have been used (The malERA Consultative Group on Vector Control 2011). For this response to be effective, however, early detection is necessary. In countries where malaria is endemic, detection is conducted through a rapid diagnostic test that targets HRP2, aldolase, and LDH proteins of *P. falciparum*. However, recently a mutation on the HRP2 protein that makes the parasite undetectable via the rapid diagnostic test has appeared in Mali (Koita et al. 2012). This association suggests that selective pressures applied by antimalarial combinations could act on avoiding detection rather than selecting for resistance against antimalarials.

Changing the environment to favor benign strains (e.g., by blocking waterborne transmission) is one category of intervention that should stably control disease because it adjusts the action of natural selection to accord with public health interests. Use of vaccines that selectively target virulence-enhancing molecules is another intervention that should be relatively stable evolutionarily,

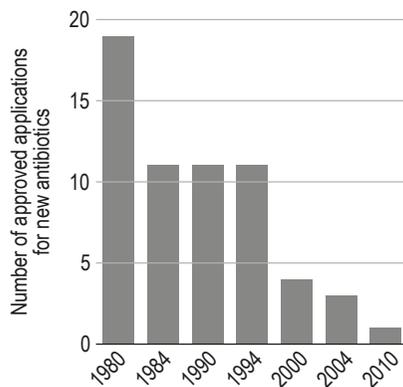


Figure 9.3 Since 1980, the number of drug applications for new antibiotics that have been approved by the U.S. Food and Drug Administration has declined dramatically (after Hede 2014).

because the vaccine introduces a selective pressure that favors mild strains. The target bacterium could evolve an entirely new virulence mechanism, but this evolutionary challenge may be greater than for antibiotic resistance because the resistance genes tend to be present in bacterial populations even before the first commercial use of antibiotics (Pollock 1967; Davies 1994; Courvalin 2010; D'Costa et al. 2011).

The targeting of secreted goods by control efforts may allow for control that is relatively stable evolutionarily, because a less vulnerable secreted good must be generated. During that time, however, intermediate forms of the good may impose a net fitness cost on the pathogen (see Brown, this volume). This hurdle may be responsible for the long-term control of the virulent *C. diphtheriae* by the diphtheria vaccine, which has been in use now for nearly a century.

The targeting of secreted goods may provide a basis for evolutionary stability of new categories of therapeutic interventions to control pathogens. Proteins secreted by pathogens to acquire nutrients, for example, may provide options for therapeutic control of infection. By rendering such molecules ineffective, a therapeutic intervention may compromise pathogens that produce this molecule, relative to those that do not (Brown et al. 2012; see also Brown, this volume). Like the virulence antigen strategy, this virulence interference strategy leaves more benign organisms in the wake of the intervention because the strategy forces the more virulent organisms to waste effort in an ineffective exploitation mechanism. Moreover, this strategy might force the target organism into an evolutionary trap because any variant that increased its investment in the mechanism, as a result of the enhanced need for the resource that the mechanism had previously provided, would be further compromised by this additional ineffective investment (Brown, this volume). Like the virulence antigen strategy, this virulence interference strategy should therefore be relatively stable evolutionarily.

Brown (this volume) supports this hypothesis with evidence from experiments on *Pseudomonas aeruginosa*, in which siderophore molecules that are released from the bacterium to scavenge iron from the environment are targeted by gallium salts. By binding to the siderophores, the gallium interferes with the bacterium's ability to gather iron from the local environment, thereby shifting the competitive balance in favor of less virulent variants that do not waste resources on siderophore production.

This intervention should be relatively stable evolutionarily because siderophores are partially public goods. Administration of gallium eliminates the ability of secretors and nonsecretors to gather iron, but places the siderophore secretors at a selective disadvantage relative to nonsecretors because the secretors incur the costs of siderophore production and secretion (Brown, this volume). Once secretors are eliminated from the population they could, in principle, be regenerated by mutation. In this case, the benefits of their siderophore production would be spread among a high proportion of nonproducers in the population as long as the bacteria are well mixed, and it would therefore

be difficult for the producers to increase in frequency in the population. If, however, the bacteria are patchily distributed so that siderophores return iron disproportionately to producers, the goods become less public (i.e., more excludable) and the possibility that the population could be reinvaded with siderophore producers would increase.

