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Julien Flaig

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A simulation based approach to individual vaccination behavior.

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A simulation based approach to individual vaccination behavior

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Résumé

Cette thèse porte sur la modélisation des comportements individuels de vaccination. Lorsque la vaccination est libre, c'est-à-dire recommandée à divers degrés mais non obligatoire, les individus peuvent décider ou non de se vacciner, et ces décisions influencent la propagation de la maladie. Nous proposons une approche de modélisation flexible qui permet de prendre en compte ces décisions individuelles dans les modèles de simulation épidémiologiques. Ces modèles sont utilisés par les décideurs publics et privés, et nos travaux visent d'abord l'utilité pratique.

Nous reprenons l'exemple de la rougeole tout au long de la thèse. La rougeole est le type même de maladie dont la propagation dépend essentiellement des comportements individuels. Il s'agit d'une maladie infectieuse extrêmement contagieuse et dont les complications peuvent être grave. Elle peut être facilement évitée grâce à un vaccin efficace et largement accessible dans les pays développés. Pourtant, elle continue de circuler parce qu'une partie de la population refuse la vaccination. En effet, sa forte contagiosité nécessite que 90% à 95% d'une population soit immunisée pour empêcher sa propagation. On parle alors d'immunité grégaire. Si les taux de vaccination sont relativement élevés dans les pays développés, ils ne permettent d'atteindre uniformément ces niveaux d'immunisation, et des épidémies de rougeole continuent de se déclarer sporadiquement.

Dans cette thèse, nous considérons un aspect bien particulier de la décision de se vacciner ou non: les comportements stratégiques et d'anticipation. Il peut sembler étrange *a priori* d'aborder ainsi les comportements de vaccination sous l'angle de la rationalité. En plus d'aller à l'encontre de faits bien établis par la recherche médicale, refuser de se vacciner peut empêcher l'ensemble de la population d'atteindre l'immunité grégaire. Or l'immunité grégaire protège, en enrayant la propagation de la maladie, les individus qui n'ont pas accès à la vaccination, soit parce qu'ils sont trop jeunes, soit parce qu'elle leur est contre-indiquée pour raisons de santé. Le refus de se vacciner a tout d'un comportement à la fois néfaste et irrationnel.

Toutefois l'attitude vis-à-vis de la vaccination ne se résume pas à son acceptation ou à son refus inconditionnels. Certains, par exemple, plutôt que la refuser, retardent la vaccination. D'autres la refusent en accusant l'administration de plusieurs vaccins en une seule injection d'avoir des effets secondaires. D'autres enfin ne se font pas vacciner pour des raisons politiques ou religieuses.

De plus, les études empiriques semblent indiquer que même des individus que l'on quali-

fierait aisément d'anti-vaccins peuvent modifier leur comportement en fonction des coûts et bénéfices respectifs de la vaccination et de la non vaccination. Remarquons enfin que la vaccination a un coût, y compris pour les individus qui n'ont pas une attitude particulièrement négative à son encontre. Sans même parler de coûts monétaires, le simple fait de prendre rendez-vous chez le médecin représente un coût. L'étude de la décision de vaccination comme évaluation rationnelle de coûts et de bénéfices paraît donc pertinente. Cette approche reste d'ailleurs flexible, en laissant par exemple la possibilité de faire varier le coût de vaccination d'un individu à l'autre.

Quant à l'étude des comportements stratégiques, elle se justifie de deux façons. En premier lieu, sur le plan théorique, la décision de vaccination est, par définition, très proche d'une interaction stratégique. C'est-à-dire que les gains d'un individu dépendent non seulement de sa propre décision, mais aussi de celles de tous les autres. Si l'ensemble d'une population est vaccinée et s'il est raisonnable de penser qu'elle le sera à l'avenir, il est optimal pour un nouvel arrivant de ne pas se vacciner. Il profitera ainsi de l'immunité des autres individus sans payer son coût de vaccination. Si au contraire personne n'est vacciné, il devient optimal de se vacciner, pour peu que le coût d'être malade soit suffisamment élevé comparativement au coût de se faire vacciner. Si, de plus, chaque individu décide en anticipant les décisions des autres, on est face à une véritable interaction stratégique.

En second lieu, sur le plan pratique, modéliser les décisions de vaccination en épidémiologie implique nécessairement de modéliser des interactions stratégiques, ne serait-ce qu'implicitement sous forme d'une boîte noire. Admettons par exemple qu'on veuille modéliser la décision de vaccination comme une fonction *ad hoc* de la prévalence. Comme la vaccination protège un individu dans le temps, cette fonction inclut inévitablement l'anticipation par les individus de la prévalence future. Or la prévalence dépend des décisions individuelles, donc notre fonction *ad hoc* représente en fait un comportement stratégique. Modéliser les comportements stratégiques explicitement, c'est-à-dire en tant que tels, permet d'éviter de recourir à des boîtes noires de ce type qui sont souvent peu convaincantes, voire présentent des contradictions internes.

Les premiers modèles de comportement de vaccination ont été proposés par des économistes. En effet, l'immunité grégaire, et plus généralement la diminution du risque d'infection lorsque la proportion de personnes vaccinées augmente dans une population, est une externalité de la vaccination. En première approximation, les individus se vaccinent pour se protéger eux-mêmes, mais cette décision a des conséquences pour l'ensemble de la population non vaccinée. Comme cette externalité est un bien public (il n'est pas possible d'empêcher un individu non vacciné d'en bénéficier), un résultat classique de la théorie économique prédit qu'elle sera produite par les individus à un niveau inférieur à ce qui serait optimal en tenant compte de la somme des bénéfices individuels. Ceci semble se vérifier empiriquement dans la mesure où l'immunité grégaire peine souvent à être atteinte dans les pays développés.

Ces premiers modèles économiques ne se concentraient pas spécifiquement sur les comportements stratégiques. Bien que compatibles avec de tels comportements, ces modèles étaient simplifiés de sorte que l'anticipation par un individu des comportements de tous les

autres soit reléguée au second plan. Ces simplifications avaient pour objectif d'obtenir des résultats analytiques à une époque, les années 1980 et 1990, où les ressources de calcul étaient limitées. Au-delà des restrictions sur la prise en compte des comportements stratégiques, le principal désavantage de ces méthodes est qu'elles n'autorisaient pas une modélisation d'aspects pertinents tels que la guérison, la naissance d'individus susceptibles, ou encore la perte d'immunité vaccinale. Les études qui entreprenaient de les modéliser devaient se cantonner à l'analyse d'états stationnaires.

Les interactions stratégiques dans la décision de vaccination ont été formalisées en théorie de jeux au début des années 2000. Les premiers modèles de "jeux de vaccination" étaient également très simplifiés sur le plan épidémiologique. Ils ont continué à se développer depuis, mais toujours, jusqu'à récemment, avec d'importantes simplifications épidémiologiques ou en se restreignant à des modèles statiques ou à l'étude d'états stationnaires. Nos travaux contribuent à cette littérature en permettant de modéliser les décisions de vaccination de façon dynamique sous des hypothèses épidémiologiques pertinentes, sinon réalistes.

Ce type de modèles présente un intérêt particulier pour plusieurs acteurs du système de santé : compagnies d'assurance, industrie pharmaceutique ou autorités de santé. Les modèles de théorie des jeux ne sont pas mobilisés par ces derniers pour l'évaluation économique des politiques de santé. Une contribution de cette thèse est de montrer (i) que les comportements individuels endogènes (qui ne sont pas posés directement comme hypothèse par le modélisateur) ne peuvent *a priori* pas être négligés dans certains modèles épidémiologiques, (ii) que les modèles de théorie des jeux sont compatibles avec les approches plus traditionnelles utilisées en économie de la santé, et enfin (iii) de proposer une méthode de modélisation qui limite les hypothèses simplificatrices de façon à être utilisable en pratique.

Lorsqu'il s'agit d'évaluer, par exemple, une politique de vaccination, les acteurs du système de santé procèdent habituellement de la façon suivante. Le coût d'un cas de la maladie est d'abord évalué. Ce coût peut être individuel ou social, monétaire ou exprimé en termes d'utilité ; cela dépendra de l'acteur à l'origine de l'étude. On compte ensuite le nombre de cas que l'on espère éviter grâce à la politique en question. Le bénéfice total de la politique est le nombre de cas évités multiplié par le coût d'un cas individuel. Ce bénéfice total est finalement comparé au coût de la politique.

Le premier problème posé par ce type d'approche est qu'il s'agit d'un raisonnement à l'état stationnaire, un choix discutable dans l'étude des maladies infectieuses. Il est vrai que les coûts et bénéfices peuvent tenir compte, par exemple, de futures complications. Cependant, comme les valeurs de ces coûts et bénéfices futurs sont actualisées, le caractère dynamique du modèle n'est que superficiel. D'autre part, ces études économiques ne peuvent pas tenir compte des comportements stratégiques et d'anticipation des individus. En d'autres termes, les individus dans ces modèles répondent éventuellement aux incitations mises en place par la politique (de façon exogène au modèle). En revanche, ils ne répondent pas de façon endogène aux effets même de la politique, ainsi qu'aux réponses des autres individus. Le Chapitre 2 de cette thèse est consacré à un exemple montrant que les comportements individuels face à une politique de santé publique peuvent donner lieu à des effets non négligeables.

Avant de développer ces applications pratiques, notre premier travail a été de présenter notre approche de modélisation et d'en illustrer la flexibilité. Cette thèse se compose de trois chapitres écrits comme des articles indépendants. Le premier chapitre est consacré à la présentation du modèle, le second à une application en santé publique, et le troisième à une discussion plus théorique du comportement de vaccination.

Dans le Chapitre 1, nous étudions la décision de vaccination face à une maladie inspirée de la rougeole. Les individus basent leurs décisions sur leur anticipation de la prévalence future de la maladie, c'est-à-dire qu'ils anticipent les décisions des autres individus. Cependant, leurs décisions influencent la propagation future de la maladie. La contagion peut donc être modélisée par un système d'équations différentielles couplées. Les unes représentent la propagation de la maladie et vont "en avant" dans le temps : la prévalence future dépend de la prévalence passée. Les autres représentent la prise de décision et vont "en arrière" dans le temps : les décisions présentes dépendent de l'anticipation du futur. Nous montrons comment poser et résoudre ce problème comme une recherche de point fixe. Nous obtenons des résultats pour un modèle avec taux de mort et de naissance, et perte d'immunité vaccinale. Nos résultats sur longue période de temps mettent en évidence des pics épidémiques récurrents. À titre de comparaison, nous produisons également des résultats pour des individus ayant un comportement adaptatif. Un comportement adaptatif consiste à baser sa décision sur la prévalence actuelle sans anticiper son évolution. Enfin, nous proposons une extension du modèle avec deux populations ayant des coûts de vaccination différents.

Le double objectif du Chapitre 2 est (i) de montrer que la boucle entre prévalence et comportements individuels étudiée dans le Chapitre 1 ne peut pas être négligée *a priori* dans les évaluations de politiques de santé publique, et (ii) de présenter un outil pour les inclure dans ces évaluations. Nous développons l'exemple de la vaccination obligatoire contre la rougeole. Notre modèle épidémiologique est le modèle SIR habituellement utilisé pour représenter la rougeole. Avant l'entrée en vigueur de la vaccination obligatoire, les parents décident librement et de façon altruiste s'ils veulent ou non vacciner leur enfant. Nous modélisons des parents anti-vaccins, et d'autres ayant une attitude plus positive vis-à-vis de la vaccination. Nos résultats suggèrent que l'anticipation de la vaccination obligatoire peut conduire à une augmentation transitoire de la prévalence avant l'éradication à long terme de la maladie. Ceci conduirait à d'importants transferts d'utilité entre générations. Ironiquement, dans notre scénario, des anti-vaccins sont parmi ceux qui bénéficient le plus de la vaccination obligatoire.

Le Chapitre 3 est plus spéculatif. Nous partons du constat que la comparaison des coûts de vaccination avec le risque d'être infecté par la rougeole peine à expliquer la couverture vaccinale relativement élevée (bien que souvent insuffisante) dans les pays développés. Nous discutons l'hypothèse selon laquelle la vaccination est un comportement coopératif. Dans ce scénario, une partie des individus forme une coalition dont les membres s'accordent pour se vacciner et punir ceux d'entre-eux qui ne se vaccineraient pas. Nous mettons en œuvre des concepts d'équilibre et de punition habituellement utilisés en théorie des jeux répétés en donnant des arguments pour leur utilisation dans le contexte de la vaccination. Nous

considérons deux types de punition contre les membres de la coalition qui manqueraient à leur engagement de se vacciner. La première consiste pour les membres de la coalition à suivre leur intérêt individuel. La seconde consiste pour eux à ne plus se vacciner. Nos résultats indiquent que la menace d'une punition peut expliquer la vaccination lorsqu'elle serait normalement sous-optimale.

Si ces travaux s'adressent en premier lieu aux acteurs du système de santé, ils ne manqueront pas d'intéresser d'autres communautés. Les théoriciens des jeux y trouveront une méthode de résolution des jeux de vaccination dynamiques, et les épidémiologistes une illustration de l'influence des comportements individuels sur la propagation des maladies.

Pour finir, soulignons quelques limites de nos travaux ainsi que des pistes de recherche. Tout d'abord, il convient de rappeler que tous nos résultats sont issus de simulations. Ils ne prétendent en aucun cas se substituer à des observations empiriques, qui pourront faire l'objet de futures. Bien entendu, les discussions habituelles sur le bien-fondé de l'hypothèse de rationalité des individus s'appliquent. Il en va de même pour les concepts de solution retenus pour les jeux de vaccination.

Ensuite, l'analyse mathématique est ici réduite au strict minimum. Nous n'avons pas développé certaines démonstrations qu'il pourrait être pertinent de considérer à l'avenir.

Enfin, la flexibilité de notre approche ne doit pas faire oublier que celle-ci n'a de pertinence que pour modéliser les comportements à la fois stratégiques et d'anticipation. Si son usage ne se restreint pas à l'étude des comportements de vaccination, il devra être justifié dans chaque cas.

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Introduction

Few experiences of social life are so frustrating as to be at the mercy of others' irrational or outright wicked behaviors. It takes failed attempts to thwart unwanted behaviors – through calls for reason, gentle persuasion, or by force – to come to the humbling realization that they may not be as gratuitous as first thought. And that individuals may not give up their self-interest so easily.

Measles vaccination refusal provides a vivid example. Measles is the typical example of a disease that could easily be avoided through vaccination but is still able to circulate because part of the population refuses vaccination. Here, individuals do not have to suffer from the behavior of, say, a distant polluter they might well never encounter. Rather, they may have to suffer from the refusal of vaccination by people in their closer circles: family, colleagues, neighbors, or the parents of their child's school friends. It goes without saying that under such circumstances, in addition to being a serious public health issue, vaccination refusal has given rise to fierce debates.

The consequences of vaccination refusal have motivated researchers to develop models of vaccination decision-making. This thesis builds upon this literature and aims at developing tools that are useful to the decision maker. We concentrate our efforts on a very specific aspect of vaccination decision-making: strategic behavior. Individuals engaging in strategic behavior base their decision not only on their own preference for vaccinating or not vaccinating, but also on what they expect others to do. As irrational as vaccination refusal may seem, strategic behavior is a relevant and now standard way to account for vaccination decisions – including refusal. This certainly calls for further explanations.

0.1 Why model strategic behavior in Measles vaccination?

Of all the Measles outbreaks in the past few years, the 2014–2015 Disneyland (California) epidemic certainly received the most extensive media coverage (Halsey and Salmon, 2015; Clemmons et al., 2015). The individuals who got infected at the amusement park or during the subsequent outbreak fall into three categories. A fraction of them had received the vaccine but their immune system had not responded to it, leaving them unimmunized. Others were children too young to get vaccinated or who could not get vaccinated for medical reasons. Finally, some were unimmunized because their parents had refused to vaccinate them.

This outbreak resulted in 147 cases in seven states in the U.S., Mexico, and Canada

(CDC, 2015). Compare this figure to the 667 cases reported in 2014 and the 188 cases reported in 2015 in the U.S. The Disneyland outbreak drew heated debate over vaccination refusal. Measles indeed, while an infectious disease with potentially serious complications, is at the same time entirely preventable. It could even be eradicated through vaccination (Moss, 2017).

An efficient vaccine has been available since the 1960s, and in most developed countries, it started to be included in vaccination schedules during the 1980s. The vaccine against Measles is often combined with vaccines against Mumps and Rubella (MMR vaccine).[1] Nowadays, the MMR vaccine is usually delivered with two shots. The second shot is not a booster dose. The immune system may not respond to the vaccine and 7% of the children who receive one dose remain unimmunized. The second dose raises vaccine efficacy from 93% to 97%. The MMR vaccine generally comes at a low cost and with little supply constraints, at least in developed countries. Of course, vaccine accessibility varies from one country to another. In France, the state covers vaccination costs. In the United States, most health plans cover Measles vaccination as a preventive service, and the government's Vaccines for Children Program offers vaccination at no cost for children who do not have a health insurance. Also in the United States, the cost of vaccines and low reimbursements put the provision of the most expensive vaccines under strain in some practices (Glazner et al., 2009; Rosenthal, 2014). The MMR vaccine, however, remains an average priced vaccine with a private sector cost per dose of about $70 reported by manufacturers in the U.S. (CDC, 2018).

Overall, it is fair to assume that the MMR vaccine, in addition to being efficient, is widely accessible in developed countries. But there is more. Vaccination against an infectious disease is not only about individual immunization. It is also about preventing virus circulation in the whole population. An infectious disease can spread because a single infectious individual may contaminate several susceptible individuals, which can result in a snowball effect. As more individuals get immunized, susceptible individuals are less likely to encounter infectious individuals and get infected. A population where the proportion of immunized individuals is so high as to stop disease transmission is said to have reached *herd immunity*. Reaching herd immunity is the objective of many public health policies because it protects individuals who cannot vaccinate for medical reasons, and those whose immune system did not respond to the vaccine.

Measles is highly contagious. Its basic reproduction number is often estimated between 12 and 18.[2] This means that a single infectious individual would infect on average 12 to 18 individuals in an entirely susceptible population. More specifically, virtually all susceptible individuals in the environment of an infectious individual get infected. The practical consequence of this is that a high vaccination coverage is necessary to reach herd immunity. The target coverage is often set to 90% or 95%, but some authors have argued that policies should aim at a 100% coverage (Salathé, 2015).

So vaccination seems to bring far-reaching benefits for a limited cost. Many authors have

[1] It may also be combined with the vaccine against Varicella (MMRV vaccine). As of 2018, the MMRV vaccine is not included in routine vaccination schedules in France.

[2] Locally, this figure can vary widely. See Guerra et al. (2017).

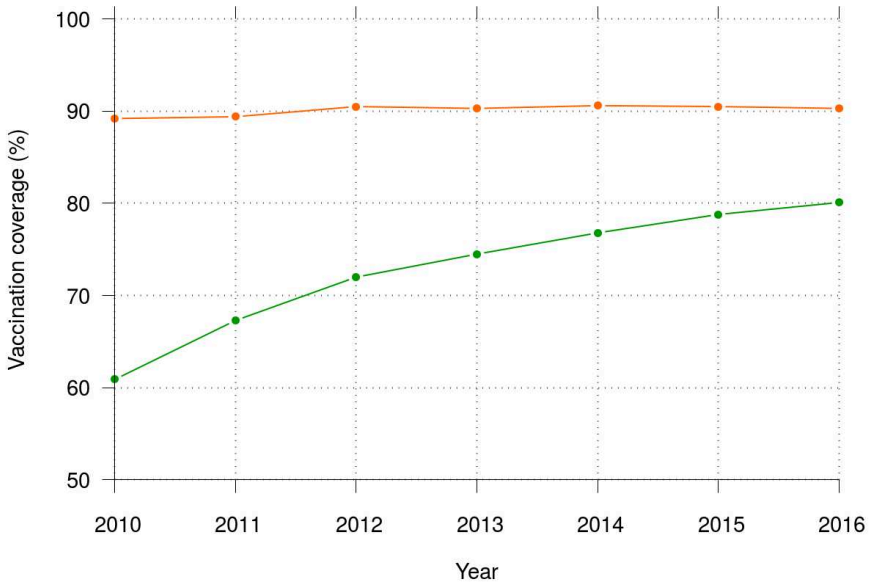

Figure 1: MMR vaccination coverage among 24 month old children in France, 2010–2016. *Orange:* one dose. *Green:* two doses. (Source: Santé publique France (2018a).)

shown the benefits of controlling or eradicating Measles, and that Measles vaccination is cost-efficient (Bester, 2016). Yet in developed countries, a portion of the population still refuses vaccination. In fact, while Measles vaccination is strongly recommended by health authorities, it is offered on a voluntary basis in many countries. In the United States, vaccination requirements are established by state legislation. Measles vaccination is mandatory for school entry in all 50 states but parents can receive medical, religious, or philosophical exemptions. In France, Measles vaccination is mandatory for all children born after January 1st 2018 but there are no sanctions against parents who fail to vaccinate their children.