One concern with this strategy is that in the vastly larger populations of target organisms in nature, variants which encode a siderophore that binds more selectively to iron than to gallium would be present or could be generated by mutation. If so, the more virulent variants that produce these more selective siderophores would be favored by natural selection in response to gallium use. Increased virulence would then return. Similarly, alternative mechanisms of iron scavenging that were not vulnerable to the gallium treatment could be evolutionarily favored. Overall, as is the case with the virulence antigen strategy, the targeting of siderophores should prove to be more stable evolutionarily than attempts to control bacteria with antibiotics.

Social Context of Interventions

Antibiotic Resistance and Vaccine Escape

Underlying the problem of antimicrobial resistance are conflicts of interests among individuals involved in various aspects of antimicrobial use. Here, too, the components of the system can be cast in terms of goods, investors, and exploiters. Patients benefit from appropriately administered antibiotics, but the consequent evolution of antibiotic resistance poses a cost for patients as they may need antibiotics in the future—a special case of the “tragedy of the commons” (Hardin 1968; Baquero and Campos 2003). Such a conflict of interest creates divergence between goals of health care providers (who focus on preventing or ameliorating disease in patients) and policy makers (who develop guidelines to lessen the development of antibiotic resistance at the population level).

Appendix 9.1 illustrates the criteria used to analyze the degree of vaccine coverage needed to protect a population. The different interests of pharmaceutical companies, insurance companies, agriculture, and health care administrators add to the formidable challenge of developing guidelines and regulations for the appropriate use of antibiotics. One resolution is to create a zone of compromise between too little disease control and too much antimicrobial resistance (Figure 9.4). Such resolutions, however, open the door to influences associated with imbalances of power. In addition, strong incentives are lacking to motivate the pharmaceutical industry to develop new vaccines because of low profit margins: a vaccine is generally used only once by each consumer, and associated costs of development and liability can be high. One approach to this problem involves assessing the potential of target organisms for evolutionary reductions in vulnerability to the intervention and adjusting control

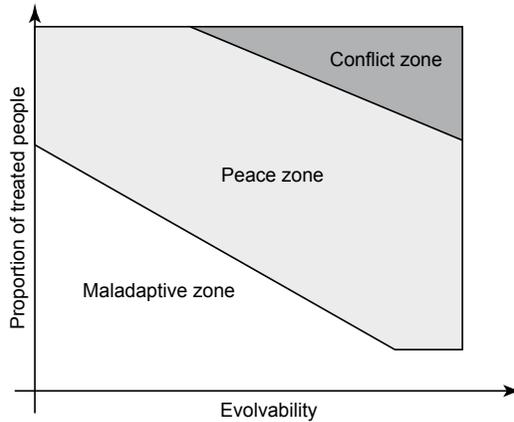


Figure 9.4 The impact of evolvability of antibiotic resistance and treatment consumption on potential conflict between health goals (i.e., reducing illness in a population) and economic goals (i.e., the profit generated from treatment). Three areas can be envisioned: In the *maladaptive zone*, neither goal is met because pathogen transmission does not decrease enough to protect the population and few treatments are sold. In the *peace zone*, both goals are met, at least partially, because pathogen transmission is significantly impacted and numerous treatments are sold. In the *conflict zone*, the goals deeply conflict, because selling more treatments can favor evolutionary changes that negate the value of the treatment.

measures accordingly (Figure 9.4). This would be associated with loss of control or, at best, a continual arms race for a substantial portion of human infectious diseases. Reducing the usage of antibiotics, for example, risks a lack of curative treatment.

These conflicts of interest can be analyzed by considering the problem in terms of goods, investors, and exploiters. Recipients of vaccines are generally considered to be investors in the “good” of vaccine efficacy because their usage generates herd immunity in the population, which in turn inhibits the future transmission of the target pathogen (see Appendix 9.1). Recipients of antibiotics are generally considered to be exploiters of the good of antibiotic therapy because antibiotic usage contributes to antibiotic resistance in the target population. The difference in characterization of the recipients of vaccines and antibiotics, however, results from the tendency for antibiotic resistance to evolve more readily than vaccine escape (i.e., an evolutionary change in target organisms so that they are less controlled by the vaccine).

When vaccine escape can evolve, the categorization of investors and exploiters becomes complicated because the vaccine users are contributing to vaccine escape. In this situation, their designation as investors or exploiters depends on whether the overall concern is generation of herd immunity or vaccine escape. With regard to vaccine escape, those who abstain from vaccination are the investors in the good of long-term vaccine efficacy, and those who become vaccinated are exploiters of this good.

Vaccine escape, however, can positively or negatively affect the overall health of the population depending on the virulence of the escape variants relative to the population of pathogens. When the virulence antigen strategy is used, vaccine recipients are investors regardless of whether one focuses on herd immunity or vaccine escape; vaccine recipients invest in the “good” of disease control generated by both vaccine-induced herd immunity and the shift to benign variants, which is generated by vaccine escape and provides additional acquired immunity for the population. In contrast, if the vaccines are developed from benign variants in the pathogen population or compounds that are more often present on benign variants, the vaccination may selectively suppress the benign variants, and the pathogen population as a whole is expected to escape to higher virulence. In this context, the vaccine recipients are exploiters of the “good” of long-term vaccine efficacy because they benefit from protection while enhancing the generation of damaging escape variants. If the vaccines do not differentially inhibit variants according to their virulence, the effects of the vaccine on the virulence of escape mutants are neutral according to these considerations. The vaccine users, however, are still fostering the spread of escape variants, and in that context are considered exploiters.

Some researchers have argued that the vaccine-induced herd immunity will favor more aggressive strains (Read and MacKinnon 2008). In a laboratory experiment, the use of a vaccine against Marek disease, which reduced mortality but did not block transmission, led to evolutionary increases in virulence (Read et al. 2015). These assessments did not evaluate whether the benign vaccine strains that were used in the vaccine disproportionately suppressed the mild variants in the pathogen population. Still, the hypothesis that incomplete vaccine-induced herd immunity can favor increased virulence needs to be considered as another possible influence of a long-term cost to the population of hosts arising from a short-term benefit to individuals (i.e., the tragedy of the commons applied to vaccination.) In this case, as in the case of vaccines that selectively inhibit benign strains, vaccine users would be investors in the good of herd-induced protection but exploiters in the sense that they are fostering the spread of more virulent escape mutants.

Similar complexities arise when the investor–exploiter concept is applied to antibiotic resistance. The general tendency is to consider antibiotic users as exploiters who contribute to antibiotic resistance. In this context, individuals who forgo use of an antibiotic can be considered investors in the “good” of antibiotic efficacy, because their abstinence from antibiotic treatment contributes to the usefulness of the antibiotic in the future by retarding the development of antibiotic resistance.

This portrayal emphasizes the problem of antibiotic resistance but oversimplifies the details of the investor–exploiter association. When no antibiotic resistance occurs in a pathogen population, antibiotic users are investors in the good of disease control, because the overall effect of antibiotic use is to reduce the prevalence of the infecting organisms, and thereby protect

treated individuals and those who would have been infected without treatment. Antibiotics will also tend to act most strongly against the more virulent variants in the pathogen population, because they are most likely to cause disease that is sufficiently severe to motivate infected individuals to obtain antibiotic treatment. When pathogens are susceptible, antibiotic treatment should favor evolutionary reductions in virulence (Ewald 1994). As antibiotic resistance is present, antibiotic users act less as investors and increasingly as exploiters because their suppressive effect on transmission and virulence decreases and their exacerbating effect on antibiotic resistance increases.

Profitability for Industry

Interference therapies, such as siderophore sequestration, would be economically favorable for research, development, and marketing because they would require repeated application. This very same aspect, however, is less attractive from the patient's point of view, because such therapies would be more costly and inconvenient than interventions that involve less persistent use. They would also likely require joint use with other therapies, further reducing their attractiveness for patients relative to therapies that involve just one drug.