Vaccination coverage targets regularly fail to be met. For illustration, we show the vaccination coverage among 24 months old children in France between 2010 and 2016 in Figure 1. Since the first dose is scheduled when children are 12 month old and the second when they are 16 to 18 month old, Figure 1 gives an indication of what were parents' vaccination decisions. Similar vaccination coverages are observed in the U.S. (Hill et al., 2017) and in other developed countries (World Health Organization, 2017).

In many developed countries, immunization levels are high enough for Measles to be considered non endemic. However immunization levels are often too low to provide herd immunity. In other words, Measles does not circulate in these countries without external input, but sporadic and local outbreaks occur whenever the virus is brought from endemic regions of the world by an unvaccinated individual. This is how the Disneyland outbreak started in 2014. Since then, many epidemics following the same pattern occurred in other developed countries. We could mention the 2017 outbreak in Italy (Giuffrida, 2015), or the late 2017–early 2018 outbreak in southwestern France which lead to the death of an unvaccinated woman (Aït El Belghiti et al., 2018). Figure 2 shows the number of Measles

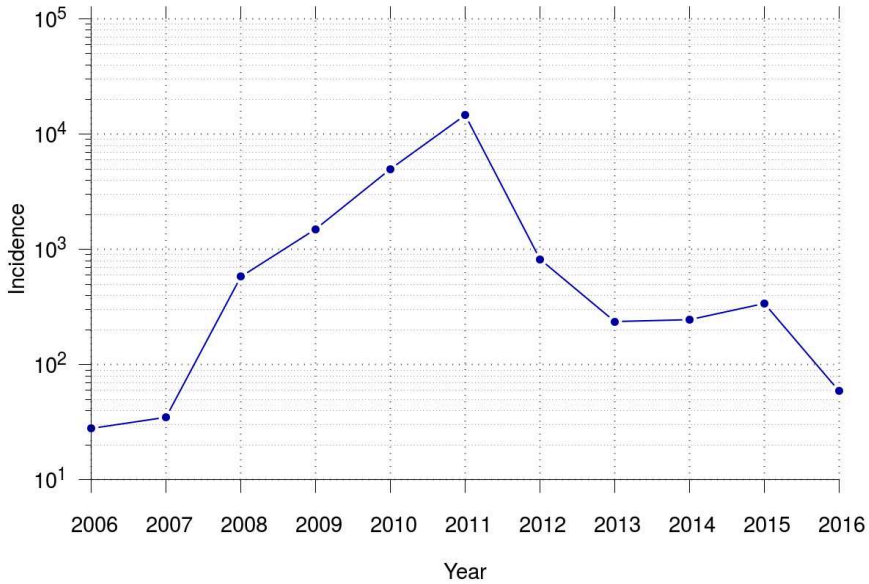

Figure 2: Measles cases reported by doctors in France, 2006–2016. (Source: Santé publique France (2018b).)

cases reported in France from 2006 and 2016. These figures are likely to be underestimates but still provide orders of magnitude. The 2008–2011 outbreak was explained by low toddler vaccination and insufficient catch-up in other cohort in previous years (Antona et al., 2013).

The serious consequences of insufficient vaccination drew attention on the so-called anti-vaccination movement. Anti-vaccination has existed ever since vaccination started to generalize in the early 19th century (Dubé et al., 2015). In the case of Measles, anti-vaccination has mainly been fueled by a fraudulent 1998 article linking Measles vaccination and autism. 20 years later, anti-vaccination has found new champions and still remains a source of concern for public health decision makers. What is commonly called the "anti-vaccination movement", however, hardly qualifies as a movement. It actually consists of a nuanced set of stances ranging from outright vaccine refusal to vaccine hesitancy. Broadly speaking, we see three main mutually non-exclusive groups of anti-vaccination arguments. Some individuals refuse vaccination on religious grounds, either because vaccination is seen as a way to interfere with God's plan, or because vaccine production uses cell lines derived from aborted fetuses. There are also political objections to vaccination. Some are rooted in conspiracy theories that governments and the media are colluding with pharmaceutical companies. Others simply see vaccination as an unacceptable governmental intrusion. Finally, some reject the vaccine itself or the vaccination method. They typically hold that vaccination is not safe, or that the risk of side effects outweighs the benefits of vaccination. They would for instance incriminate vaccines' components, vaccine combination, or vaccination schedules.

Anti-vaccinationists ignore sound medical advice and their propaganda is often somewhat excessive. To make matters worse, they can at least in part be held responsible for the infection of young children and sick individuals who cannot vaccinate for medical rea-

sons. Needless to say, this makes anti-vaccinationists obvious and easy targets for journalists, scholars, and policy makers.

There is a large body of literature investigating vaccine refusal and vaccine hesitancy, and attempting to devise strategies to increase vaccine uptake. See Sadaf et al. (2013), Wang et al. (2014), Corben and Leask (2016), and MacDonald et al. (2018) for extensive reviews on this topic. What these studies have in common, is that they all focus on the specific reasons underpinning anti-vaccination, and use them as a starting point for policy making. As we will see, we look at vaccination behavior from a different angle in this thesis. But there is still an interesting takeaway. These studies all rest implicitly on the optimistic assumption that even anti-vaccinationists can be lead to vaccinate if the right incentives are implemented. Said differently, they assume that anti-vaccinationists would vaccinate if the cost of vaccination were low enough or the cost of not vaccinating were high enough. And their empirical findings seem to be in line with this assumption. In the United States for instance, exemption rates increased in states where philosophical or personal belief exemptions were introduced in addition to medical and religious exemptions. That is in states where it became easier to apply for an exemption. On the contrary, exemption rates are lower where the procedure for obtaining an exemption is more complicated, and thus more costly. Individuals claiming an exemption where vaccination is mandatory can certainly be described as anti-vaccinationists. Yet far from being unswerving in their refusal of vaccination, some of them[3] will respond to incentive changes and adapt their behavior.

What about individuals who are not anti-vaccinationists? Can we expect that individuals who normally vaccinate in countries where vaccination is not mandatory will do so under any circumstances? The issue of vaccination behavior goes much deeper than the case of anti-vaccinationists alone. Indeed, vaccinating is also costly for individuals who have a more positive attitude toward vaccination. Vaccination expenditures, of course, are not always fully covered. But we could also mention many other possible costs such as the inconvenience of bringing a child to the doctor, the fear of needles, or adverse events. If we accept that anti-vaccinationists may adapt their vaccination behavior to incentives, then there is no reason to believe *a priori* that this will not be true of the rest of the population. Actually, there is strong empirical evidence for a link between prevalence and child vaccination. See Smith et al. (2017) for the influence of perceived susceptibility on individual vaccination decisions. See Philipson (1996) and Goldstein et al. (1996) for aggregate observations in the case of Measles. See Oster (2018) for a more recent study in the case of Pertussis. If prevalence is low, the incentives to vaccinate are also lower. Memory and the lack of experience with the disease can make things worse. This is true for the whole population, not just anti-vaccinationists, and could explain – among other factors – why the last steps to eradication are more challenging than the reduction of prevalence when the disease is endemic (Klepac et al., 2013; Saint-Victor and Omer, 2013).

Economic theory explains well why vaccination decreases when prevalence is too low, and why vaccination coverage targets are not met. Indeed, the decrease in infection risk in a

[3] An example of unshakable anti-vaccinationism can be found in Duffell (2001).

population[4] is a positive externality of individual vaccination. This externality has public good attributes. It is nonrivalrous since the fact that an individual enjoys low infection risk does not increase the risk of others. It is also nonexcludable since there is no way to preclude an individual from enjoying low prevalence in the population. A classic result of economic theory is that in such situations, if individuals only follow their private incentives, they will engage in *free riding* and the public good will be underprovided[5] (Mas-Colell et al., 1995, p. 361). In the context of vaccination, free riders are individuals with lower incentives to vaccinate (e.g. because they have a more negative attitude toward vaccination) that benefit from the effort of those who vaccinate because their incentives are higher. Of course we can expect that more individuals will choose to free ride as prevalence decreases, thus forbidding eradication. This "external" side of vaccination behavior has without doubt received the most attention. Keep in mind, however, that vaccination decision-making has a private component (vaccinated individuals are immunized). We will see in Chapter 2 and Chapter 3 that this also has consequences in terms of welfare and incentives when comparing scenarios: if the vaccine is perfect (that is when 100% of shots do work), individuals who vaccinate under different scenarios pay the same cost for the same benefit in each scenario.

Free-riding can be accounted for in epidemiological simulation models by considering individuals with *adaptive behaviors*. Individuals with adaptive behaviors (see Xu and Cressman (2014), for instance), decide whether or not to vaccinate by weighting the benefits of vaccination against its costs. This individual cost-benefit analysis, however, is simply based on the current risk of being infected, that is on prevalence at the time of decision. Conceptually, models of imitation or memory fall into the same category: vaccination decisions depend on past and present prevalence.

We see two major limitations to these approaches. First, they implicitly assume that individuals (falsely) believe that prevalence will remain constant forever. This is of course unrealistic. Since, as we mentioned before, perceived susceptibility has been shown to be a major determinant of vaccination, we cannot make this assumption. Indeed, the benefits of immunity come *after* vaccination, so they depend on *future* prevalence. If susceptibility truly is a determinant of vaccination, then including *anticipation* of future prevalence in a behavioral model of vaccination is unavoidable. This leads us to the second limitation of models featuring only adaptive behaviors. Namely, they cannot fully account for strategic interactions because individuals in these models do not anticipate future vaccination decisions. They may free ride *de facto*, but not as part of a real strategy. That is, they will benefit from the vaccination of individuals who vaccinated before them, and they will respond by lowering their own coverage, but they will not base their decision on what they expect others will do in the future.

In fact, the two limitations we just pointed out in adaptive behavior models are essentially the same. Insofar as prevalence is determined by vaccination decisions and vaccination decisions depend on prevalence, anticipating others' behavior is the same as anticipating

[4] And so herd immunity, when it is reached.

[5] In the sense that more of the public good would be produced based on the sum benefit of individuals in the population. Assumptions about who pays what will vary depending on the scenario.

prevalence. However, it gives us two *different* rationales for focusing on strategic interaction in our investigation of vaccination behavior. The first rationale is that if we are to consider realistic *prevalence* anticipation, then the model will necessarily feature some degree of strategic behaviors since future prevalence depends on others' vaccination, and future vaccination decisions depend on present decisions. We may want to model strategic interaction because a realistic model of vaccination behavior from the point of view of epidemiology will feature strategic behavior anyway. If it is not modeled explicitly, strategic behavior will appear as an implicit assumption. The second rationale is that we may want to model strategic behavior explicitly simply because vaccination decision-making, insofar as individuals base their decisions on others' decisions, is strategic by definition: the payoff of an individual depends on his own decision, but also on the decisions of all other individuals. This is a more theoretical argument justifying that strategic behavior in vaccination decision-making should be investigated for its own sake.

0.2 Vaccination games

Strategic vaccination behavior has been formalized as *vaccination games*. In a vaccination game, the players are rational and far-sighted individuals who maximize their lifetime utility by deciding whether or not to vaccinate. They are often but not always atomistic. They base their decision on a private cost-benefit analysis. The cost of vaccination is usually a constant, and the benefit of vaccination depends on prevalence, which in turn depends on the vaccination decisions of *all* other players. In a dynamic setting, this is in contrast with adaptive models where the benefit of vaccination only depends on past vaccination decisions.

The objective of vaccination game models is to call attention to aggregate effects that are relevant to policy making (e.g. insufficient voluntary vaccination) and arising from individual behaviors (e.g. free riding). This approach is relevant not only to vaccination modeling, but also to any preventive behavior that has a cost for those engaging in it and positive externalities for the whole population. We will mention some applications to self-quarantine and to the prevention of sexually transmitted diseases.

The technical difficulty in vaccination games lies in the fact that decision-making interplays with prevalence, which has its own complex dynamics. Authors managed to dodge this difficulty in different ways. We will see how models of vaccination behaviors evolved from no account of epidemiology whatsoever to ever more complete accounts, and how the approach developed in this thesis builds upon this literature. The first attempts used non game theoretic methods. It is important to look at those studies to better understand the contribution of game theory, and to gain insight on the interpretation of game theoretic results.

The early work by Fine and Clarkson (1986) stands out in several respects. Their approach may seem naive at first sight. In their model, homogeneous individuals decide whether or not to vaccinate by weighting the risk of infection against the risk of vaccination adverse event. The authors did not consider an epidemiological model linking vaccination decisions and infection risk. They simply assumed *ad hoc* relationships between vaccination coverage

and infection risk reduction. Their reasoning was static (implicitly steady state). Interestingly, however, they discussed their results in terms of "strategies", thus foreshadowing later game theoretic works. Also, they computed what they called the "critical level of vaccination coverage" below which a rational individual vaccinates and above which he refuses vaccination. We will see that this critical level actually corresponds to a mixed strategy Nash equilibrium, a notion that was introduced in the context of vaccination decision-making only twenty years later. Finally the authors – epidemiologists – bothered to produce numerical results,[6] which would largely be neglected in the subsequent economic studies.

Until the 2000s, the literature was dominated by studies using traditional non game theoretic economic methods. Besides a marked preference for analytical results over numerical results, these authors typically derived their results by assuming an underlying non-degenerate distribution of the population over the vaccination cost (Brito et al., 1991) or the equivalent (Geoffard and Philipson, 1996). They described vaccination behavior in terms of *thresholds*: for instance the vaccination cost above which individuals do not vaccinate, or the prevalence level above which they do. Such thresholds partition the population between those who vaccinate and those who do not. The corresponding vaccination coverage can be obtained simply by summing the population distribution over the right interval. This vaccination coverage, however, may not be interpreted *primarily* as the result of strategic behavior.

This is best illustrated by Brito et al. (1991). In this study, the population has a non-degenerate distribution over the vaccination cost c. The threshold of interest is the vaccination cost c^* such that all individuals who have a vaccination cost $c < c^*$ vaccinate and those who have a vaccination cost $c \geq c^*$ do not vaccinate. The model is static without an explicit epidemiological component. The authors simply assumed that the utility of being unvaccinated u_{nv} was strictly increasing with the vaccination coverage. Since more people vaccinate as the threshold c^* increases, u_{nv} is a strictly increasing function c^*. Of course the net utility of vaccination u_{v} decreases with the vaccination cost c incurred by an individual who vaccinates. From these assumptions, the authors could determine a unique equilibrium value of c^*.

This equilibrium threshold is such that $u_{\mathrm{v}}(c^*) = u_{\mathrm{nv}}(c^*)$. Consider for instance a candidate threshold c^* such that $u_{\mathrm{v}}(c^*) > u_{\mathrm{nv}}(c^*)$. In this case, the *marginal individual* with vaccination cost c^* has an incentive to vaccinate because the vaccination coverage corresponding to the candidate threshold c^* is too low. The same reasoning goes for a candidate c^* such that $u_{\mathrm{nv}}(c^*) > u_{\mathrm{v}}(c^*)$. Here the vaccination coverage corresponding to c^* is too high and the marginal individual has an incentive to free ride. So the equilibrium vaccination coverage can be interpreted as arising from the successive decisions of marginal individuals: individuals with a lower vaccination cost vaccinate first and then individuals whose vaccination cost is just equal to the current threshold vaccinate until there is no incentive to do so. It is true that at equilibrium, no individual has an incentive to deviate, so the equilibrium is not inconsistent with strategic behavior. But this equilibrium relies heavily on the underlying

[6] Actually numerical values of analytic expressions. This is still very different from numerical *solutions* such as those computed in this thesis, but to us this approach was headed in the right direction.

population distribution over the vaccination cost, and less on the incentives linked to the disease itself as will be the case in game theoretic models.

Of course we might find cases where the most relevant effects are driven by the presence of thresholds in a distributed population. An obvious example are age distributions, that are certainly to be considered more carefully in some contexts. Moreover, reasoning in terms of distributions and thresholds has some advantages. Brito et al. (1991), for instance, were able to provide welfare arguments by summing welfare functions over the population distribution. Noticeably, such results can be obtained without specifying the distribution: we may compare different scenarios by comparing different integrals over the same distribution.

We have already argued that it is *a priori* reasonable to focus on strategic behavior when investigating vaccination decision-making. Further, it seems relevant to look at strategic behaviors that stem from the features of the disease itself (time to recovery, infectiousness, etc.), under realistic epidemiological assumptions, and independently of any assumed underlying distribution of the population. We believe that non game theoretic economic methods have reached their limits in the study of vaccination behavior for at least two reasons. First, these authors have invariably used strong simplifying assumptions that reduced drastically the scope of their results. This might in part be explained by a strong inclination for analytic results, or by limited computational resources at the time of publication. Some simplifications were necessary to obtain results in terms of a single threshold value. This is especially true in dynamic settings. We may then suspect that the only purpose of assuming underlying distributions was to give some substance to results that would have otherwise boiled down to simple threshold values. The second limitation of methods relying on population distributions and threshold values, is that they are ill-suited to numerical simulation. Performing numerical simulations in such frameworks would require to specify all underlying distributions. But then, when analyzing the results, it would become difficult to disentangle the effects due to the strategic problem faced by individuals from effects due to the shapes of the specified distributions. Finally, notice that most epidemiological models cannot be solved analytically, even when they do not feature individual decision-making. Building models of vaccination behavior while avoiding to use numerical methods might have provided early insights in a time where the use of computers was not as widespread as today. Yet in the long run, this approach was bound to come to a dead end.

Further examples from this literature include the works by Geoffard and Philipson (1996), Francis (1997), and Geoffard and Philipson (1997). Geoffard and Philipson (1996) studied the use of protection against a sexually transmitted disease in a dynamic setting. Their model includes an explicit epidemiological model (which was not the case in Brito et al. (1991)). The disease is described with a SI (*Susceptible* and *Infectious*) compartmental model without vital dynamics or recovery, so the prevalence can only increase. The population is distributed over the threshold prevalence above which an individual uses protection. While the results depend on time, decision-making is not dynamic: formally, individuals maximize their lifetime expected utility, but their decisions only depend on the current prevalence. This is similar to a model of adaptive behavior, or can be interpreted as the repetition of static models. We

see that time dependency here is somewhat artificial.

The same SI epidemiological model was used by Francis (1997), this time in the context of vaccination. Here, overlooking anticipation is more difficult to justify as the benefit of vaccination also depends of future prevalence. In the model proposed by Francis (1997), homogeneous (same vaccination cost) individuals decide at what time it is optimal to vaccinate. Since the prevalence can only increase, this is equivalent to finding a threshold prevalence level. In this framework, all individuals vaccinate at once when the threshold is reached, and no individual has an incentive to deviate. However, this is only true under the assumption that prevalence only increases. Consider for instance a situation where individuals recover from the disease so that prevalence decreases if enough individuals vaccinate. In this scenario, an atomistic individual may have an incentive to deviate if all other individuals vaccinate.