In contrast, virulence antigen vaccines would need to be administered much less often, generally once or twice during a person's lifetime. This could reduce the economic incentive for research and development, but would make this intervention attractive to patients. Similarly, from the perspective of public health investments, virulence antigen vaccines promise a large health return on the investment in vaccine development and administration. The diphtheria vaccine, for instance, has been more successful in this regard than any other vaccine, with the exception of the one vaccine that globally eradicated its target pathogen: the smallpox vaccine.

Integrating Biological and Epidemiological Considerations into Economic Models

Whereas bioeconomic studies have focused on the economic objective of the agent (e.g., patients, pharmaceutical companies), purely epidemiological studies concentrate primarily on treatment protocols of anti-infective drug use and techniques. As a result, epidemiological studies may target the prevalence of infection and effectiveness of treatments at a future point of time (e.g., 12 months from now), whereas economic studies analyze the use of drugs by various economic agents (e.g., a patient, physician, hospital manager, or public health agent), or of society as a whole. Furthermore, economic studies determine the welfare that accrues to the agents or society. A further distinction resides in the fact that treatment protocols do not necessarily involve optimization of an agent's or society's objective, whereas economic models generally do.

Economic models assume that an economic objective is pursued by agent $i = \{1, 2, \dots\}$ or society $i = 0$ at time t in the context of infection prevalence, $I(t)$, and other epidemiological variables such as treatment effectiveness, $E(t)$. The state variables of the economic objective are $I(t)$ and $E(t)$ (for a discussion of the economic agents that can be involved, see Herrmann, this volume). Given the intertemporal aspects of disease communication and prevalence, the economic objective of an agent may cover a period of time; for instance, a monopolistic firm that sells a new antibiotic benefits from a patent with a limited time horizon. The agent is free to choose from a set of given treatment opportunities for the disease $f(t)$, which we denote the control variable. Notice that control and state variables, $f(t)$, $I(t)$, and $E(t)$ can be vectors, depending on the epidemiological context. For instance, $f(t)$ includes the different treatment techniques (antibiotic use, classical vaccination, virulence antigen vaccination) and $I(t)$ comprises all the infections that are analyzed. We assume that the evolution of infection and other epidemiological variables follow the law of motion:

$$\frac{dI(t)}{dt} = G[I(t), E(t), f(t)] \quad (9.1)$$

$$\frac{dE(t)}{dt} = H[I(t), E(t), f(t)], \quad (9.2)$$

where functions $G[I(t), E(t), f(t)]$ and $H[I(t), E(t), f(t)]$ are determined by the epidemiological context (e.g., see Bonhoeffer et al. 1997) as well as the initial conditions, $I(0) = I_0$ and $E(0) = E_0$. Clearly, the alternative treatment strategies and their degree of evolutionary stability discussed above would impact on the functional forms, $G[I(t), E(t), f(t)]$ and $H[I(t), E(t), f(t)]$.

We denote $W_i[I(t), E(t), f(t)]$ the instantaneous welfare at time t of economic agent i ($i > 0$). An example of this would be the instantaneous profit made by a generic pharmaceutical producer or the social welfare of the overall population (e.g., individuals and firms, $i = 0$).

The objective Γ_i of an economic agent, $i = \{1, 2, \dots\}$, or society, $i = 0$, allows us to control for the spread of a disease, $I(t)$, and its virulence (or bacterial resistance), $E(t)$, via treatment opportunities, $f(t)$, and takes the form:

$$\Gamma_i = \max \int_0^{T_i} e^{-r_i t} W_i[I(t), E(t), f(t)] dt, \quad (9.3)$$

subject to the laws of motion and initial conditions (I_0, E_0) specified above. Notice that $f(t)$, the control variable, should include all treatment opportunities that are available to the particular economic agent or society as a whole. The planning horizon, T_i , and discount rate, r_i , may depend on the economic agent. More myopic agents may use higher discount rates (thus valuing the future less) or shorter planning horizons.

In the objective above, we assume a deterministic context in which the evolution of epidemiological variables can be perfectly foreseen and all treatment opportunities are known. The model could also account for uncertainty related to model parameters (e.g., affecting the speed of the evolution of infection prevalence or treatment effectiveness).

Intergenerational Equity Issues Related to Discounting

The utilitarian objective of aggregating the instantaneous welfare of agent i or social welfare ($i = 0$) gives more weight to the near future and less weight to the long run. This is done through the discount factor e^{-rt} .

While such a time preference for the short run clearly characterizes the behavior of economic agents, it can be criticized from a social perspective ($i = 0$). Economists refer to such discounting as the dictatorship of the present (Chichilnisky 1996). In our context, it may allow for lower levels of infection prevalence and lead to higher levels of infection in the long run. This clearly raises an issue of *intergenerational equity*.

Discounting future welfare of agents, however, reflects the arbitrage that a dollar invested in health care today could have been better invested elsewhere in the economy (e.g., public education, public transport systems), to increase societal welfare. Furthermore, exponential discounting (as it is done in the utilitarian objective above) is time consistent; that is, the optimal policy, $[(I^*(t))]$, remains unchanged if the optimal state path, $[(I^*(t), (E^*(t))]$, is followed and the objective optimized again.

To address the problem of potential dictatorship of the present, a low (even zero) discount rate can be used from a social perspective. Weitzman (1998) proposes that the far future should be discounted at its lowest possible rate. It has also been suggested that discounting should depend on the state and control variables. Le Kama and Schubert (2007) propose endogenous discounting for intertemporal models that depend on the environmental quality. In particular, a lower environmental quality is associated with lower discount rates, thus giving more weight to the future while keeping the solution time consistent. In our context, the discount rate would be positively related to antibiotic treatment effectiveness, for instance, and could be easily integrated in the above analysis. However, it cannot be forced upon private economic agents.

Time Horizon May Depend on the Type of Infection Analyzed

From an economic perspective, the time horizon, T_i , depends on the economic agent that is analyzed. In the case of a firm selling a new anti-infective drug, the time horizon corresponds to the patent length. Here, the economic objective is to maximize intertemporal profits (i.e., the aggregated profits over the patent length) while the patent is pending. When T_i is finite, however, one should generally account for a bequest function, to capture the sum of profits

made after the patent has been suspended and generic firms have become competitors to the incumbent firm.

In some cases, a relevant time horizon is apparent from current knowledge about the problem for a health agency or pharmaceutical company. In the development of the influenza vaccine, for example, assessment of antigens is made annually and the vaccine is altered accordingly. Here the time horizon for the submodel would be one year to allow the investments to span the duration over which each vaccine is to be used, and the intertemporal objective Γ_i would comprise the sum of annual objectives.

New Alternative Treatments May Surface and Others May Become “Extinct”

The arrival of new anti-infective drugs is uncertain as is any research and development outcome. However, the money invested in research and development is dependent on the given epidemiological context. For instance, higher levels of antibiotic resistance may spur efforts made by private firms, but this may be insufficient, as the current antibiotic crisis demonstrates. More profitable opportunities may arise for the industry (e.g., the development of drugs for chronic diseases) or uncertainty in how a newly developed antibiotic might interact with other existing drugs on the market (e.g., common pools of antibiotic treatment effectiveness) may impede work.

The economic methodology can serve as a useful tool to inform public decision makers on the social value of managing existing drug therapies and developing new ones. This analysis can be carried out based on the existing market structure in the pharmaceutical industry. Comparing the outcome of this analysis with what would be socially optimal, it is possible to determine whether public subsidies would be needed to encourage the level of research and development at a high enough level, so as to resolve the anti-infective crisis.

Figure 9.5 illustrates a possible evolution of infection prevalence in relation to antibiotic treatment effectiveness, assuming a typical SIS disease transmission model, when two different objectives are followed. The x-axis measures the prevalence of infection, the y-axis the level of antibiotic effectiveness, and the z-axis the intertemporal welfare related to two bioeconomic objectives: Γ_0 and Γ_1 . Let trajectory (0) refer to evolution of infection and antibiotic effectiveness when society pursues the objective of using an existing antibiotic to minimize the social cost of infection, and trajectory (1) be associated with a monopolist selling the antibiotic. The vertical columns refer to the welfare that accrues to the potential consumers of the antibiotic (infected and uninfected individuals) and the producer or providers of the antibiotic (pharmaceutical company, hospital, physician).