With this simple scenario, we can appreciate how anticipation in some dynamic settings can create strategic interactions. Recall that in the static setting proposed by Brito et al. (1991), vaccination coverage was driven by the distribution of a behavioral parameter, vaccination cost, that pertains only remotely to strategic behavior. Yet, while the focus of the study was not on strategic behavior, the aggregate outcome was still consistent with strategic behavior. Anticipation in dynamic settings reveals strategic interactions that are less apparent – or less distinctive – in static settings. Having said that, we must stress that anticipatory behavior and strategic behavior are two different notions. Individuals *do* anticipate in the setting proposed by Francis (1997), but their lack of control over prevalence precludes strategic interaction. Geoffard and Philipson (1997) tried to go beyond the limitations of SI compartmental models with a SIR (*Susceptible*, *Infectious*, and *Recovered*) model but they only gave analytic results on steady states.

The work by Francis (1997) also gives us a better understanding of why a distribution of the population over the vaccination cost is only incidental to the core issue of strategic behavior. Simply consider an extension of the model to the case of several individuals with different vaccination costs. Here, individuals with lower vaccination cost would vaccinate first, thus slowing down the increase in prevalence but not reversing it – all thresholds would eventually be reached and individuals would vaccinate by increasing cost of vaccination. In this scenario, individuals are not influenced by the individuals vaccinating after them, so the setting is not strategic.

The first formal game theoretic account of vaccination decision-making was proposed by Bauch et al. (2003). Their model is static and features homogeneous atomistic individuals who decide whether or not to vaccinate by weighting the expected utility of vaccinating against the expected utility of delaying vaccination. This framework is very similar to that found in Brito et al. (1991): in both models, an equilibrium is reached when the utility of vaccinating equals the utility of not vaccinating. But with one major difference. In the model by Brito et al. (1991), the equilibrium vaccination coverage resulted from the equilibrium threshold vaccination cost c^*. It was derived from an assumed population distribution over the vaccination cost by summing the population with vaccination cost $c < c^*$. In contrast, the equilibrium vaccination coverage in Bauch et al. (2003) depends on strategic interaction

	V	NV
V	$+,+$	$+,++$
NV	$++,+$	$-,-$

Figure 3: Normal-form representation of a static two-player vaccination game. V: vaccinating, NV: not vaccinating. "$+$" stands for higher payoffs and "$-$" for lower payoffs.

only, without reference to any underlying distribution of the population.[7]

Let us look at a version of the static game formalized by Bauch et al. (2003) with only two players instead of a continuum of atomistic players. A typical instance of this game is illustrated in Figure 3. The outcomes (V, V) and (NV, NV) where both players vaccinate or do not vaccinate are unstable. If both individuals vaccinate, one of them will be tempted to deviate, and reap the benefits of herd immunity while avoiding to pay his vaccination cost. If no player vaccinates, then they will not be protected against the disease and will have an incentive to vaccinate. There are two Nash equilibria where one individual vaccinates and the other does not. In this simplistic setting, the equilibrium vaccination coverage would be 50%. Since both players are identical, knowing precisely *which* player vaccinates and which one does not is irrelevant, so we can directly discuss the results in terms of equilibrium vaccination coverage. Once again, this vaccination coverage is the result of strategic interaction and relevant epidemiological assumptions only.

We may note in passing that the vaccination game presented in Figure 3 is close to the *game of chicken* (or *hawk-dove game*). In their paper, Bauch et al. (2003) drew a parallel with the prisoner's dilemma, but this is misleading. In a prisoner's dilemma version of the vaccination game, an individual vaccinating while the other does not would get the worst possible payoff in the game. This will not be the case in the most typical vaccination scenarios (e.g. with perfect or close to perfect vaccines) insofar as vaccinated individuals get the benefit of being immunized. When the vaccine is not perfect, a vaccinating individual may be worse off if the other individual does not vaccinate, compared to a situation where all individuals vaccinate. This setting would correspond to the "real" game of chicken. Also, in a prisoner's dilemma vaccination game, the payoffs when no one is vaccinated would not be the worst possible payoffs, and no one vaccinating would eventually be the Nash equilibrium.

The two-player game in Figure 3 can be extended to $N > 2$ players. It would again result in an equilibrium coverage likely to be different from 100% or 0% in most (though not all) instances of the game. By assuming that the population is formed by a continuum of identical atomistic individual, Bauch et al. (2003) could interpret the vaccination coverage as resulting from individual *mixed strategies*. When playing a mixed strategy, individuals choose to vaccinate with some probability P. Since all individuals are identical, the equilibrium strategy is the same for all, and results in a vaccination coverage $p = P$. This passage to the limit greatly reduces the dimensionality of the problem and is a foundation of a branch of game theory, *mean field game theory*. In this thesis we will not use the formal framework of

[7] Apart from the distribution over health statuses, of course. But this distribution is *endogenous* while the distributions we have discussed to far were assumed *exogenously*.

mean field game theory even though our results and methods are close.

Another non-negligible contribution of Bauch et al. (2003) is that they provided a specific scenario (preemptive vaccination under bioterrorist threat) justifying to use a one period static model. Their model is also based on an explicit epidemiological model and numerical simulations. This might denote a more marked leaning toward real life issues than some previous studies, but perhaps also be the result of an increase in available computing power. Bauch and Earn (2004) used the same framework in a more general dynamic setting but they restricted themselves to the investigation of steady states only.

Since then, many studies have used static or steady state models. Yet this is certainly insufficient for most epidemiological applications. Indeed, epidemics are fundamentally time dependent. In fact, the problem with epidemics lies not so much in steady state prevalence levels as in dynamic phenomena. To illustrate, consider such common issues as the build up of a pool of susceptible individuals as unimmunized children are born over time, or the arrival of an infectious individual in a steady state population.

In this thesis, we will strive for full time dependent solutions of the vaccination decision problem. We will solve for the proportion of the population vaccinating and for prevalence at each time over an horizon, while retaining explicitly the most relevant epidemiological features of the disease in the model. In dynamic models, individuals base their decision on *value functions* that are the expected lifetime utility of being in a given state or health status at a given time. They engage in *anticipatory* or *forward-looking* behavior. In the context of vaccination, individuals will compare the value of being susceptible with the value of being vaccinated at each time. There is a technical challenge here, on which we will elaborate when we will present our approach in Section 0.4.

Before moving on, we only need to mention some authors who have tackled this challenge. Reluga (2010, 2013) developed a model of social distancing. In his model, individuals can decide to invest in self-quarantine to protect themselves. However the contact rate is a function of the sum investment in the population, hence the game. The mapping from investment levels to contact rates was assumed by the author. Laguzet and Turinici (2015b) considered a SIR model and vaccination decision-making, but without vital dynamics and lifelong immunity of vaccinated individuals (no waning vaccine efficacy). Finally, Salvarani and Turinici (2018) produced results very similar to ours with a mean field game approach. Their epidemiological model features an imperfect vaccine and loss of immunity over time, but their application case allowed them to overlook vital dynamics.

To sum up, we argued (but this fact is now widely acknowledged) that the spread of some infectious diseases such as Measles heavily depends on individual vaccination decision-making. We then made a case for focusing on the strategic interaction implied by vaccination behavior, while at the same time modeling the peculiarities of the disease with some realism in a dynamic setting. We saw how game theoretic approaches allow to model what is essential, both in individual behavior and in disease dynamics. Yet we might still wonder about the real life needs of practitioners and decision-makers who use epidemiological models. Vaccination policies, for instance, were assessed long before researchers started to study vaccination games.

So how do these relatively new models articulate with already existing methods? And most importantly, are they of any use? We found rationales for modeling strategic behavior in vaccination decision-making, but would doing so change anything to results found by public health professionals using more traditional methods? After all, strategic interactions might make sense for describing vaccination decision-making, they might even occur in real life, and still yield only second order effects. Besides, we emphasized the need for epidemiological realism in models of vaccination behavior, and yet even the most recent models in this literature (including ours, as we will see) remain extremely simplistic compared to some epidemiological models developed by epidemiologists. We need to look at some models and methods used by health economists to better understand how our models can be used to tackle real life issues.

0.3 Some methods in health economics

So far, we have only mentioned the costs and benefits of vaccination from the point of view of an individual. Yet other participants in the health system may be interested in weighting benefits of vaccination against its costs. Public health authorities typically seek to maximize citizens' welfare while minimizing the cost of a vaccination campaign. A health insurance company may face a trade-off between promoting prevention (e.g. through vaccination) or reimbursing medical care of sick individuals. Finally, the profit of a pharmaceutical company depends on the demand for vaccines, or more generally on vaccination policies decided by health authorities. All these need to perform *economic evaluations* of epidemics and of control policies from their own point of view.

When referring to economic evaluation, a distinction is usually made between *cost-benefit analyses* in which the cost and benefits of a policy[8] are monetary, and *cost-effectiveness analyses* in which costs are usually monetary but the outcome measure is not. Examples of non monetary outcomes include the number of averted cases, or the number of gained life years. *Cost-utility analyses* are cost-effectiveness analyses in which gains are in terms of a utility measure, *QALYs* (*quality-adjusted life years*). In this thesis, we loosely refer to economic evaluations as "cost-effectiveness analyses". In our simulations, we solve for the time evolution of Measles prevalence: costs and benefits in whatever unit follow immediately from this result, but we leave such computations outside the scope of the thesis. In Chapter 2, which is dedicated to an application of our vaccination decision models to cost-effectiveness analyses, we discuss outcomes in terms of welfare gains and losses for *individuals*. However the effects we bring out may translate into gains and losses for any health system participant.

Health economics is a wide field of study. Health economists have analyzed topics so diverse as health insurance or medicine pricing. Still, there is one ubiquitous method in the discipline, and that is economic evaluation. One of the main challenges here, is that economic evaluations of health interventions or public health policies require to evaluate heterogeneous

[8]These methods where developed to evaluate and compare health interventions in general, not only public health policies.

and sometimes subjective costs and benefits. In addition to the difficulty of enumerating all relevant costs and benefits in a single public health policy, comparing two policies can also prove delicate. One policy might be more beneficial on one aspect while the other might be more advantageous on another aspect.

QALYs were introduced as measure of utility in health economics in order to tackle this issue. QALYs aggregate two dimensions: quality of life and life years. They are obtained simply by multiplying a measure of the quality of life with life time. Quality of life is normalized to 1 for perfect health and to 0 for death. In this framework, a health intervention increasing life by 10 years with a quality of life of 0.4 brings $0.4 \times 10 = 4$ QALYs and is equivalent to another intervention that would extend life by 8 years with a quality of life of 0.5. QALYs are now widely used along with an alternative utility measure, DALYs (disability-adjusted life years), which takes the opposite perspective by counting life years lost due to premature death, and years of good health lost due to disability.

Of course, quality of life is itself an aggregate. It can be estimated via questionnaires or by other methods. We give one of the most simple for illustration: standard gambles (see Gafni, 1994). In standard gambles, sick individuals are asked to choose between (i) not doing anything and so keeping their current quality of life q, and (ii) entering a lottery where they can be cured with probability p and die with probability $1 - p$. The quality of life q of a sick individual is then estimated as the value of p such that sick individuals indifferent between the lottery and remaining sick ($q = 1 \times p + 0 \times (1 - p)$).

Measuring gained and lost QALYs raises obvious methodological questions. Health economists have devoted much effort to develop and implement ever more specific evaluation methods. In the case of Measles, the QALY cost of being sick was for instance estimated by Thorrington et al. (2014) to approximately 7 QALDs (quality-adjusted life days, 1 QALD equals 1/365 QALY). They used a questionnaire based instrument, the EQ-5D-3L (van Reenen and Oppe, 2015). Patients were asked to describe their health state based on 5 dimensions: pain/discomfort, anxiety/depression, mobility, self-care, and usual activities. The 5 dimensions were then weighted so as to obtained an index between 0 and 1. The final result was obtained by averaging over different age categories.

Once the cost of a single Measles case has been estimated – whether individual or societal, monetary or in terms of utility – the most straightforward way to assess a control policy is to multiply this cost by the number of averted cases without any reference to a dynamic epidemiological model. This approach was exemplified by Zwanziger et al. (2001) and by Hinman et al. (2004). They performed economic evaluations of an increase of Measles vaccination coverage, and of MMR vaccination respectively.

Both studies are based on *decision trees*.[9] In the study by Zwanziger et al. (2001), the decision tree is a list of scenarios faced by an infected individual along with their probabilities, and individual and societal costs. The tree includes among other things necessary health care, missed days of work, and Measles complications such as Meningitis and death. From this

[9] Zwanziger et al. (2001) do not mention this method explicitly, but they implement it in effect. Notice also that "decision" in this context refers to the decisions made by the user of the decision tree, and not to vaccination decisions made by agents in the model.

tree, the authors could compute the individual and societal costs of a single case of Measles as the net present value over lifetime of the expected cost of all scenarios. Then, they assumed that raising vaccination coverage to 90% would lead to herd immunity. When herd immunity is reached, all preventable cases are prevented – an unimmunized individual can be infected by a traveler, but the disease does not propagate. From historical data, they could compute a baseline incidence level, and so the number of averted cases compared to this baseline if herd immunity is reached. The saved cost was computed as the number of averted cases times the cost of a single case. Finally, they compared the cost of increasing vaccination coverage to 90% to the saved cost of averted cases. Here, we see that two steady states were actually compared: the baseline (constant) incidence level, and herd immunity with assumed zero incidence. However, those steady state do not correspond to an epidemiological model – in one of them, herd immunity is simply assumed.

The study by Hinman et al. (2004) is slightly more elaborate. Their decision tree includes Measles infection, *i.e.* an equivalent of the tree used by Zwanziger et al. (2001). Since they investigated MMR vaccination, they added Mumps and Rubella infections to the tree along with their respective complications. One major difference with Zwanziger et al. (2001), is that vaccination and the probability of infection themselves were included to the tree. Individuals vaccinate with some probability and the vaccine works with some other probability. Adverse events may occur, and individuals may get infected with Measles, Mumps, or Rubella, and incur the corresponding costs. The authors considered two scenarios: available MMR vaccine and prevaccine era. They also modeled several age classes. Probabilities were estimated from historical data for each scenario, and each age class. The authors could then compute net present values over lifetime under each of the two scenarios and make comparisons. Here again, only steady states were compared. This time, the authors considered an implicit epidemiological model, but with *constant* infection probabilities.

From a very down-to-earth perspective, we know that the dynamic features of an epidemic are critical (recall the build up of a pool of susceptible individuals over time, etc.). If epidemics were only steady state, that is if it were possible to switch instantaneously from one steady state to another, then much of their burden would be readily avoided. In other words, steady state models do not allow to appraise *how* steady states are reached, specifically at what pace, and with or without damped oscillations. In the context of vaccination, knowing how fast and how "smoothly" and epidemic may be controlled is of obvious relevance.

This specifies an *optimal control* problem. There is an extensive more or less theoretical mathematical literature on the topic of optimal vaccination policies. For illustration, we may only mention the works by Hethcote and Waltman (1973) and by Laguzet and Turinici (2015a). Both tackled the problem of optimal vaccination policy to control a disease described by a SIR compartmental model. A vaccination policy is specified by the vaccination rate at each time. Vaccination has a cost, and so has the disease. The objective is to choose a vaccination policy such that the total cost is minimized subject to some constraints.

Hethcote and Waltman (1973) used the traditional dynamic programming technique. It consists in discretizing the state space (here the number of susceptible and infected individ-

uals) and then use the principle of dynamic programming (or Bellman equation) to solve for the best control (vaccination rate) from each state at each time, starting from final time and moving backward. They assumed no vital dynamics so the total number of infected individuals over the time horizon was simply the sum of infected and recovered individuals at final time. This assumption allowed the author to set a constraint on the total number of infected individuals in a simple way. Laguzet and Turinici (2015a) considered the same optimal control problem in a more general technical setting. They concluded their study with an application to cost-effectiveness analyses.

Many applications do not require to solve for an optimal vaccination policy. Dynamic models can be used to compare predefined vaccination strategies. This was done by Beutels and Gay (2003) in the case of Measles vaccination with a compartmental model of five compartments. More recently, Littlewood et al. (2015) performed a cost-effectiveness analysis of adding Varicella vaccination to the MMR vaccine (MMRV vaccine) under different vaccination strategies. They also used a compartmental model to run simulations.

One argument for using steady state models in economic evaluations is that the underlying dynamic phenomenon is too complicated to be properly accounted for. Rather than putting effort into dynamic modeling intricacies that are bound to fail, the authors following this line of reasoning usually strive for highly specific and elaborate cost estimations based on tools such as decision trees. As for the epidemiological component of their studies, they choose a simple "accounting" method that consists in enumerating the number of, say, averted cases based on coarse-grained historical data. This might be perfectly fine in the most simple cases, when the unfolding of events over time is inconsequential. But clearly, when it comes to infectious disease epidemics, an explicit dynamic model of the most salient features of the disease seems necessary more often than not.[10] What does not seem to be always realized, is that steady state accounting models used in such cases actually *are* dynamic models in that they make assumptions about what happens over time. Simply, these assumptions remain implicit and often groundless.

The same goes for strategic settings. Recall that strategic settings are when individuals are free to make decisions and the payoff of each individual is influenced by the decisions of all other individuals, so that they base their decisions on what they expect others to do. Just as using a steady state model in a dynamic setting amounts to a risky implicit assumption about the dynamics of the system, overlooking strategic behavior in a strategic setting amounts to an equally bold assumption about individual behavior. Individual strategic behavior cannot be discounted *a priori* from economic evaluations in a strategic setting.

Individual behavior pervades naturally in many economic evaluations. Indeed, the response of individuals to an intervention or public health policy is often decisive to its success. Yet this kind of individual responses usually found in the literature bears no relation to strategic behavior. To better see this, and appreciate what strategic behavior implies in the context of economic evaluations, consider the difference between responding to the incentives directly implemented by a policy, and responding to the incentive changes caused by others'

[10] What is "salient" remains in part a matter of appreciation.

behavior. In a strategic setting we can expect that individuals will not on only respond to the policy itself, but also to the behavior of all other individuals. The key distinction to make here is between *exogenous* incentive changes (those caused by the policy we are evaluating), and *endogenous* incentive changes (those caused by modeled agents).

Examples of nonstrategic behaviors investigated in economic evaluations can be found in the review by Lorenc et al. (2011). The reviewed papers are evaluations of strategies for promoting HIV testing among men who have sex with men. They measured the response of the target audience to various promotion campaigns. A further example can be found in DePasse et al. (2017). Here, the authors used an agent-based model to evaluate the cost efficiency of offering several Influenza vaccine options instead of one. In the scenario where several options were available, vaccination coverage was increased exogenously by the authors in order to fit data. As for the "choice" of a specific vaccine option by individuals, it was drawn at random.

In Chapter 2 we will show with an example, mandatory vaccination, that individual strategic behavior cannot be overlooked *a priori* in cost-effectiveness analyses. This work does not question the relevance of economic evaluations in general. On the contrary, we will make our case on the same premises. For instance in Chapter 2 (and Chapter 3), we will assume that the cost of being infected with Measles for an individual is equal to the 7 QALYs found by Thorrington et al. (2014). This will be an *input* of our models.[11] The *outputs* will be the resulting vaccination decisions and prevalence. Insofar as prevalence and vaccination decisions determine costs and benefits – from the point of view of any health system participant – our models are compatible with usual economic evaluation methods. We will add only one further premise by allowing for strategic interaction in vaccination decision-making. We will see that this can yield non-negligible effects in economic evaluations.

Before giving more details on our approach, we must emphasize that the complexity of the epidemiological models used in vaccination game models is not behind that of the epidemiological models used for economic evaluations. This is all the more true of the models presented in this thesis since we are striving for some realism. It is true that epidemiologists have developed complex models describing, for instance, contact networks or spatial distributions. In the field of health economics, however, epidemiological models are usually far more simple. First, many are simple steady state models. They are used by researchers but also widely by practitioners (see Whitney et al. (2014) for an example published by the Centers for Disease Control and Prevention). Then, the dynamic models that are sometimes used are most often simple SIR models or the like. Their complexity is comparable to the dynamic models found in the vaccination game literature, and to our models in particular.

[11] More generally, the very detailed costs that are often computed in studies using steady state models can be used as input of dynamic models.