In this representation, the prevalence of infection attains lower levels in the social optimum as compared with the trajectory implied by the monopolistic use of the antibiotic. This occurs in typical disease transmission models when

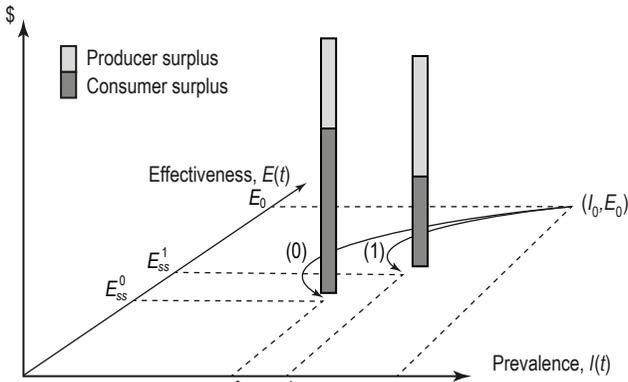


Figure 9.5 Trajectories of infection prevalence and antibiotic effectiveness, leading from initial state (I_0, E_0) toward steady states (I_{ss}^k, E_{ss}^k) , with $k = 0, 1$. Aggregated payoffs for consumers and producers are also shown. Trajectory (0) shows the socially optimal evolution ($k = 0$); (1) shows the evolution under monopoly (private optimum, $k = 1$). Note: Trajectories (0) and (1) shown here in state space (I, E) are characterized by an undershooting pattern, which allows infection levels to fall temporarily below their long run steady-state levels. This typically occurs in SIS models, where infections may evolve nonmonotonically, while effectiveness may decrease monotonically (for more details, see Wilen and Msangi 2003; Herrmann and Gaudet 2009).

more antibiotics are used initially in the social optimum. As a consequence, the level of antibiotic effectiveness can also be lower in the short and long term, as compared with the monopoly regime. This can be socially desirable if the social cost of infection sufficiently outweighs the social value of antibiotic effectiveness. The vertical columns show how intertemporal welfare is divided among the population (infected and uninfected “consumers”) and the producer (the monopolist). The sum of the producer and consumer surplus is necessarily higher in the social optimum as compared with the monopoly outcome. Notice, however, that the producer surplus is higher, while the consumer surplus is lower in the monopoly outcome as compared with the social optimum.

Such an analysis may appear simplified as it relies on deterministic disease models (Herrmann and Gaudet 2009; Herrmann 2010). However, it does allow us to determine the long-run evolution of variables of interest (e.g., infection prevalence and antibiotic effectiveness), as different economic objectives are followed. When applied to a newly developed drug, it provides information on the potential market size for a drug (infection prevalence) and the quality of a drug (antibiotic effectiveness) that will result when a private economic agent, such as the monopolist selling the drug, maximizes intertemporal, aggregated profits. Thus, this analysis delivers information about the potential profitability of a newly developed drug for a private firm. The private return (or profit) expected from investing in research and development will generally be lower than the social return (social welfare), which points to the potential need to provide incentives to spur the innovation of new drugs.

When the analysis is applied to an existing drug, it can show the critical level at which antibiotic effectiveness is reached, making this drug extinct and necessitating the development of a new drug. Again, the question arises whether the expected private return is sufficient to incentivize the private firm to invest in further research and development. Our analysis here shows that the incentives to develop a new drug cannot be disentangled from its profitability, and hence its awaited market size (infection prevalence) and evolution of quality (effectiveness) of the drug. Public intervention is not only needed to encourage research and development, but also at the level of using the drug once it has been developed.

Integration of Levels

One of the advantages of the sort of model described above is that it can incorporate the spectrum of interactions at play in a complex system, such as human health care, while being flexible with respect to changing conditions, including those attributable to evolution. As discussed, investor–exploiter interactions occur at various levels (Figure 9.6; see also Herrmann, this volume): the outcome of interactions at one level can influence the outcome at others.

In the case of diphtheria, the within-host growth advantage of toxigenic bacteria (toxin investors) over nontoxigenic bacteria (toxin exploiters) favors a high frequency of toxin investors in unvaccinated populations of humans. Coughing can transmit both strains to new hosts, where a new round of growth perpetuates the dominance of toxin investor. The epidemiological record indicates that this perpetuation is stable so long as vaccines are not introduced. In vaccine recipients (i.e., human vaccine investors), however, toxin investors are selectively disadvantaged because they waste resources on the production of ineffective toxins. This leads to eventual stable dominance by benign exploiter strains, which generate additional immunity to all strains because all strains have essentially the same antigenic composition, after toxin-associated

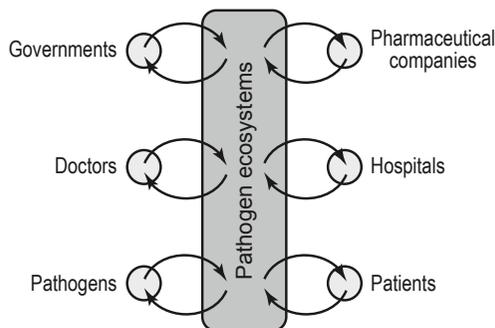


Figure 9.6 Pathogen-mediated social dilemmas are coupled by pathogen ecosystem dynamics (prevalence, resistance, and virulence), wherein agents interact with each other.

antigens are taken into account. In a vaccinated population, the dominance of toxin exploiters is virtually complete, leading to the virtual elimination of diphtheria, even though *C. diphtheriae* are still widely distributed (Ewald 2002). This elimination of symptomatic infection virtually eliminates exposure of the bacteria to antibiotics because asymptomatic individuals do not seek antibiotic treatment. The use of this vaccine, therefore, virtually eliminates the presence of humans who are antibiotic exploiters (because antibiotic usage is extremely low and hence antibiotic resistance is not a pressing problem). The vaccine causes humans to be antibiotic investors in the sense of investing in lower virulence, because antibiotics will tend to suppress the most virulent strains. This outcome occurs because the infrequent use of antibiotics should be associated with antibiotic sensitivity, and antibiotics need only be used for rare infections that are symptomatic due to a high infecting dose or a novel virulence mechanism. Thus, the virulence antigen strategy converts vaccine users into investors in herd immunity and lower virulence and antibiotic users into investors in lower virulence, and eliminates the exploiter role for antibiotic users. The virulence antigen strategy resolves the tragedy of the commons in both vaccination and antibiotic use. The diphtheria vaccination program demonstrates this resolution by generating not only extraordinary success at controlling diphtheria but an association with a general paucity of antibiotic resistance among *C. diphtheriae* strains (von Hunolstein et al. 2002).

If an economic model analyzing social optima places a priority on health promotion, the model should identify this outcome as optimal because it eliminates diphtheria, even if it results in low profits for the manufacturers of antibiotics and only moderate profits for the vaccine manufacturer and health care workers. The extraordinary success of diphtheria vaccination can thus be attributed to an intervention that disfavors bacterial investors of toxin production and favors the human vaccine investors (i.e., those who agree to be vaccinated).

Although this assessment accounts for three different investor–exploiter pairings, other pairings are also present. Table 9.1 provides a listing of some of these investor–exploiter pairings, often present simultaneously in health settings, that are associated with human infectious diseases. Here, we have investigated only a few of the issues raised by considering these pairings. Incorporating these differences of interest into health decisions remains a major challenge for future efforts to control the damage caused by infectious diseases.

Conclusion

Human infectious disease involves many interacting players that can be cast in the context of investor–exploiter dichotomies, and there is a tendency for goods to be shared and consumed among all players. The interests of players may often conflict and change during epidemiological and evolutionary

Table 9.1 Some investor–exploiter pairings that are often present simultaneously in health settings.

Players	Goods	Investor	Exploiter	Goal of Investors
Pathogens	Extracellular molecules, virulence factors	Pathogens that produce the molecules	Nonproducers that benefit from the molecules	Reproduction, survival, transmission
Patients	Herd immunity Antibiotic effectiveness	Vaccine recipients Patients who refuse antibiotics	People who refuse vaccines Patients who take antibiotics	Patient health, survival
Animal husbandry	Herd immunity Antibiotic effectiveness	Vaccine users People who restrict antibiotic use	Nonusers of vaccines People who administer antibiotics to animals	Disease control and agricultural productivity
Pharma firms	Antimicrobial sensitivity	Developers of antibiotics	Imitators	Maximize profit over finite planning horizons
Hospitals	Reduction of nosocomial infections	Enactors of sanitation	Contributors to lax sanitation	Reduce infections and associated costs
Insurance companies	Client policies	Promoters of vaccination	People who refuse vaccination	Maximize profit
Populations, countries	Public health			