0.4 Actionable models of strategic vaccination behavior

To review, we have argued that dynamic vaccination games are highly relevant models of vaccination behavior because strategy and anticipation are essential features of vaccination decision-making. There is however still a lack for dynamic vaccination game models in general settings, that is with full complexity (vital dynamics, waning vaccine efficacy, etc.) rather than specific scenarios. The dynamic vaccination game approach developed in this thesis avoids *ad hoc* simplifying assumptions. Consequently, it relies mostly on numerical solution methods. Several similar models have been developed until recently. We have already mentioned studies by Reluga (2010, 2013), Laguzet and Turinici (2015b), and Salvarani and Turinici (2018). The work of Salvarani is the most advanced in our opinion and, as we will see, is quite similar to ours, even though both models were developed independently.

Importantly, we do not aim at solving complex models for their own sake. One of our objective is to engage with public health professionals. We argued in Section 0.3 that vaccination game models were compatible with cost-effectiveness analyses used by health economists. We also claimed that individual strategic behavior cannot be overlooked in a setting that is essentially strategic, just as time dependency cannot be overlooked *a priori* where dynamic phenomena seem to be an essential feature. Out of context, however, this argument remains weak (even a tautology) and lacks practical implications. In Chapter 2 we will use our vaccination game model to discuss an example of public health policy, and thus provide practitioners with tools.

Our modeling approach needs to be flexible enough and adaptable to economic evaluations, while at the same time allowing to tackle complex and large problems. Let us give some details about the main features of this approach. We use a continuous time setting with infinite time horizon. The time evolution of the epidemic will be described by differential equations. We retain the Nash equilibrium as solution to our vaccination game. The solution will be the proportion of individual who vaccinate at each time. It can also be interpreted as a mixed strategy Nash equilibrium, that is the probability that an individual vaccinates at each time.

Let $\Lambda(t)$ denote the proportion of individuals who vaccinate at time t between time 0 and final time T, if they have access to vaccination at this time. The strategy Λ translates into a prevalence path, which in turn translates into costs for individuals. Of course, the best response of an *individual* to strategy Λ does not need to be Λ. For instance if $\Lambda(t) = 1$ for all t, an individual may have an incentive to free ride on others' vaccination. A strategy Λ^* is a Nash equilibrium if the best response of each individual to Λ^* is Λ^* itself at each time. Finding a Nash equilibrium is equivalent to finding a fixed point of a best response function.

In a dynamic setting, of course, the fixed point is not a scalar but a function of time. Salvarani and Turinici (2018) solved this fixed point problem with a *fictitious game* approach. They started with an initial candidate strategy Λ_0 and assumed that all individuals were playing Λ_0. Then they computed the best response Λ_1 of an individual as the solution of a quadratic programming problem, under the constraint that Λ_1 should remain close to Λ_0.

They repeated until a convergence criterion was reached.

We took another (yet similar) approach, that does not require to solve an optimization problem at each step.[12] We compute Λ as the solution of a fixed point problem as well, and we do it iteratively too. Like Salvarani and Turinici (2018), we evaluate the best response to a candidate solution at each step. However, instead of doing so by solving an optimization problem, we compute an approximate best response.

In our setting, individuals maximize their lifelong expected utility. At each time, the expected lifelong utility of being in a given health status for an individual making optimal decisions is given by a *value function*. So here, a candidate strategy played by all individuals will translate into a prevalence path, which will in turn translate into value functions. Given these value functions, the approximate best response of an individual is given by the functions χ illustrated in Figure 4. If the net value of vaccination at time t is $\Delta V(t)$, then the approximate best response at this time is $\Lambda(t) = \chi(\Delta V(t))$.

These functions are known as *smoothed best response functions* (Fudenberg and Levine, 1998) or *quantal response functions* (McKelvey and Palfrey, 1995, 1998). They have mostly been used to make sense of data in experimental economics. Some authors have given interpretations of smoothed best responses in terms of error terms – either due to unobserved individual preferences, or to individual computation errors.[13] We will not concern ourselves with such interpretations in this thesis.

Nor will we provide a measure of the quality of our approximation. In use cases of our model, we will choose the slope of the smoothed best response function at 0 such that a small variation (relative to the considered case) of the net value of vaccination ΔV around 0 (indifference) leads to a 0 or 1 response. Put the other way, responses different than 0 and 1 will only be obtained when individuals are virtually indifferent between vaccinating and not vaccinating, so the resulting equilibria will in effect approximate mixed strategy Nash equilibria.

Besides allowing to compute best responses in a simpler way than by solving an optimization problem, smoothed best responses have the technical advantage of providing some flexibility in solving. Our iterative fixed point search algorithm converges more easily when the slope at 0 is smaller, so there is a trade-off between the quality of our approximation and the speed of convergence.

Our models comprise two components. The first is a compartmental epidemiological model describing the time evolution of the population in each health status (susceptible, infectious, etc.). The second component governs the time evolution of the value function corresponding to each health status. This results in a system of coupled differential equations. The link between the two components is made via the smoothed best response function.

Let n the number of compartments or health status. Let x and V two continuously differentiable functions from $[0, T]$ to $\mathbb{R}^n$ giving respectively the population in each health status at each time and the value of being in each health status at each time. For all t

[12] Which does not mean that convergence is better or faster in our case.

[13] In another context, the famous work by McFadden et al. (1973) provides such analysis.

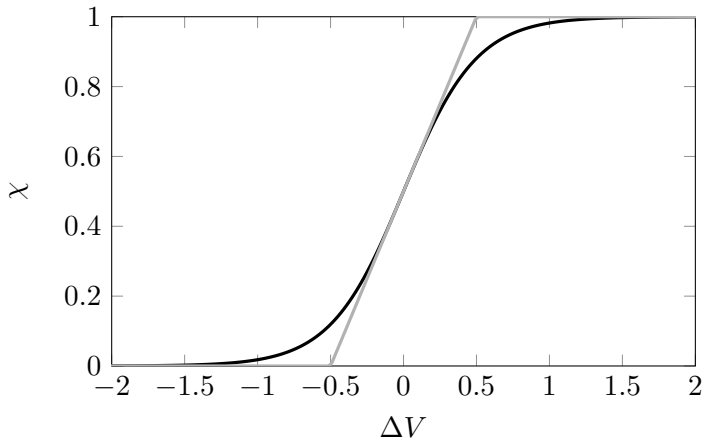

Figure 4: Smoothed best response functions for a slope of 1 at 0. ΔV is the net value of vaccination. *Black:* Sigmoid (Chapters 1 and 2). *Gray:* Ramp function (Chapter 3).

between time 0 and final time T, the system of coupled equations is of the form

$$\frac{d}{dt}x(t) = f_1(x(t), V(t)) \tag{1}$$

$$-\frac{d}{dt}V(t) = f_2(x(t), V(t)) \tag{2}$$

$$x(0) = x_0, V(T) = V_T \tag{3}$$

where f_1 and f_2 are continuous.

Here we need to emphasize one peculiarity of dynamic vaccination games. As the payoff of individuals depends on their immunity and prevalence in the future, they engage in anticipatory behavior and base their vaccination decision at time t on the prevalence (that is x) at later times. Of course this decision has an influence on future prevalence. This results in a forward-backward system. Equation (1) goes forward in time. We know x at time 0 (e.g. the initial prevalence), and given a strategy, we can compute x until final time T. Conversely, Equation (2) goes backward in time. We do not know V at time 0 but we can set $V(T)$. For instance, infinite time is achieved by setting $V(T)$ to a steady state value of V for T large enough. Then, given a prevalence path, we can compute V from time T back to time 0.

Solving Equations (1)–(2) as a fixed point problem is a way to tackle the technical difficulty of this forward-backward system. There are other methods to do so. Reluga (2010, 2013), for instance, used a *shooting method*. He solved Equations (1)–(2) backward in time starting from multiple values of $x(T)$ until finding a satisfying $x(0)$.

Our relaxed fixed point iteration method is summarized in Algorithm 1. In practice we solved Equations (1)–(2) with explicit or semi-implicit Euler methods. Algorithm 1 was used as the most basic component of more elaborate schemes. For instance we used *continuation methods* in some cases. This consists in solving the problem for some parameter values for which it is easy to solve (say a low slope parameter in the smoothed best response), and then use the solution as starting point of the fixed point iteration algorithm with more difficult

parameter values.

input : x_0, V_T, step, crit, model parameters
output: approximate equilibrium strategy Λ^*
initialize Λ_0, dist:=crit+1;
while *dist* > *crit* **do**
  compute the solution x to Equation (1) based on Λ_0;
  compute the solution V to Equation (2) based on x and Λ_0;
  compute the best response Λ_1 to x via V and the smoothed best response function;
  dist:=distance(Λ_0, Λ_1);
  Λ_0+=step $\times$ ($\Lambda_1 - \Lambda_0$);
end
$\Lambda^* := \Lambda_0$;

Algorithm 1: Relaxed fixed point iteration

Our first task in this thesis was to introduce this modeling approach and illustrate its versatility. Only then were we able to show practical applications, either to policy making or to theoretical work. This thesis consists of three chapters, each of which was written as a selfstanding paper.

In **Chapter 1**, we introduce our approach for a disease close but not identical to Measles. This choice was driven by the need to include waning vaccine efficacy in order to illustrate the reach of our approach. We also included vital dynamics, which is not done in many vaccination game models. With this model, we show how the interplay between individual anticipatory vaccination decisions and the otherwise biological dynamics of the disease may lead to the emergence of recurrent patterns. For comparison, we provide results for individuals with adaptive behavior.

Chapter 2 has two objectives. The first is to show with an example that anticipatory behavior cannot always be overlooked in cost-effectiveness analyses. The second objective is to illustrate how our approach can be used in economic evaluations. We investigate the effect of anticipatory behavior in a scenario where Measles vaccination becomes mandatory. When mandatory vaccination is announced in advance, we show that individuals may alter their vaccination behavior, thus causing an increase in prevalence before Measles is ultimately eradicated. These transition effects lead to non negligible welfare differences between generations. We consider an anti-vaccinationist subpopulation with a higher vaccination cost, and exhibit scenarios where anti-vaccinationists are among those who benefit the most from mandatory vaccination.

Finally, **Chapter 3** is a more theoretical investigation of vaccination behavior based on our modeling approach. We discuss whether coalitions of vaccinating individuals can account for the relatively high observed vaccination coverages. We explain why and how retaliation concepts usually found in repeated games can be used in the context of vaccination, even though individuals vaccinate only once. This allows us to model how vaccinating individuals might retaliate against those who refuse vaccination. We show that retaliation threats can sustain vaccination where it would otherwise be suboptimal for individuals.

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Chapter 1

Canonical modeling of anticipatory vaccination behavior and long term epidemic recurrence

This chapter is based on an article coauthored with N. Houy and P. Michel published in the Journal of Theoretical Biology *(Flaig et al., 2018).*

Abstract

Vaccination is one of humanity's main tools to fight epidemics. In most countries and for most diseases, vaccination is offered on a voluntary basis. Hence, the spread of a disease can be described as two interacting opposite dynamic systems: contagion is determined by past vaccination, while individuals decide whether to vaccinate based on beliefs regarding future disease prevalence. In this study, we show how the interplay between such anticipating behavior and the otherwise biological dynamics of a disease may lead to the emergence of recurrent patterns. We provide simulation results for (i) a Measles-like outbreak, (ii) canonical fully rational and far-sighted individuals, (iii) waning vaccine efficacy and vital dynamics, and (iv) long periods of time, *i.e.* long enough to observe several vaccination peaks. For comparison, we conducted a similar analysis for individuals with adaptive behavior. As an extension, we investigated the case where part of the population has an anti-vaccination stance.

Keywords: epidemics, behavior, vaccination, game theory, forward-backward system, backward induction.

Vaccination is one of the most efficient tools humanity possesses to fight epidemics. The collective consequences of vaccination depend on its cost, its effectiveness, and disease dynamics. Many theoretical works have studied optimal vaccination policies (from Hethcote and Waltman (1973) to Laguzet and Turinici (2015a)). When vaccination, as is often the case, is administered on a voluntary basis, a further mechanism comes into play: the interaction between disease dynamics and human behavior – a now widely acknowledged fact (see Funk

et al. (2010, 2015)). On the one hand, disease dynamics has an impact on human behavior through prevalence, individual beliefs about the future course of the epidemic, and spreading of information or beliefs about it. On the other hand, human actions such as vaccination, social distancing, treatment adherence, or even fleeing, influence disease dynamics. Observations of the strong impact of human behavior on disease dynamics include Philipson (1996); Jansen et al. (2003); Riley et al. (2003); Nishiura (2007); Bayham et al. (2015).

It is all the more crucial to investigate human behavior in the case of vaccination decision as vaccination contributes to herd immunity. Yet individual vaccination decisions may not be aligned with social interests: individuals make their decisions out of self-interest while their actions also bear on the whole population. Herd immunity is merely an externality of vaccination decisions, and therefore the result of voluntary vaccination is generally not socially optimal in this respect. Besides, it can be readily understood how in the long run this discrepancy between private and social interests may give rise to recurrent epidemic patterns – low prevalence may lead to low vaccination rates, which in turn may lead to high contagion, higher vaccination rates, and again low prevalence.

Theoretical modeling of vaccination behavior, however, remains a challenge. When faced with a transmittable disease, an individual may decide on a course of action based on his beliefs regarding future developments of the epidemic. That is, each individual may *anticipate* developments to come. Now, if all individuals do this, the very evolution of the epidemic is modified. Ultimately, the spread of a disease can be described as two entangled yet conflicting dynamical systems. The spread of a disease restricted to its biological[1] features evolves *forward* in time: future developments are only determined by the current state of the epidemic. On the other hand, individuals base their vaccination decision at least in part on *backward* reasoning: they act now upon what might happen in the future. The spread of a disease is influenced by individual decisions while in turn influencing these decisions.

In order to solve this problem, several approaches have been proposed. Some authors tackled the problem with a full consideration of the forward-backward dimension described above. Yet these studies, in order to obtain tractable results, had to decrease the complexity of other dimensions. Other authors simplified the dynamics system, at least compared to the model we will present here: Geoffard and Philipson (1996); Chen and Cottrell (2009) studied SI models, and Geoffard and Philipson (1997); Laguzet and Turinici (2015b) studied SIR models without waning vaccine efficacy. Others restricted the scope of their study. Geoffard and Philipson (1996, 1997), for instance, produced a qualitative description of some features of the solution. In the same vein, Chen and Cottrell (2009) investigated equilibrium existence, uniqueness, and potential coexistence of two equilibria in a given setting. Finally, Reluga and Galvani (2011) restricted themselves to the study of steady states.

An alternative stream of literature somehow decreases the complexity of the coupled system by disregarding backward reasoning in human behavior. Bauch et al. (2003); Bauch and Earn (2004) sparked renewed interest in vaccination policy and individual choices with

[1] We describe epidemics as *biological* insofar as they do not depend on human behavior. As will be made clear later, this distinction depends on problem specification: some parameters may or may not be modeled as decision variables. Consider for instance the contact rate between individuals.

one period (*i.e.* static) models. Further instances of one period models were provided by Reeling and Horan (2015); Codeço et al. (2007); Shim et al. (2012). In order to introduce dynamic decision-making in this framework, Bauch (2005) (followed by Reluga et al. (2006); d'Onofrio et al. (2011); Fu et al. (2011); Yang et al. (2016)) proposed models with imitation behavior. Just as the spread of a transmittable disease when individual behavior is ignored, imitation only depends on past and current states of the epidemic: imitation dynamics goes forward in time. This outlook on the problem was also adopted by Fenichel et al. (2011). They assumed that individuals falsely believe that the current epidemiological state will persist (Voinson et al. (2015) added cognitive biases to this framework). Similarly, Buonomo et al. (2008); Epstein et al. (2008); Coelho and Codeço (2009); Funk et al. (2009); Bhattacharyya et al. (2015) all modeled information and/or beliefs with forward dynamics in time.

At this point, we must emphasize that we by no mean argue that real life vaccination decision (or for that matter any other behavior pertaining to the study of epidemics) is only driven by backward reasoning. Nor do we claim that imitation or the past evolution of an epidemic are irrelevant to our case. However, we believe that there is currently a need for modeling the entangled backward and forward dynamics described above in all their complexity with canonical – though somehow unrealistic – perfectly informed, fully rational and far-sighted individuals. Simulation results are to be used as benchmarks to better evaluate the weight of the different factors that can influence decision-making in populations faced with a transmittable disease. This is to be done by measuring how real life data departs from the predictions of the canonical model proposed here.

In the present paper, we address the challenge of coupled forward-backward dynamics posed by canonical modeling of vaccination decision-making. We consider

- a SIVR (Susceptible, Infectious, Vaccinated, Recovered) epidemiological dynamic model with vital dynamics and waning vaccine efficacy, and
- backward reasoning by far-sighted, fully rational, and selfish individuals.

Close to our work are Reluga (2010) and Reluga (2013) in the context of social distancing. The main difference between these studies and ours is that, since we consider waning immunity and vital dynamics with growing population, our set of equations is larger and convergence is more difficult to obtain. Indeed, the proportion of vaccinated individuals is not constrained to always grow in our model, which increases dramatically the array of possible vaccination strategies. We solve this complex system, and we believe that we are the first to obtain recurrent behavioral patterns (in our case, vaccination peaks) with a canonical forward-backward model and full complexity of population dynamics.

We describe our model in Section 1.1. Section 1.2 is dedicated to the results of our model for a Measles-like disease and a vaccine with waning efficacy. Our base case (Section 1.2.1) involves a population of identical individuals. For comparison, we provide results in the case of adaptive behavior (Section 1.2.2). Finally, we investigate populations in which some individuals have an anti-vaccination stance, that is a higher vaccination cost (Section 1.2.3). Section 1.3 concludes.

1.1 Model

We consider a SIR model with vaccination and vital dynamics. Individuals can be either *susceptible* (S), *infected* (I) or *recovered* (R). In addition, susceptible individuals have the possibility to access vaccination on a voluntary basis and become *vaccinated* (V). The disease is transmitted under the assumption of homogeneous mixing of the population. Vaccination has a waning efficacy so that vaccinated individuals can become susceptible after some time. Birth and death rates can differ and hence do not necessarily imply constant population size.

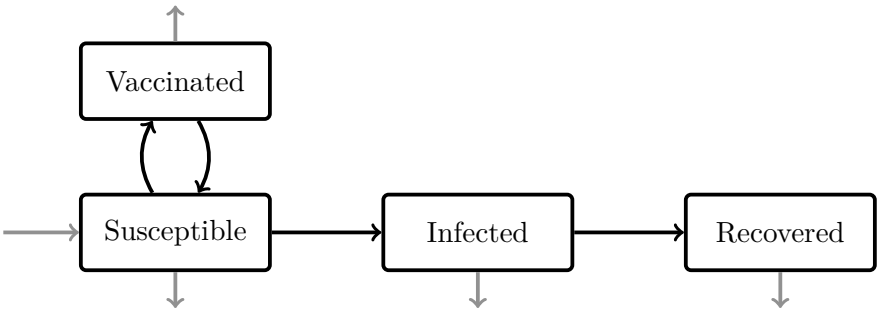


Figure 1.1: Illustration of the SIRV model. *Black:* epidemiological transitions. *Gray:* vital dynamics.

A susceptible individual is assumed to base his decision to vaccinate on a rational far-sighted cost-benefit analysis. Hence, vaccination decision depends on the values the individual expects from being vaccinated and from remaining susceptible, and on the immediate cost (monetary, psychological, logistical, etc.) of vaccination. Formally, the problem of finding an individual's optimal vaccination policy over time can be solved by ways of dynamic programming via Bellman equations. Solving Bellman equations yields the *intertemporal value function* of individuals in each health status. Given his current health status, an individual's value function is the discounted future value he expects to get if he follows his optimal policy. Since we consider waning vaccine efficacy, *both* the value of remaining susceptible *and* the value of getting vaccinated at a given time depend on predictions about future epidemiological states. A vaccinated individual may lose immunity and get the value of being susceptible with non zero probability. To our knowledge, we are the first to solve the canonical forward-backward problem with four value functions, two of them depending on contagion dynamics.

Also, we consider for the sake of realism that individuals cannot vaccinate at any time: in real life, only a fraction of them has access to vaccination simultaneously. This feature is represented by rate α (see Table 1.1) in our model.[2] In contrast to models where vaccine is available at once to the whole population, individuals in our model anticipate that not vaccinating when they have a chance implies waiting until the next opportunity to do so. This, however, does not remove the game theoretic dimension of our problem even though

[2]We performed a sensitivity analysis on α. Dividing α by two does not bear upon short term epidemiological results and vaccination decision. While the epidemic is not affected in the long run, the long term vaccination decision changes noticeably, as shown in Figure B.2.

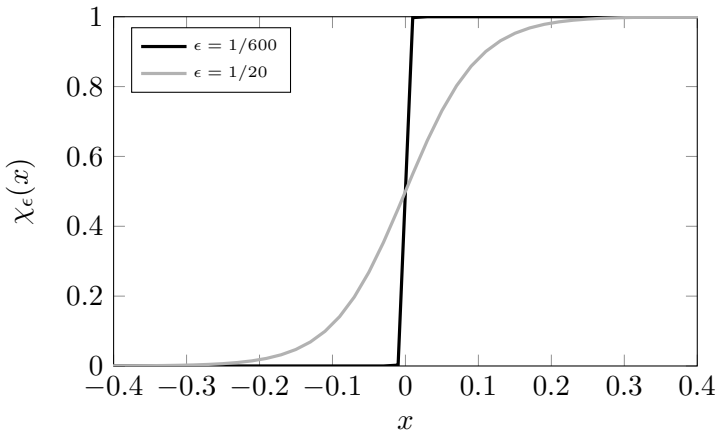


Figure 1.2: χ_ϵ for relevant values of ϵ.

individuals do not play against each other in each instant. We have a sequential game in which Nature randomly picks the playing order in each moment, and allows a maximum αdt zero-measure set of individuals to vaccinate.

For numerical tractability, and yet certainly as a realistic assumption, we use the concept of smoothed best response (Fudenberg and Levine (1998)). When facing a choice between two alternatives leading to intertemporal values V_1 and V_2 respectively, an individual chooses V_1 with probability $\frac{e^{(V_1/\epsilon)}}{e^{(V_1/\epsilon)}+e^{(V_2/\epsilon)}}$, or introducing function $\chi_\epsilon : x \mapsto \frac{1}{1+e^{-x/\epsilon}}$ for all $\epsilon \in \mathcal{R}^+$, he chooses V_1 with probability $\chi_\epsilon(V_1 - V_2)$.[3] In Figure 1.2, we show function χ_ϵ for the different values of ϵ used in our simulations.[4] Notice that as ϵ tends to 0, the probability of playing any strategy that is not a best response goes to 0.

For a given ϵ, the epidemiological side – strictly speaking – of our model is governed by Equations 1.1a–1.1d. T is the final time, $s^\epsilon(t)$ (resp. $i^\epsilon(t)$, $v^\epsilon(t)$, $r^\epsilon(t)$) denotes the number of susceptible (resp. infected, vaccinated, recovered) individuals at time t in $[0, T]$. For concision, we introduced $n^\epsilon(t) = s^\epsilon(t) + i^\epsilon(t) + v^\epsilon(t) + r^\epsilon(t)$ and function $\xi_\epsilon : x \mapsto x\chi_\epsilon(x)$ for x in $\mathbb{R}$. The individual decision process is described by Equations 1.2a–1.2d, where $V_S^\epsilon(t)$ (resp. $V_I^\epsilon(t)$, $V_V^\epsilon(t)$, $V_R^\epsilon(t)$) is the value function of a susceptible (resp. infected, vaccinated, recovered) individual at time t in $[0, T]$.

[3]The same approach was used by Xu and Cressman (2014, 2016) with individuals making decisions based only on the present state of the epidemiology.

[4] We used two different ϵ values so as to ease equation solving for some of our simulations. This, however, is of little consequence as to our results. Consider for instance the difference in utility between being sick and being healthy for the average duration of the infectious period (see Table 1.1 for parameter values). This difference in utility is $5 \times (10 - 2) = 40$ on average, ignoring the discount factor for this short period. It can readily be made sure that $\chi_{1/20}(40)$ and $\chi_{1/600}(40)$ are both close enough to 1 for our purpose. χ between 0 and 1 will denote indifference in our model.

$$\frac{d}{dt}s^\epsilon(t) = -\, s^\epsilon(t)\left[\alpha\chi_\epsilon(V_V^\epsilon(t) - V_S^\epsilon(t) - c) + \lambda\frac{i^\epsilon(t)}{n^\epsilon(t)} + \mu\right] + \nu n^\epsilon(t) + \gamma_V v^\epsilon(t) \tag{1.1a}$$

$$\frac{d}{dt}i^\epsilon(t) = -\, i^\epsilon(t)\left(\gamma_I - \lambda\frac{s^\epsilon(t)}{n^\epsilon(t)} + \mu\right) \tag{1.1b}$$

$$\frac{d}{dt}v^\epsilon(t) = -\, v^\epsilon(t)(\gamma_V + \mu) + \alpha s^\epsilon(t)\chi_\epsilon(V_V^\epsilon(t) - V_S^\epsilon(t) - c) \tag{1.1c}$$

$$\frac{d}{dt}r^\epsilon(t) = -\, r^\epsilon(t)\mu + \gamma_I i^\epsilon(t) \tag{1.1d}$$

$$-\frac{d}{dt}V_S^\epsilon(t) = u_g - (\delta+\mu)V_S^\epsilon(t) + \lambda\frac{i^\epsilon(t)}{n^\epsilon(t)}(V_I^\epsilon(t) - V_S^\epsilon(t)) + \alpha\xi_\epsilon(V_V^\epsilon(t) - V_S^\epsilon(t) - c) \tag{1.2a}$$

$$-\frac{d}{dt}V_I^\epsilon(t) = u_b - (\delta+\mu)V_I^\epsilon(t) + \gamma_I(V_R^\epsilon(t) - V_I^\epsilon(t)) \tag{1.2b}$$

$$-\frac{d}{dt}V_V^\epsilon(t) = u_g - (\delta+\mu)V_V^\epsilon(t) + \gamma_V(V_S^\epsilon(t) - V_V^\epsilon(t)) \tag{1.2c}$$

$$-\frac{d}{dt}V_R^\epsilon(t) = u_g - (\delta+\mu)V_R^\epsilon(t) \tag{1.2d}$$

A detailed description of the parameters is given in Table 1.1. The construction of Equations 1.1a–1.2d is made explicit by the alternative formulation in Appendix A.1.

Equations 1.1b and 1.1d are the same as in usual SIR models. We assume that the death rate μ is the same for healthy and infected individuals. Infected individuals are recovering at rate γ_I. Equation 1.1a too, is very similar to the equation describing the susceptible population in a SIR model: each day, a susceptible individual has an average λ encounters in which he could potentially get infected. A proportion $i(t)/n(t)$ of these encounters occur with an infected individual. Also, individuals are born susceptible at rate ν. Our model departs from SIR models in that susceptible individuals decide whether or not to vaccinate based on a cost-benefit analysis. At time t, the higher the net value to vaccinate $V_V^\epsilon(t) - V_S^\epsilon(t) - c$, the closer to 1 the probability of deciding to vaccinate given by function χ_ϵ.

Let us now elaborate on Equations 1.2a–1.2d satisfied by the value functions. Again, an alternative formulation of these equations is provided in Appendix A.1 for the interested reader. u_g and u_b are the instantaneous utilities of being in good and bad health respectively. Individuals are forward-looking, hence the value functions decrease at rate u_g or u_b (depending on the considered health status) with time. δ is the time discount factor and we normalize the value of being dead to 0, so all value functions increase at rate $(\delta+\mu)$. That is the value of being say, susceptible, at time t decreases by $(\delta+\mu)\times(0 - V_S(t))$. Similarly, the value of being in a given health status decreases by the net value of each health status transition weighted by the rate of this transition.

Existence and uniqueness of a solution to Equations 1.1a–1.2d follow from Theorem 1.[5]

Theorem 1
The system of Equations 1.1a–1.2d has a unique solution for any $\epsilon > 0$.

Proof. See Appendix A.2.

1.2 Results

1.2.1 Base case: population of identical individuals

Base parameter values are summarized in Table 1.1. We use parameter values that are characteristic of Measles. Measles is a widely studied disease whose epidemiological features allow for rich modeling in our framework. Also, Measles vaccine is offered on a voluntary basis, and has recently been in the spotlight due to alleged side effects deterring part of the population from vaccinating. We model a vaccine that is efficient for 10 years on average and costs 10.[6] Vital dynamics is characteristic of a developing country.[7]

Our base case features a perfectly mixed population of identical individuals. That is, all individuals have the same vulnerability to the disease and rate of recovery, have the same preference for being healthy over being sick, and face the same vaccination cost.

Equations 1.1a–1.2d are solved numerically using techniques close to fixed-point iterations.[8] We set initial conditions for Equations 1.1a–1.1d, and final conditions for Equations 1.2a–1.2d. Notice that from Equation 1.2d,

$$V_R^\epsilon(t) = \left(V_R^\epsilon(T) - \frac{u_g}{\delta+\mu}\right) e^{-(\delta+\mu)(T-t)} + \frac{u_g}{\delta+\mu}, \tag{1.3}$$

and then V_I^ϵ (Equation 1.2b), can be solved analytically. In our model, recovered individuals stay recovered for the rest of their life, and u_g, δ and μ do not depend on time, so V_R^ϵ does not depend on time. Consequently, V_I^ϵ does not depend on time either, and we can set both V_R^ϵ and V_I^ϵ to their respective steady state values. We then use the steady state values of V_R^ϵ and V_I^ϵ to set the final value of V_S^ϵ and V_V^ϵ.[9] For all simulations, we make sure that final time T is large enough so that the influence of final conditions on the result is null.[10]

[5] Notice that in a related study, Chen and Cottrell (2009) found possible multiple equilibria. This is due to the way they modeled imperfect vaccine efficacy, and in particular to the independence of vaccine failure at each encounter. Indeed, in their study, when vaccine efficacy is low, a high prevalence implies a high infection probability at each encounter and hence an incentive not to vaccinate balancing the incentive to vaccinate.

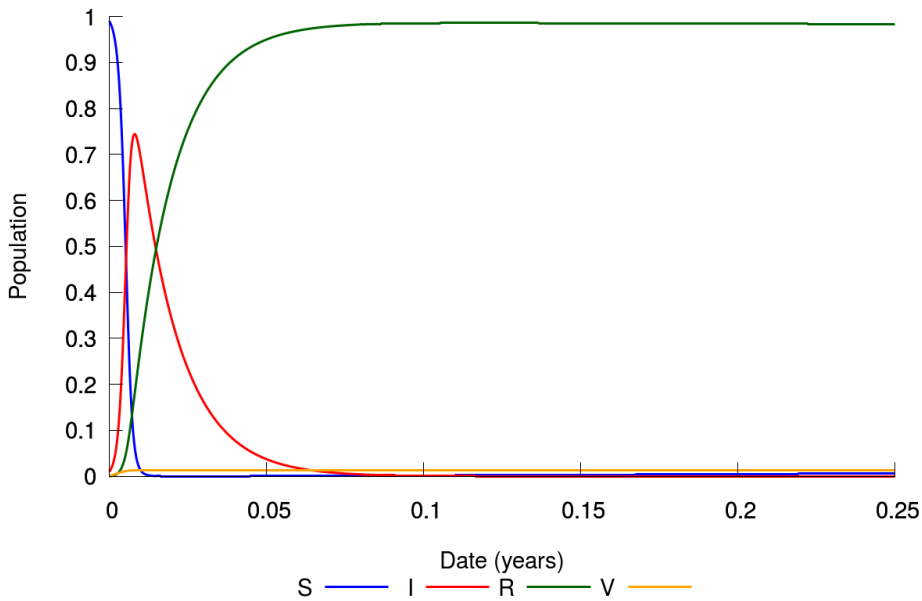
[6] This cost represents 1/4 of the cost of being sick on average, disregarding epidemiological changes after infection (see calculation in Footnote 4).

[7] All parameter values are only illustrative and do not reflect any specific real life case. A ±10% sensitivity analysis on all parameters is shown in Figure B.3.

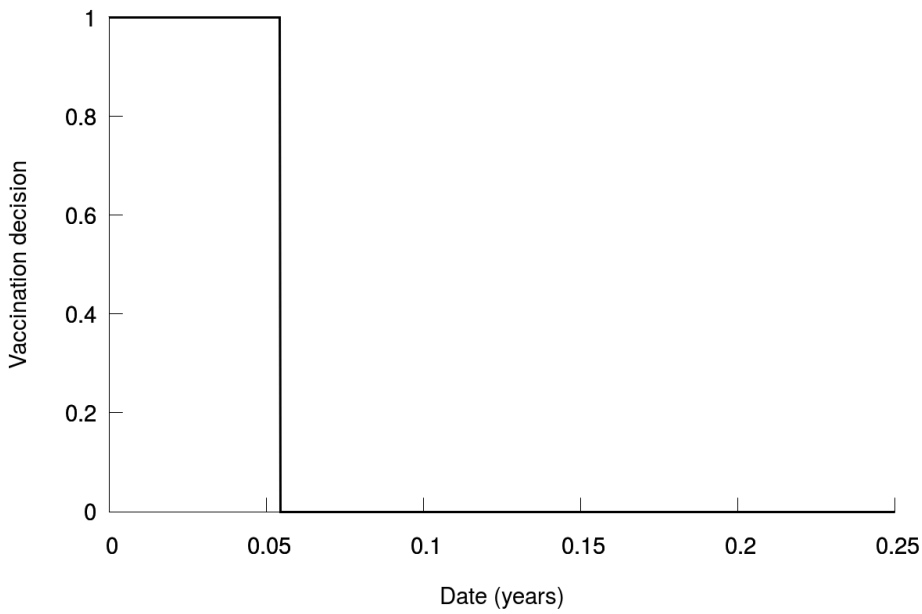
[8] Rather than shooting techniques, as is done in Reluga (2010). Source code is available on request.

[9] We know that the value of being vaccinated V_V^ϵ and the value of being susceptible V_S^ϵ are both higher than the value of being infectious V_I^ϵ, but lower than the value of having recovered V_R^ϵ. In practice, the final value of V_S^ϵ and V_V^ϵ is set to V_I^ϵ or $(V_I^\epsilon + V_R^\epsilon)/2$ depending on the simulation, with no consequence as for the results presented here.

[10] Typically, T is taken larger than 350 years.

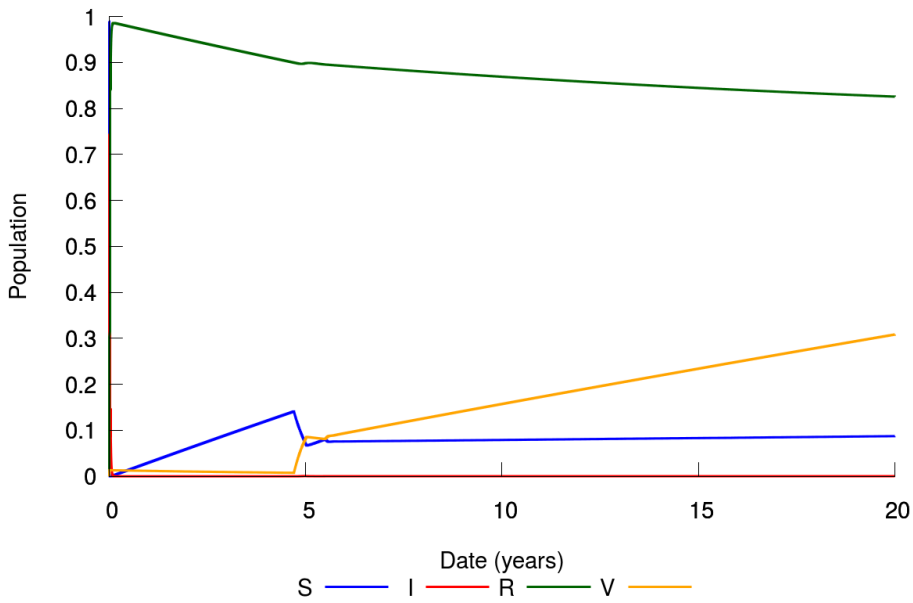


(a) Epidemiology

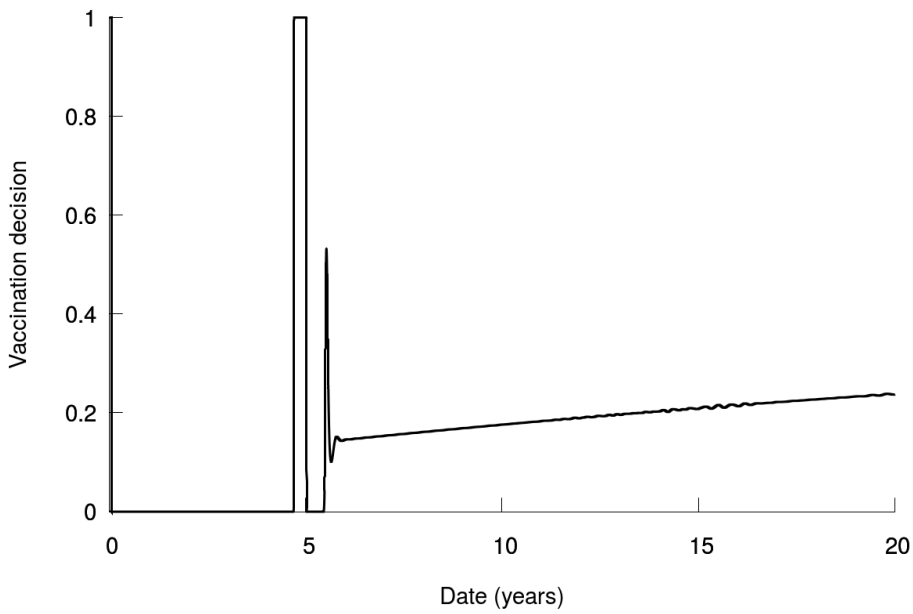


(b) Vaccination decision

Figure 1.3: Epidemiological results and vaccination decision ($\chi_\epsilon(V_V^\epsilon(t) - V_S^\epsilon(t) - c)$) over the first quarter of the epidemic, with $\epsilon = 1/600$ and $n^\epsilon(0) = 1$.



(a) Epidemiology



(b) Vaccination decision

Figure 1.4: Epidemiological results and vaccination decision ($\chi_\epsilon(V_V^\epsilon(t) - V_S^\epsilon(t) - c)$) over the first 20 years of the epidemic, with $\epsilon = 1/600$ and $n^\epsilon(0) = 1$.

Notation	Value	Description
Epidemiology		
λ	2.8	Contact rate.
α	0.0068	Potential vaccination rate.
γ_V	2.74×10^{-4}	Vaccination efficacy waning rate.
γ_I	0.2	Rate of recovery.
Decision-making		
u_g	10	Instantaneous utility to be in good health.
u_b	2	Instantaneous utility to be in bad health.
δ	8.1×10^{-5}	Time discount rate.
c	10	Cost of vaccination.
Vital dynamics		
μ	5.48×10^{-5}	Death rate.
ν	8.22×10^{-5}	Birth rate.
Initial state		
$s^\epsilon(0)$	$0.99 \times n^\epsilon(0)$	Initial number of susceptible individuals.
$i^\epsilon(0)$	$0.01 \times n^\epsilon(0)$	Initial number of infectious individuals.
$v^\epsilon(0)$	0	Initial number of vaccinated individuals.
$r^\epsilon(0)$	0	Initial number of recovered individuals.

Table 1.1: Parameter values. Time unit is day, utility and cost are dimensionless.

In Figures 1.3–1.4, we show the output of our model (Equations 1.1a–1.2d) for $\epsilon = 1/600$ over the first quarter and over the first 20 years of the epidemic.[11] In the first days of the outbreak, individuals anticipate that the prevalence of the disease will be high and hence vaccinate. At epidemic peak, more than 70% of the population is infectious and all individuals that have access to vaccination vaccinate. After that, as the pool of susceptible individuals decreases, the disease prevalence drops, and when it is low enough (and anticipated to remain so for a long time), individuals stop vaccinating. Because of vital dynamics and waning vaccination efficacy, the pool of susceptible individuals grows again and a second wave of vaccination is observed about five years after the introduction of the disease. Vaccination dynamics is then strongly damped and has an increasing frequency over time. A state is finally reached where a portion of the individuals that have access to the vaccine vaccinate at all time.