timescales. Investor pathogens may secrete compounds that enhance their acquisition of benefits by themselves as well as by exploiter pathogens. Targeting these compounds may yield vaccines or treatments resistant to evolutionary responses that negate their effects (e.g., vaccine escape and antimicrobial resistance). Vaccine recipients are investors in herd immunity, which provides protective benefits. When herd immunity is very high, the negative effects of vaccines may outweigh the beneficial effects to the individuals: those who do not accept vaccines are exploiters of the herd immunity who contribute to the possible reemergence of the target pathogen. Recipients of antibiotics exploit the therapeutic benefits of antibiotics while contributing to antibiotic resistance in the general population. When resistance genes are not present, however, the users of antibiotics are investors in the control of the pathogen in the population. Consideration of these roles can be critical, for example, in hospital environments, where control of infection with antibiotics can protect the patient population but also contribute to the emergence of antibiotic resistance. In addition to these considerations at the level of microbes and public health are economic incentives of physicians, hospitals, and pharmaceutical companies. Each has its own priorities for investment and exploitation, which may differentially influence health-care activities. These interactions need to be incorporated into economic models that recommend multifaceted investments in health care.

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Appendix 9.1: Public Health Considerations for Vaccine Usage

For infectious diseases with permanent immunity, such as measles, the critical proportion of a population that needs to be vaccinated to eliminate disease can be calculated based on the basic reproductive ratio, R_0 , which is quantified as follows:

$$R_0 = \frac{\beta N}{\sigma + \mu}, \quad (9.4)$$

where N is the number of individuals (assumed here to be entirely susceptible or are infected), β is the transmission rate of the pathogen, σ is its recovery rate, and μ is the host life span. This number represents the number of secondary infections caused by one infectious individual within a host population entirely susceptible during the individual's infectious period. A common goal of any public health strategy is to decrease R_0 below 1, in order to drive the pathogen to extinction.

Vaccination strategies rely on a decrease of the number of susceptible individuals (represented here by N). $R_0 < 1$ if $p < 1/R_0$, where p is the proportion of susceptible individuals. Therefore, the minimal proportion of population to vaccinate for expecting eradication is:

$$P_c = 1 - \frac{1}{R_0}. \quad (9.5)$$

For instance, measles has an estimated R_0 of 17, which means that $1 - 1/17$, or $\sim 94\%$, of the population need to be vaccinated to create a herd immunity that prevents infectious invasion. Because transmission is dampened as the proportion of susceptible individuals declines, this threshold of vaccination should be sufficient to eliminate the pathogen. This threshold does not account for population heterogeneity or pathogen evolution, and thus must be considered carefully with regard to the relevance of these factors in the targeted pathogen.

Vaccine uptake and pathogen transmission could be strongly linked in a dynamic manner. Indeed, when a sufficient number of people are vaccinated, and effects of herd immunity are prevalent, the perception of the risk of getting vaccinated may become greater than the perceived risk of getting the infection. Such a decrease in the perceived risk of infection can have a dramatic impact on vaccine uptake if individuals act solely out of self-interest.

This dilemma, known as the “vaccination game,” has been well studied: epidemiological dynamics is coupled with a theoretical game approach that considers individuals getting vaccinated according to their self-interest (Bauch and Earn 2004). By considering a simple situation where everybody has the same information, it has been demonstrated that increases in perceived risk of vaccination yield a larger decrease of vaccine uptake for the pathogen with high transmission profile (i.e., large R_0), which is difficult to restore after the end of a vaccine scare. Moreover, this theoretical approach shows that for any non-null perceived risk of vaccination, the expected vaccine uptake is always less than the eradication threshold. Although these results must be nuanced according to the strong assumptions of this framework (especially the homogeneous spread of the information), they nevertheless highlight the importance of considering the feedback between epidemiological dynamics and individual decisions based on self-interest.