1.2.2 Individuals with adaptive behavior

So as to draw a parallel with the existing literature, we model the same disease as in Section 1.2.1 in the case where individuals adopt an adaptive behavior. Individuals with adaptive behavior do not anticipate the evolution of the epidemic at an aggregate level, even though they do anticipate the evolution of their own health status. Susceptible individuals with adaptive behavior, for instance, anticipate the loss of utility corresponding to being sick for about 5 days – the average length of infection, but mistakenly expect disease prevalence to remain unchanged in the future. Hence, in this model, value functions are stationary and

[11] Results for $\epsilon = 1/20$ are provided in Appendix B.

solutions to Equations 1.2a–1.2d under $\frac{d}{dt}V_S^\epsilon(t) = \frac{d}{dt}V_I^\epsilon(t) = \frac{d}{dt}V_V^\epsilon(t) = \frac{d}{dt}V_R^\epsilon(t) = 0$ *at any time* t.[12] The system dynamics only goes forward in time.

In Figures 1.5–1.6 we display results for a population of individuals with adaptive behavior over the first 20 years and the first quarter of the epidemic, and for $\epsilon = 1/600$.[13] The first peak of vaccination lasts more that twice longer for adaptive individuals since they do not anticipate the very low prevalence to come for the following 5 years. Still, in the case of our Measles-like disease, this difference in vaccination decisions yields qualitatively almost no difference in prevalence for the first quarter of the epidemic. Indeed, the speed of contagion is so fast that when decisions differ, almost all individuals, whether far-sighted or with adaptive behavior, have already been infected.

In the long run, the vaccination dynamics of adaptive individuals is very different from that of far-sighted individuals. While after the sixth year a portion of the latter vaccinates at all times, the former have a more polarized vaccination behavior. Either all adaptive individuals or none of them want to vaccinate. Adaptive individual vaccination peaks occur with increasing frequency. Anticipation of future epidemiological states by far-sighted individuals flattens vaccination decisions.

While we are not making policy recommendations in the present article, we can expect the selected modeling approach to have policy implications. In the case shown here, for instance, a model with adaptive agents would predict that the demand for vaccination never settles, when our model with rational expectation would predict that with time, individuals become close to indifferent to vaccination.

1.2.3 Populations with different costs to vaccinate

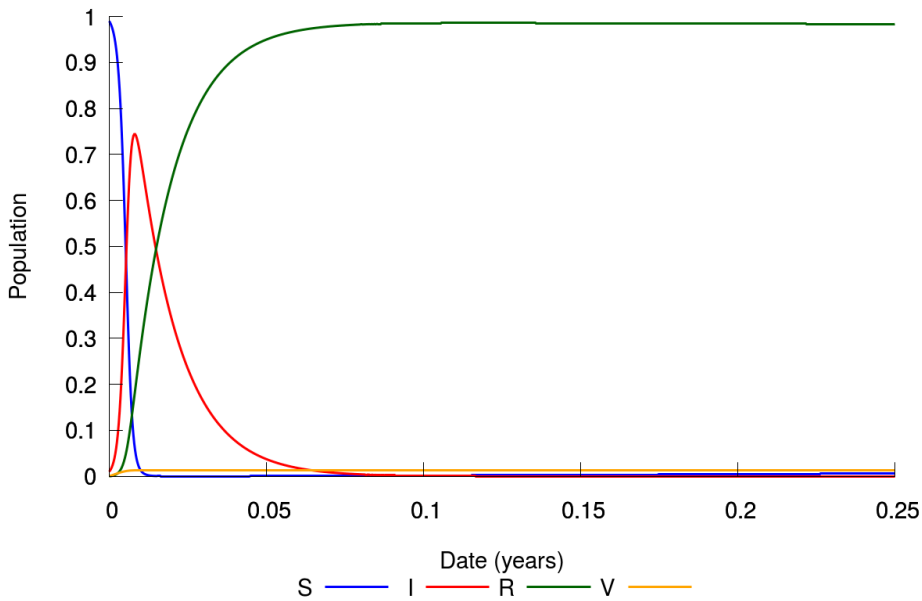
The population we have been modeling so far was made of identical individuals. Preferences, notably, were the same for all individuals. Yet we expect real life individuals to have differentiated preferences. Besides, as we are considering far-sighted individuals who need to anticipate the future of the epidemic, we need to take into account the fact that an individual's decision may be influenced by his knowledge of others' preferences and hence others' influence on future epidemiological states.

In this section, we model two populations – still homogeneously mixed – only differing in their attitude toward vaccination. Different attitudes toward vaccination are modeled by different costs to vaccinate. *Population 0* has the same vaccination cost $c = 10$ as the population modeled to this point (Sections 1.2.1–1.2.2). *Population 1* has a more anti-vaccination stance and a cost to vaccinate $c = 12$.[14] Obviously, the vaccination behavior of individuals in Population 1 is different from that of individuals in Population 0. This disparity influences the course of the epidemic, which is anticipated by individuals in Population 0, in turn modifying their behavior compared to the case where they were the only individuals in

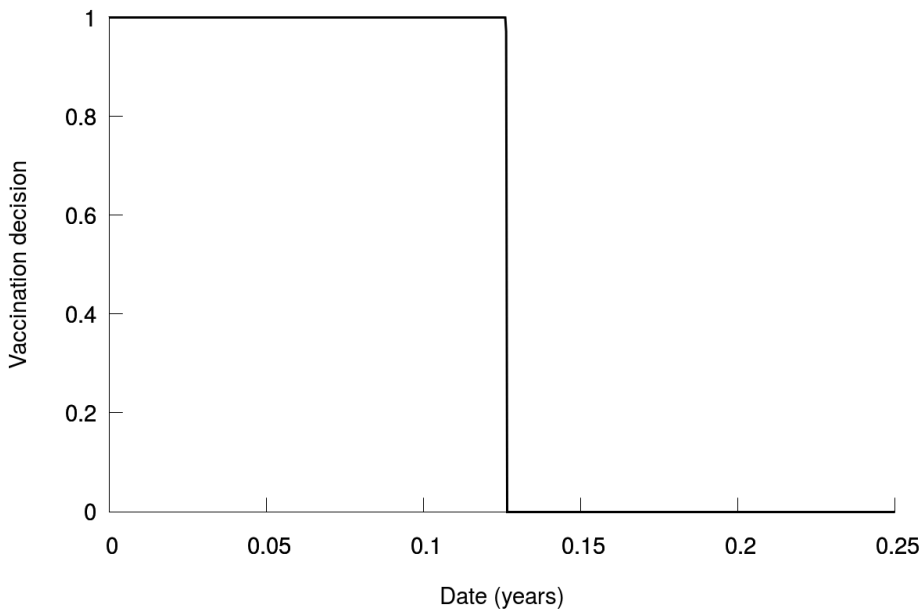
[12] That is, the value functions do depend on time. Numerically, we solve this system for each date, subject to the current state of the epidemic.

[13] In Figure B.4 in Appendix, we show the same results for $\epsilon = 1/20$.

[14] This difference can be accounted for by ideology but it can also be interpreted more materialistically: individuals may face different insurance policies, more expensive access to medical services, etc.

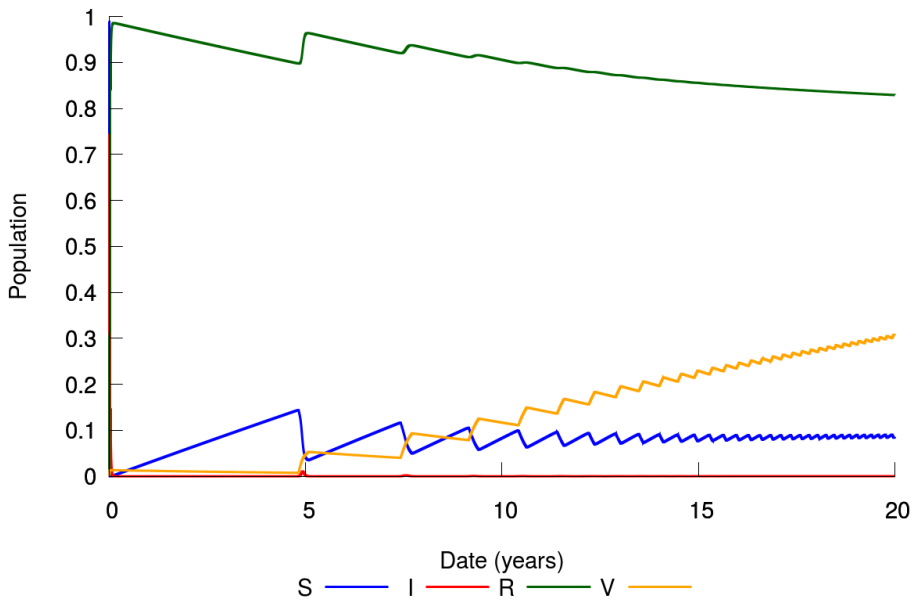


(a) Epidemiology

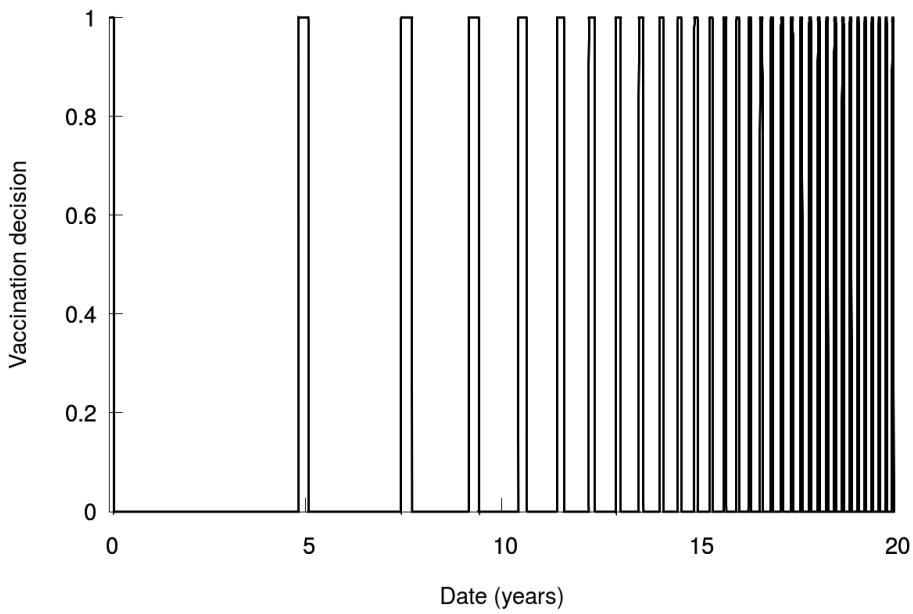


(b) Vaccination decision

Figure 1.5: Epidemiological results and vaccination decisions over the first quarter of the epidemic, with $\epsilon = 1/600$ and $n^{\epsilon}(0) = 1$ – Individuals with adaptive behavior.



(a) Epidemiology



(b) Vaccination decision

Figure 1.6: Epidemiological results and vaccination decisions over the first 20 years of the epidemic, with $\epsilon = 1/600$ and $n^{\epsilon}(0) = 1$ – Individuals with adaptive behavior.

the population. Similarly, individuals in Population 1 anticipate decisions made by individuals in Population 0.

We investigate the effects of vaccination cost heterogeneity by varying the proportion of the whole population belonging to Population 1 between 0% (all individuals are in Population 0[15]), and 100% (all individuals are in Population 1). In each simulation, 1% of Population 0 and 1% of Population 1 is initially infected.

Results are displayed in Figures 1.7–1.8.[16] Individuals in Population 0 vaccinate more that individuals in Population 1. Indeed, the former have a lower cost to vaccinate than the latter and yet face the same disease prevalence at all times.

Individuals in each population tend to vaccinate more as the ratio of individuals in Population 1 increases. Indeed, more individuals in Population 1 implies a lower overall vaccination rate. Because higher prevalence is then anticipated by all individuals, more people vaccinate in each population. This reasoning fails at some points in time since the whole dynamics of the epidemic is modified by the change in vaccination policy of both populations. Indeed, a change in vaccination policy may influence the waveform of the disease dynamics and hence the lack of coherence between both cases may imply shifted local maxima and local minima of vaccination decisions.

1.3 Conclusion

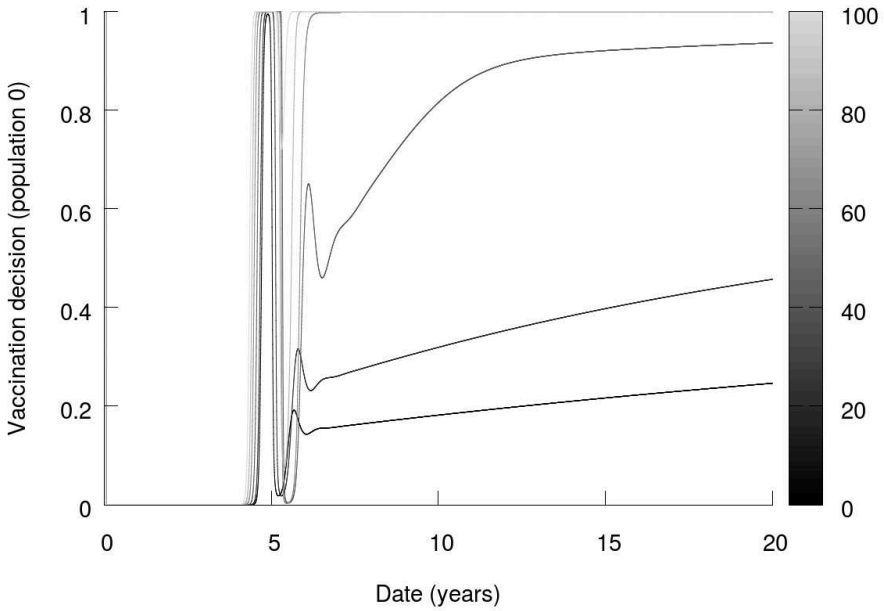
Investigating the interplay between the strictly speaking *biological* dynamics of an epidemic, and individual vaccination *decision-making*, is certainly critical to the design of operational health policies. In this line, there is a need for an appropriate benchmark. We claim that this benchmark is to be provided by the behavior of canonical fully rational and far-sighted individuals. The resulting forward-backward system of equations, however, is difficult to solve: it is computationally challenging to obtain the functional fixed-point of the system. The problem is even harder to solve over long time horizon, with vital dynamics, and with waning vaccine efficacy – in this case several vaccination peaks arise, which increases dramatically the complexity of decision-making. It is even more challenging when we consider individuals with different preference types.

In this study, we exposed the evolution of such an epidemiological system taking into account (i) the forward dynamics of an epidemic, and (ii) the backward individual decision-making process. We simulated a Measles-like outbreak in this setting. We obtained several vaccination peaks in the long run due to vital dynamics and waning vaccine efficacy. We compared the results of our canonical candidate benchmark with those of another possible benchmark found in the literature: adaptive vaccination decision-making. As a first extension of our model, we also modeled heterogeneous preferences in the simple case where two populations with a different stance toward vaccination coexist. Once adapted for more complex

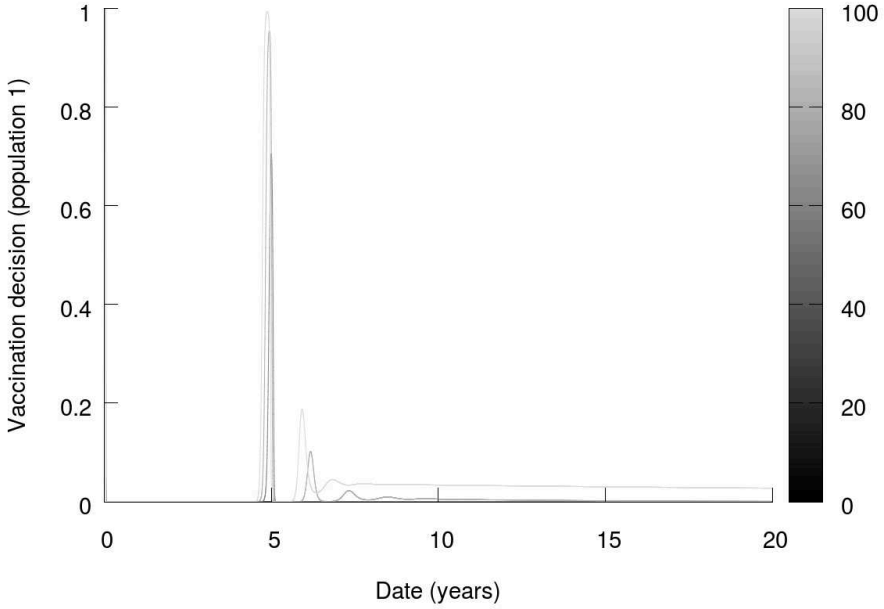
[15] This corresponds in fact to the base case presented in Section 1.2.1.

[16] Figures C.4–C.5 in Appendix show more details. Figures C.2–C.3 and Figures C.6–C.7 in Appendix display the same results for vaccination cost in Population 1 of $c = 11$ and $c = 15$ respectively.

epidemic models, we believe that our approach will be able to produce benchmark results for real life epidemics in cases where vaccination is offered on a voluntary basis.

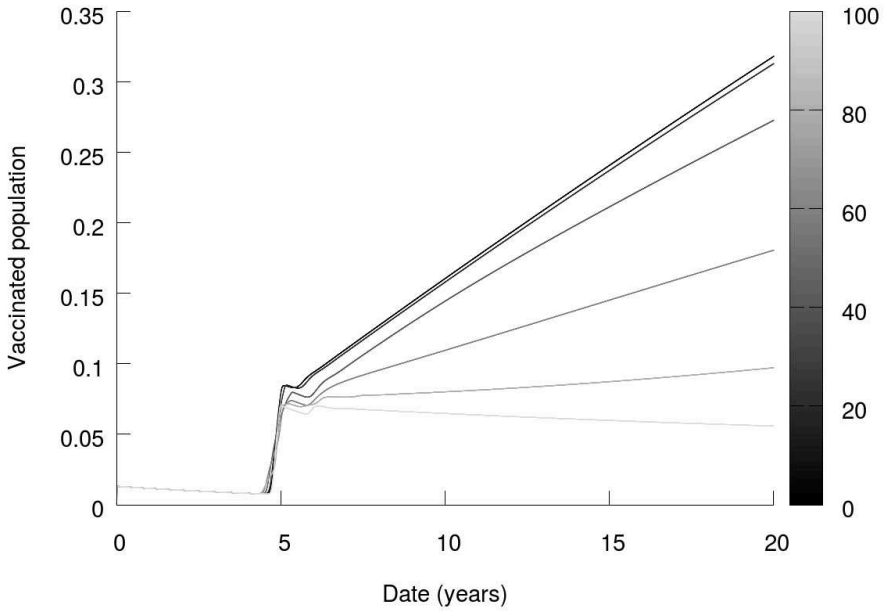


(a) Population 0

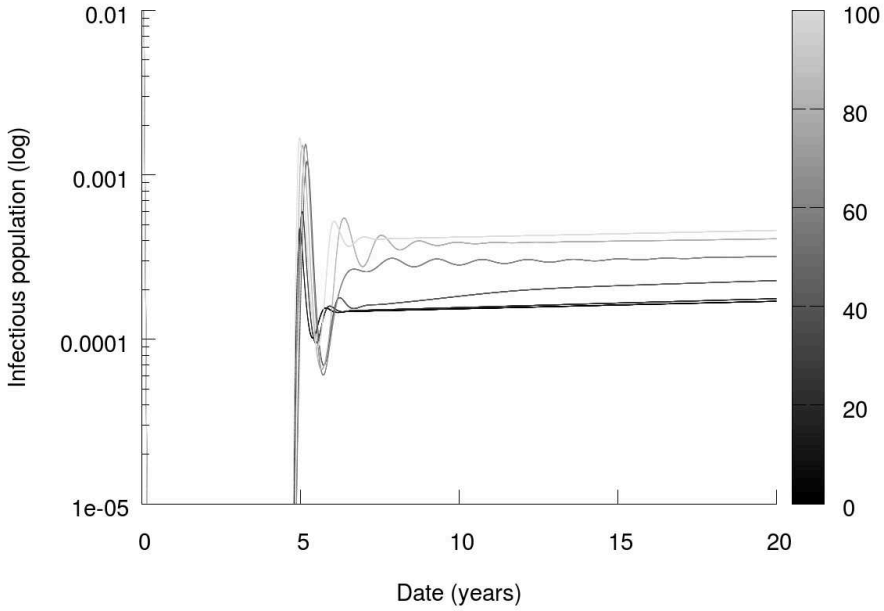


(b) Population 1

Figure 1.7: Vaccination decisions for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 12$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.



(a) Total number of vaccinated individuals in both populations



(b) Total Number of infectious individuals in both populations

Figure 1.8: Epidemiological results for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 12$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.

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Chapter 2

Cost-effectiveness analysis revisited: The case of Measles mandatory vaccination

This chapter is based on an article coauthored with N. Houy and P. Michel.

Abstract

Individuals may respond to an epidemic by engaging in preventive behaviors that, in turn, influence the course of the epidemic. We argue that such feedback loops need to be considered in the cost-effectiveness evaluations of public health policies. We elaborate on the example of mandatory Measles vaccination. Our framework is a SIR compartmental model. Before vaccination becomes mandatory, parents decide altruistically and freely whether to vaccinate their children. We model anti-vaccinationist and vaccinationist parents. We provide numerical evidence suggesting that individual anticipatory behavior may lead to a transitional increase in Measles prevalence before steady state eradication. This would cause non negligible welfare transfers between generations. Ironically, in our scenario, anti-vaccinationists are among those who benefit the most from mandatory vaccination.

Keywords: cost-effectiveness analysis, mandatory vaccination, Measles, MMR, behavior.

In economic evaluations of disease control policies, costs are usually weighted against the number of averted cases and other possible benefits. Costs and benefits may be expressed as money, or in terms of well-being. They may be direct or indirect. Tools were developed to reckon, measure, and add up a wide range of – sometimes subjective – aspects of a disease, from physical and psychological pain to the monetary cost of missing work (Weinstein et al., 2009; Sassi, 2006). Even though it is debated (Holmes, 2013; Evans and Pagani, 2014; Beresniak and Dupont, 2016), cost-effectiveness analysis is now a routine procedure in public health (see Drummond et al. (2015) for a comprehensive textbook on the subject).

What modern economic evaluation methods have yet in common, is their limited account of individual responses to the *outcomes* of a public health policy. Some studies look *retrospectively* upon individual behaviors insofar as they were directly affected by a policy (see

Walker (2003); Lorenc et al. (2011) for instance). Other authors, like DePasse et al. (2017), attempt to *anticipate* the effects of individual responses to policies but individual decisions are either random or assumed in their models. Besides, they too focus on responses to the *direct* effects of a policy, and not on responses to *indirect* incentive changes implied by this policy. As a rule, in cost-effectiveness analyses, individual behavioral responses to incentive changes are overlooked *a priori*.[1]

We see two reasons explaining why such individual behaviors are not considered in cost-effectiveness analyses before policy implementation. First, we think that they may be implicitly deemed second order effects without further consideration. Second, considering feedback loops between individual behaviors and epidemics can be a complex task, especially when it comes to *forward looking* behaviors influencing the future spread of the disease. Let us elaborate on those two explanations.

It might be argued that individual behavior is not always relevant to disease control. Some real life examples might even be brought up. However, this does not imply that behaviors should be disregarded in all cases. Measles is a typical example of a disease whose spread hinges essentially, at least in *developed countries*, on individual behaviors. This has been dramatically illustrated by the MMR vaccine controversy (McIntyre and Leask, 2008). Measles is a highly contagious infectious disease with potentially severe complications – around one out of five cases in the United States requires hospitalization (Orenstein et al., 2004; Centers for Disease Control and Prevention, 2015). Because it displays a very high reproduction number (12 to 18, see Guerra et al. (2017)), high levels of immunization (90 to 95%, see Nokes and Anderson (1988)) are necessary to reach herd immunity. An effective vaccine against Measles has been available in developed countries since the 1960's and has been included in routine immunization programs since the 1980's. Besides, in some countries such as France and the United Kingdom, vaccination expenses are covered by the state or health insurances. Yet, despite the apparent incentives to vaccinate and low vaccination costs, a fraction of the population still refuses vaccination. While Measles is not endemic in developed countries,[2] this unvaccinated subpopulation allows for sporadic epidemics whenever the virus is brought from endemic regions of the world (World Health Organization, 2017). Examples of such epidemics include the 2014–2015 California outbreak (Clemmons et al., 2015; Halsey and Salmon, 2015) and more recently, the 2018 epidemics in Ireland, Italy (WHO Europe, 2018), and southwestern France (Santé Publique France, 2018). The first objective of this paper is to illustrate how individual behaviors can substantially influence disease dynamics, and show that they can be relevant to economic evaluation. Our study may convince public health professionals that individual behaviors, and specifically the feedback loop between prevalence, public policies, and individual decision-making, cannot be disregarded in many economic evaluations. It must be noted that this work is not an application of well-established economic evaluation

[1] Some authors have discussed such individual responses, yet not as part of cost-effectiveness analyses. See Ahituv et al. (1996) and Geoffard and Philipson (1996) for instance.

[2] The situation may however vary within a developed country. In 2016 in the United States, for instance, the MMR coverage among uninsured children aged 19–35 months was as low as 77.3%. Vaccination coverage may also differ from one minority to another. See Hill et al. (2017).

methods. Rather, we use mathematical modeling and numerical simulation to look into some of the foundations of these methods.

Let us now turn to the complexity argument for overlooking individual behavior in economic evaluations – the technical difficulty of analyzing the feedback loop between individual behaviors and disease dynamics. Arguably, individuals accept or refuse vaccination because it is in their interest to do so. That is, they vaccinate if the risk of getting infected outweighs their vaccination cost. This cost encompasses vaccination expenses, but also medical visit inconvenience, fear of needles, going against one's own religious beliefs, or fearing side effects (see Kata (2010) for a review of anti-vaccination arguments). As for the risk of getting infected, it depends on the number of infectious individuals, which in turn depends on how many people got vaccinated in the past, and will in the future. Hence the technical difficulty of modeling situations where individuals make decisions by anticipating the *future* disease dynamics, this dynamics depending itself on *past* and *present* decisions. In order to circumvent these difficulties, some authors have considered only backward-looking behaviors like memory- (Bhattacharyya et al., 2015) or imitation- (Reluga et al., 2006; Fenichel et al., 2011; Poletti et al., 2012; Voinson et al., 2015) driven behaviors, or behaviors depending on the current epidemiological situation only (Xu and Cressman, 2016).[3] In the present study, we use the canonical model described in Flaig et al. (2018) in order to tackle the full complexity of the case. The second objective of this paper is to provide public health professionals with computational tools allowing them to include individual behaviors in economic evaluations.

In order to meet both of our objectives – showing that individual behaviors can have a first order impact in cost-effectiveness analyses, and providing tools to overcome the technical complexity of taking these behaviors into account – we study the example of Measles vaccination in France, were MMR vaccination was made mandatory for all children born after January 1st 2018. We use numerical simulations to show that individual anticipatory behaviors may give rise to substantial generational effects – about six times larger than the effects a traditional cost-effectiveness analysis would highlight. Also, counter-intuitively and ironically enough, we show that anti-vaccinationists may be among those who benefit the most from mandatory vaccination.

Our model is presented in Section 2.1. Simulation results are analyzed in Section 2.2. First, we show the effect of anticipatory behaviors on the dynamics of Measles (Section 2.2.1). Then, we compare the welfare of the different generations and subpopulations (Section 2.2.2). Section 2.3 concludes.

2.1 Model

2.1.1 Epidemiological assumptions

We describe Measles dynamics with a SIR compartmental model with homogeneous mixing. Individuals are born *Susceptible*. Following infection, individuals remain *Infectious* for five

[3]See Flaig et al. (2018) for more references on behavior modeling in epidemiology.

days on average.[4] Then, they *Recover* and stay immunized for the rest of their lives. Birth and death rates are low and equal, which is characteristic of developed countries. We overlook passive immunity through maternal antibodies. While most infants are born immune to Measles, they usually become susceptible several months before scheduled vaccination. Also, studies have found that children lose immunity earlier where Measles is not endemic. For a recent review of this topic, see Guerra et al. (2018).

Real life vaccination schedules vary depending on the vaccine and from one country to another (World Health Organization, 2017). We model a MMR-like vaccine, with a simplified vaccination schedule. We assume that children have access to vaccination when they are 14 months (420 days) old. Hence, two age categories are relevant for our study: younger and older than 14 months. Vaccination is only offered as part of routine vaccination schedules, and has an efficacy of 97% (Centers for Disease Control and Prevention, 2015). Figure 2.1 sums up the epidemiological assumptions.

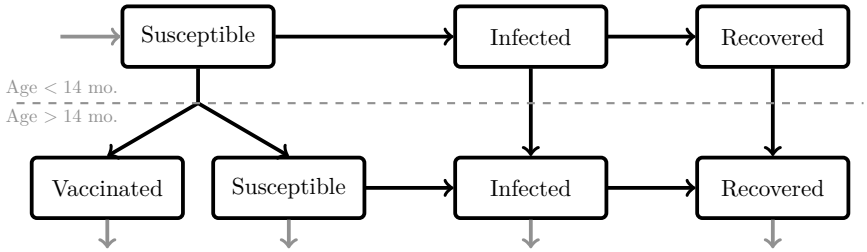


Figure 2.1: Compartmental model for Measles with vaccination. Gray arrows: births and deaths.

2.1.2 Behavioral assumptions

Being healthy brings utility, while being sick has a relative cost. For the sake of simplicity, the total cost of being sick is paid immediately upon infection. This simplifying assumption is made possible by the short duration of the symptoms, and the low discount rate value of 3% annually. Costs and utilities are in QALDs (1 QALD is 1/365 QALY). Sick individuals incur a total cost of 7 QALDs (Thorrington et al., 2014). This figure includes symptoms, time off school or work, hospitalization, and missed days of work by parents of sick children.[5] Vaccination has a cost too (monetary, logistical, ideological, etc.) that must be paid when vaccination is voluntary, but also when it is mandatory. We use this cost to model two types of individuals: *anti-vaccinationists* and *vaccinationists*. In our model, the former are simply assumed to have a higher vaccination cost than the latter. We call "vaccinationists" individuals that are not anti-vaccinationists for the sake of concision. When vaccination is voluntary, individuals (at 14 months of age) freely choose whether they want to get vaccinated based on a personal intertemporal and far-sighted cost-benefit analysis. When vaccination is mandatory, all susceptible 14 month old children get vaccinated.

[4] Infected individuals are infectious four days before rash onset (Centers for Disease Control and Prevention, 2015). Our assumption is that sick individuals are (self-)quarantined after five days of positive infectiousness.

[5] Notice here that individuals consider their private costs, and not a social cost of being sick.

Here we assume that individuals decide for themselves even though they are 14 months old. This assumption is equivalent to considering perfectly altruistic parents making the decision of having their child vaccinated considering his best interest (Ramsey, 1928). This assumption seems to be in line with observations in the case of MMR vaccination decision-making (Brown et al., 2010).

Timing is as follow: before time 0, individuals believe that voluntary vaccination will last forever and they behave accordingly. We start our simulations at time 0 with the epidemic steady state corresponding to this behavior. At time 0, authorities announce that vaccination will be made mandatory at time $t_{\mathrm{mv}} > 0$. Hence, between time 0 and t_{mv}, vaccination is still voluntary but individuals can anticipate the future effects of mandatory vaccination.

2.1.3 Equations

For all time t between 0 and final time T, the population in each health status is governed by equations (2.1)–(2.7). $s_{a,j}$ (resp. $i_{a,j}$, $r_{a,j}$, $v_{a,j}$) is the susceptible (resp. infected, recovered, vaccinated) population

- in age class $a \in \{\mathrm{y}, \mathrm{o}\}$: younger or older than 14 months,
- of type $j \in \{\mathrm{v}, \mathrm{av}\}$: vaccinationist or anti-vaccinationist.

Equation 2.8 is the Bellman equation governing the value $V_{\mathrm{S}}^{\mathrm{o}}$ of being susceptible *and* older than 14 months, that is the value of having missed or not seized the chance to receive the vaccine.

$$\frac{d}{dt}s_{\mathrm{y},j}(t) = \alpha_j \nu n_{\mathrm{o}}(t) - \left(\frac{1}{l} + \lambda\frac{i(t)}{n(t)}\right) s_{\mathrm{y},j}(t) \tag{2.1}$$

$$\frac{d}{dt}s_{\mathrm{o},j}(t) = \frac{1}{l}\left(1 - \theta\Lambda_j(t)\right) s_{\mathrm{y},j}(t) - \left(\mu + \lambda\frac{i(t)}{n(t)}\right) s_{\mathrm{o},j}(t) \tag{2.2}$$

$$\frac{d}{dt}i_{\mathrm{y},j}(t) = \lambda\frac{i(t)}{n(t)}s_{\mathrm{y},j}(t) - \left(\frac{1}{l} + \gamma_I\right) i_{\mathrm{y},j}(t) \tag{2.3}$$

$$\frac{d}{dt}i_{\mathrm{o},j}(t) = \lambda\frac{i(t)}{n(t)}s_{\mathrm{o},j}(t) + \frac{1}{l}i_{\mathrm{y},j}(t) - \left(\mu + \gamma_I\right) i_{\mathrm{o},j}(t) \tag{2.4}$$

$$\frac{d}{dt}r_{\mathrm{y},j}(t) = \gamma_I i_{\mathrm{y},j}(t) - \frac{1}{l}r_{\mathrm{y},j}(t) \tag{2.5}$$

$$\frac{d}{dt}r_{\mathrm{o},j}(t) = \frac{1}{l}r_{\mathrm{y},j}(t) + \gamma_I i_{\mathrm{o},j}(t) - \mu r_{\mathrm{o},j}(t) \tag{2.6}$$

$$\frac{d}{dt}v_{\mathrm{o},j}(t) = \frac{1}{l}\theta\Lambda_j(t)s_{\mathrm{y},j}(t) - \mu v_{\mathrm{o},j}(t) \tag{2.7}$$

$$-\frac{d}{dt}V_{\mathrm{S}}^{\mathrm{o}}(t) = u_{\mathrm{g}} - \left(\delta + \mu + \lambda\frac{i(t)}{n(t)}\right) V_{\mathrm{S}}^{\mathrm{o}}(t) + \lambda\frac{i(t)}{n(t)}\left(\bar{V}_{\mathrm{V}} - C\right) \tag{2.8}$$

A description of the parameters with their values is given in Table 2.1.

Notation	Value	Description
Epidemiology		
λ	2.8	Contact rate
γ_I	1/5	Rate of recovery
θ	97%	Vaccine efficacy
Decision-making		
u_{g}	1	Utility of being in good health
C	7	Total cost of being sick
c_{v}	1.02×10^{-3}	Vaccination cost of vaccinationists
c_{av}	9.41×10^{-3}	Vaccination cost of anti-vaccinationists
α_{v}	96%	Proportion of vaccinationists
α_{av}	4%	Proportion of anti-vaccinationists
δ	8.1×10^{-5}	Discount rate
ϵ	10^{-5}	Slope parameter of the sigmoid χ_ϵ
Vital dynamics		
ν	3.42×10^{-5}	Birth rate
μ	3.42×10^{-5}	Death rate
$1/l$	1/420	Aging rate

Table 2.1: Parameter values. Time unit: day. Costs and utility in QALD.

The total population of individuals older than 14 months at time t is

$$n_{\mathrm{o}}(t) = \sum_{j \in \{\mathrm{v,av}\}} s_{\mathrm{o},j}(t) + i_{\mathrm{o},j}(t) + r_{\mathrm{o},j}(t) + v_{\mathrm{o},j}(t).$$

A proportion α_{av} of the $\nu n_{\mathrm{o}}(t)$ children born at time t are anti-vaccinationist (or equivalently, have anti-vaccinationist parents), and a proportion $\alpha_{\mathrm{v}} = 1 - \alpha_{\mathrm{av}}$ are vaccinationist (Equation 2.1). We set α_{av} to 4%. Results are similar for higher values of α_{av}. We provide results for $\alpha_{\mathrm{av}} = 1\%$ in Appendix D as a robustness check.

Aging is probabilistic in our model. At each time, individuals younger than 14 months (Equations (2.1), (2.3), and (2.5)) grow older than 14 months with probability $1/l \times dt$. Individuals older than 14 months (Equations (2.2), (2.4), (2.6), and (2.7)) die with probability μdt. We assume that infected individuals do not have a higher death rate (instead, for the sake of simplicity, this probability is included in the cost of being infected).

Under homogeneous mixing assumption, susceptible individuals (Equations 2.1 and 2.3) are infected with probability $\lambda \times i(t)/n(t) \times dt$ at time t, where

$$i(t) = \sum_{\substack{a \in \{\mathrm{y,o}\} \\ j \in \{\mathrm{v,av}\}}} i_{a,j}(t)$$

is the total number of infected individuals at time t, and

$$n(t) = \sum_{\substack{a \in \{\mathrm{y,o}\} \\ j \in \{\mathrm{v,av}\}}} s_{a,j}(t) + i_{a,j}(t) + r_{a,j}(t) + v_{a,j}(t)$$

is the total population at time t. Infected individuals (Equations 2.3 and 2.4) then recover at rate γ_I.

As long as vaccination is not mandatory, children decide to vaccinate by comparing the value $V_{\mathrm{S}}^{\mathrm{o}}$ of being susceptible (Equation 2.8) with the value V_{V} of being vaccinated.

Remember that individuals are forward-looking: value functions are (future) expected utilities. Therefore, if u_{g} is the utility of being in good health during one day, $V_{\mathrm{S}}^{\mathrm{o}}$ decreases by u_{g} each day spent susceptible as one day of good health is past. In other words, $V_{\mathrm{S}}^{\mathrm{o}}$ decreases at rate u_{g}. The same reasoning goes for health status transitions. As time passes and transitions are forgone, their net value is subtracted from the value of being susceptible.

The value of being dead is normalized to 0. Then, the value of dying at time t for a susceptible individual is $-V_{\mathrm{S}}^{\mathrm{o}}(t)$. Since vaccination provides lifelong immunization, V_{V} is equal to its steady state value $\bar{V}_{\mathrm{V}} = u_{\mathrm{g}}/(\delta + \mu)$. Recovered individuals also enjoy lifelong immunization so we approximate the net value of getting infected at time t by $\bar{V}_V - C - V_{\mathrm{S}}^{\mathrm{o}}(t)$, where C is the total cost of being sick. The discount rate δ stands for time preferences.

We represent decision-making by a *smoothed best response* function (Fudenberg and Levine, 1998; Xu and Cressman, 2014). Children refuse vaccination with non zero probability, even when the net value of vaccination exceeds the value of being susceptible, and the probability of choosing either option gets close to 0.5 as the net value difference between the two gets close to 0. In addition to easing computation, smoothed best responses remain consistent with real life behaviors. We use the sigmoid $\chi_\epsilon : x \mapsto \dfrac{1}{1 + \exp\left[-x/\epsilon\right]}$ as smoothed best response function. If the value difference between two alternatives, say 1 and 2, is $\Delta V = V_1 - V_2$, then alternative 1 of value V_1 is chosen with probability $\chi_\epsilon\left(\Delta V\right)$.

Let $\Lambda_j(t)$ denote the proportion of children of type j who reach 14 months at time t, and who receive the vaccine. With $t_{\mathrm{mv}} \in [0, T]$ standing for the date at which mandatory vaccination comes into force, Λ_j is given by

$$\Lambda_j(t) = \begin{cases} \chi_\epsilon\left(\theta\left(\bar{V}_{\mathrm{V}} - V_{\mathrm{S}}^{\mathrm{o}}(t)\right) - c_j\right) & \text{if } t < t_{\mathrm{mv}} \\ 1 & \text{otherwise} \end{cases}$$

where θ is the efficacy of the vaccine. In the following simulations, $\epsilon = 10^{-5}$. The derivative of χ_ϵ at 0 is $\chi'_\epsilon(0) = 25,000$. This means that *locally*, a change of $1/25,000$ QALD corresponds to a 100% change in vaccination decision: we make sure that individual decisions are reactive enough to incentive changes.

2.1.4 Solution method

We solve Equations (2.1)–(2.8) numerically using a fixed-point iteration algorithm. Solutions are computed for a total population of 1. Since birth and death rate are equal, the total population is constant. This allows us to solve with the total population older than 14 months set to its steady state value $\bar{n}_{\mathrm{o}} = 1/(1 + \nu l)$.

In order to solve, we need initial conditions for Equations (2.1)–(2.7), and a final condition for Equation (2.8). We choose final time T so that solutions to Equations (2.1)–(2.7) are

reasonably close to their steady state by time T.

Initial conditions of Equations (2.1)–(2.7) are set to the *steady state* that is reached when (i) vaccination is available on a voluntary basis, and (ii) mandatory vaccination has not yet been announced. This initial state depends on the proportion α_{av} of anti-vaccinationists in the population, and on the respective vaccination costs c_{v} and c_{av} of vaccinationists and anti-vaccinationists. After setting α_{av}, we adjust c_{v} and c_{av} so as to obtain a steady state corresponding to an incidence of 250 Measles cases per year in a population of 6×10^7 persons, that is the approximate population of France. Measles incidence may vary greatly from one year to another. 250 cases correspond to the 2014 incidence in France. This steady state incidence level serves as benchmark in the welfare analysis.

2.2 Results

2.2.1 Epidemiology

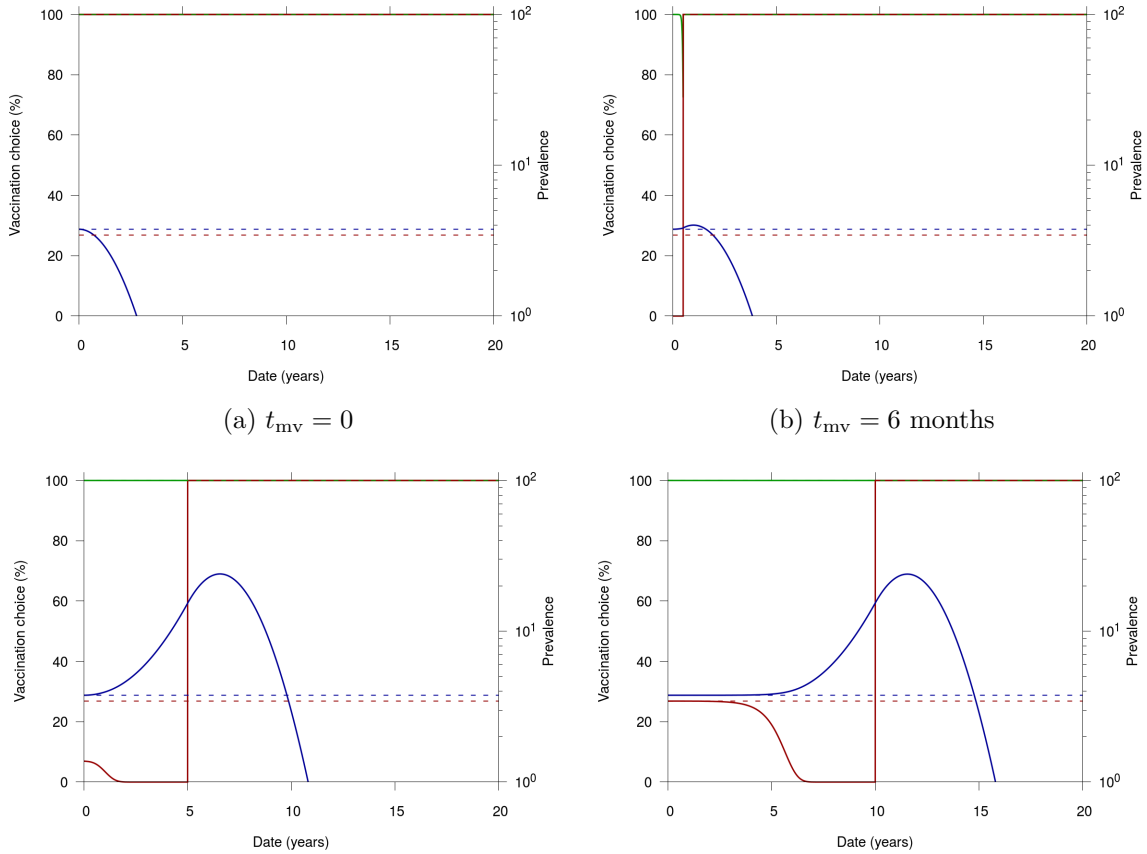
Figure 2.2 shows the instantaneous prevalence and vaccination decisions for four different values of t_{mv} under the assumption that a proportion $\alpha_{\text{av}} = 4\%$ of the population is anti-vaccinationist. Before mandatory vaccination is announced, 100% of vaccinationists vaccinate in this scenario. 25% of the anti-vaccinationists do the same.

In Figure 2.2a, mandatory vaccination immediately comes into force upon announcement at time 0. All children reaching 14 months are vaccinated against Measles, and the prevalence drops to eradication levels.

Things turn out differently when mandatory vaccination is announced before coming into force. In Figure 2.2b, mandatory vaccination is announced 6 months in advance. Before vaccination comes into force, anti-vaccinationists anticipate that Measles will ultimately be eradicated thanks to mandatory vaccination. This means that they will enjoy eradication for most of their life, whether vaccinated or not. Consequently, they engage in *free riding* and do not vaccinate. Between time 0 and t_{mv}, 0% of anti-vaccinationists receive the vaccine. They do not pay the vaccination cost, yet they will benefit from the constrained effort of those who will vaccinate under mandatory vaccination. To some extent, vaccinationists free ride too but only right before t_{mv}. The drop in vaccination between time 0 and t_{mv} leads to a slight increase in prevalence.

This increase in prevalence amplifies as mandatory vaccination is announced earlier (Figures 2.2c and 2.2d). Indeed, the longer the interval between time 0 and t_{mv}, the longer the drop in vaccination can last. At some point, the increase in prevalence makes free riding suboptimal for vaccinationists. Besides, as mandatory vaccination is put off to a later time after announcement, eradication is also delayed and it becomes optimal for some anti-vaccinationists to vaccinate their children.

Figure 2.3 displays the same results for all values of t_{mv} ranging from 0 to 10 years. It shows how a spike in Measles cases develops as mandatory vaccination is announced earlier before implementation. This spike in prevalence and the eventual eradication of the disease imply that individuals will fare very differently depending on their birthdate and their vacci-



(a) $t_{\mathrm{mv}} = 0$

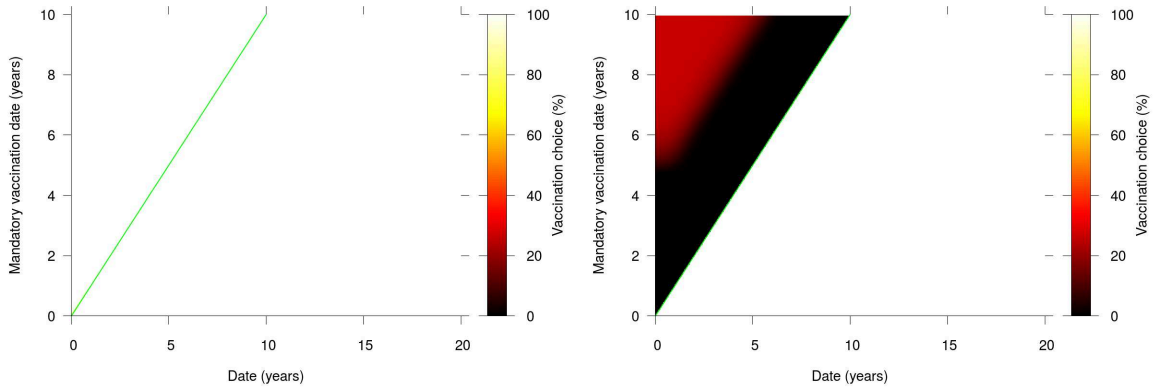
(b) $t_{\mathrm{mv}} = 6$ months

(c) $t_{\mathrm{mv}} = 5$ years

(d) $t_{\mathrm{mv}} = 10$ years

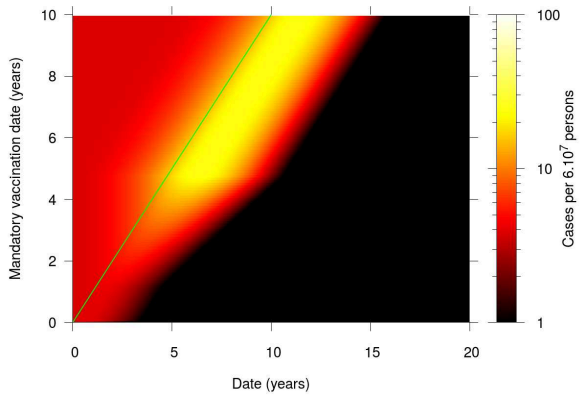
Figure 2.2: Prevalence and vaccination decisions. *Green (left axis):* vaccination decision by vaccinationists. *Red (left axis):* vaccination decision by anti-vaccinationists. *Blue (right axis):* instantaneous prevalence per 6×10^7 persons. *Dashed:* initial (steady) state.

nation status at a given date. Hence we must look into intertemporal effects by undertaking a full welfare evaluation.



(a) Vaccination decision by vaccinationists

(b) Vaccination decision by anti-vaccinationists



(c) Instantaneous prevalence

Figure 2.3: Vaccination decisions and prevalence for a mandatory vaccination date (t_{mv}) between 0 and 10 years. *Green:* date $t = t_{\mathrm{mv}}$.

2.2.2 Welfare

Let us turn to welfare analysis. In order to be comprehensive, we need to consider the welfare of (i) individuals who are born after the announcement of mandatory vaccination (at time 0), and (ii) individuals that were born before that time. For each of these categories, we compare

1. the value of being susceptible[6] at each time between 0 and T when vaccination becomes mandatory at time t_{mv}, with
2. the value of being susceptible under a benchmark scenario where vaccination is voluntary, that is under our initial epidemic steady state conditions.

Under the mandatory vaccination scenario, the value of being susceptible and older than 14 months is given by $V_{\mathrm{S}}^{\mathrm{o}}$, the solution of Equation (2.8). We compute the value of being susceptible, younger than 14 month, and of type $j \in \{\mathrm{v}, \mathrm{av}\}$ at time $t \in [0, T]$ as

$$\begin{aligned} V_{\mathrm{S}}^{\mathrm{y},j}(t) = u_{\mathrm{g}}dt + (1-\delta dt)\Bigg[\lambda\frac{i(t)}{n(t)}\left(\bar{V}_{\mathrm{V}} - C\right)dt \\ + \frac{1}{l}\Lambda_j(t)\theta\left(\bar{V}_V - c_j\right)dt \\ + \frac{1}{l}\Lambda_j(t)\left(1-\theta\right)\left(V_{\mathrm{S}}^{\mathrm{o}}(t+dt) - c_j\right)dt \\ + \frac{1}{l}\left(1-\Lambda_j(t)\right)V_{\mathrm{S}}^{\mathrm{o}}(t+dt)dt \\ + \left(1 - \lambda\frac{i(t)}{n(t)}dt - \frac{1}{l}dt\right)V_{\mathrm{S}}^{\mathrm{y},j}(t+dt)\Bigg]. \end{aligned} \tag{2.9}$$

The probability tree in Figure 2.4 may clarify Equation (2.9).

Figure 2.5 displays the welfare gains of mandatory vaccination for children depending on their birthdate and their vaccinationist or anti-vaccinationist stance.

All individuals born after Measles eradication benefit from mandatory vaccination (light blue area on the right of each graph). This illustrates an instance where state intervention solves the vaccination public good problem. This scenario and the corresponding welfare gain are well-known (Bauch et al., 2003). Usually, cost-effectiveness analyses provide precisely this welfare gain as only measure of the impact of mandatory vaccination.

However, individuals who are born when prevalence is peaking – when mandatory vaccination is announced long enough before implementation – are worse-off (Figure 2.5). Indeed, newborns spend 14 months without having access to vaccination, which makes them especially vulnerable to infection. During this period, only herd immunity is protecting them.

The individuals benefiting the most from mandatory vaccination are those who will not be obliged to vaccinate and who still see many others undergo this obligation. The first of those two effects will be stronger for anti-vaccinationists because they have a higher cost to

[6] Since we consider lifelong immunity after successful vaccination or recovery, only susceptible individuals have their welfare depending on health policies.

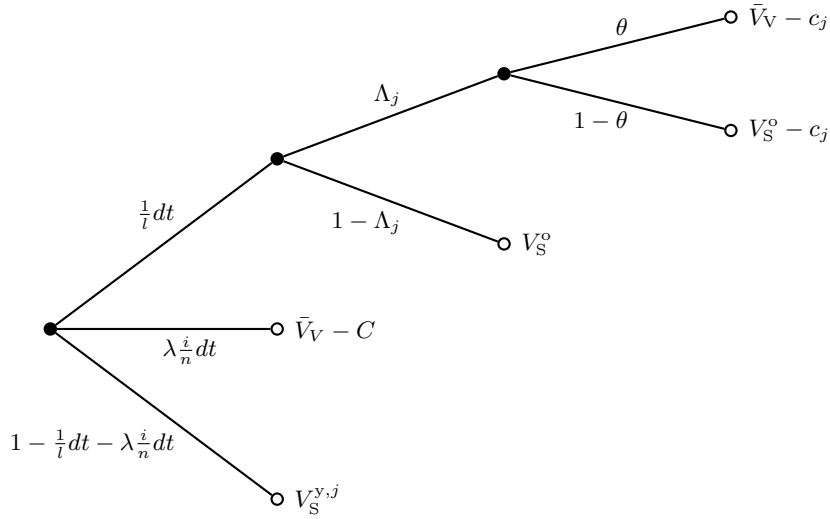
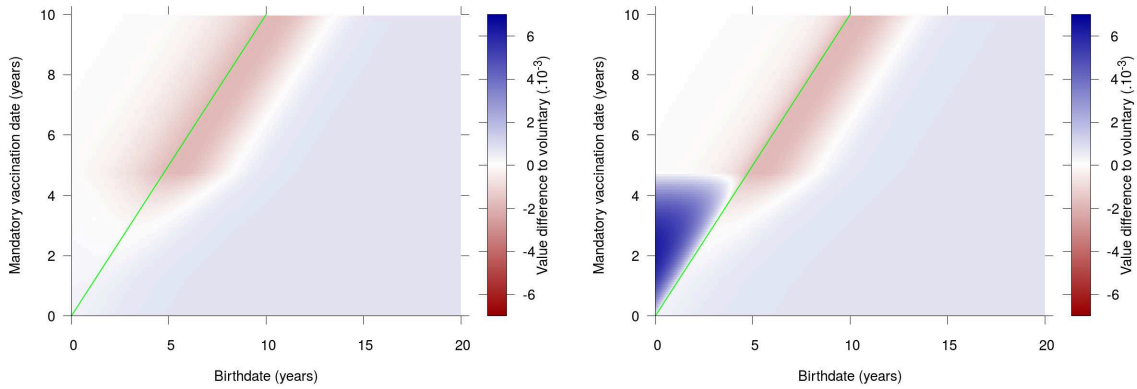


Figure 2.4: Probability tree for individuals of type j.



(a) Vaccinationists (b) Anti-vaccinationists

Figure 2.5: Value difference between mandatory vaccination scenario and benchmark scenario for children born after time 0. *Green:* birthdate $t = t_{\mathrm{mv}}$.

vaccinate. The second effect will be stronger if mandatory vaccination is implemented quickly after its announcement so that there is not enough time for free riding to translate into a spike in Measles cases. In this case, ironically enough, anti-vaccinationists who are able to free ride are among those who benefit the most from mandatory vaccination (Figure 2.5b). Namely, anti-vaccinationists in this situation benefit *around six times more* from mandatory vaccination than vaccinationists born *after eradication*. Obviously, the specific magnitude of this transfer of welfare between subpopulations and generations depends on many parameters. Yet, we argue that it cannot be overlooked *a priori* in a cost-effectiveness analysis.

To be exhaustive in our evaluation, we also need to take into account the population that was born *before* time 0. Figure 2.6 shows the difference between the value of being susceptible at time 0 and the value of being susceptible in our benchmark steady state voluntary vaccination scenario.

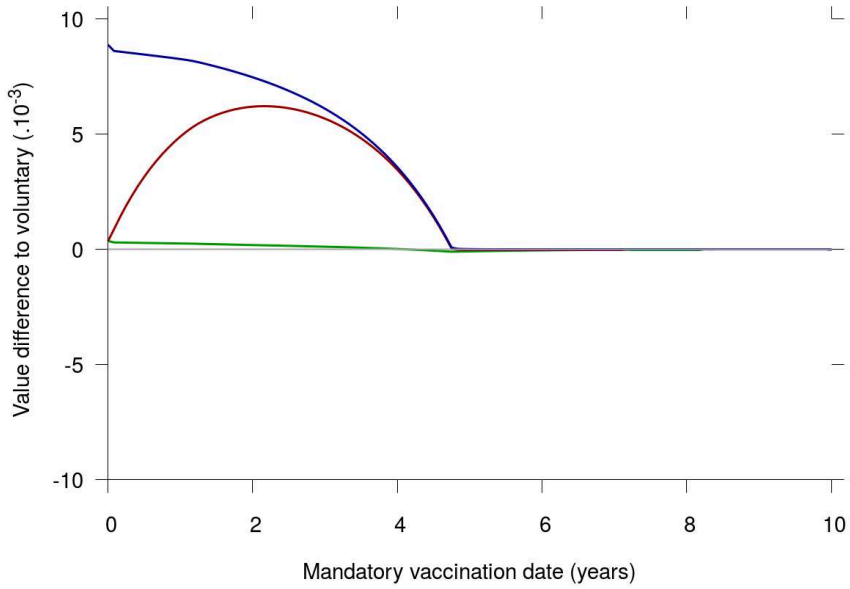


Figure 2.6: Value difference at time 0 for susceptible children born before time 0. *Blue:* individuals older than 14 months. *Green:* vaccinationists younger than 14 months. *Red:* anti-vaccinationists younger than 14 months.

At time 0, individuals are indifferent to mandatory vaccination when it comes late after the announcement (in our instance, more than about 5 years after announcement). This is due to time discounting, and to the fact that a larger increase in prevalence offsets the benefits of subsequent eradication.

Susceptible individuals who are older than 14 months at time 0 (blue curve in Figure 2.6) are either those who refused vaccination, or those whose immune system did not respond to vaccination. From their point of view, the sooner mandatory vaccination is implemented the better: the less significant the spike in prevalence following the announcement and the sooner the eradication – hence the lower the infection probability.

Since we model aging as a Poisson process, it is equivalent for a child to be younger than 14 months at time 0, or to be born exactly at time 0. Then, the green and red curves in Figure 2.6 corresponding to children younger than 14 months at time 0 can be read directly on Figure 2.5 with 0 x-axis value. Interpretation is the same as above.

2.3 Conclusion

Cost-effectiveness evaluations of disease control policies allow to compare substantially different courses of action. In this direction, much effort has been made towards ever more precise measures of the costs of diseases for individuals and society, whether in money or in terms of utility. Still, however much detailed these measures might become, we argue that disregarding individual behaviors in cost-effectiveness evaluations is *a priori* problematic for two reasons. First, this approach overlooks possible feedback loops between the spread of a disease, policies, and individual behaviors. Such feedback loops may influence the ultimate

outcome of a policy – even in the very long run. Second, insofar as human behavior is based on anticipation, public health policies transfer large amount of welfare between generations, or more generally between subpopulations.

In this article, we draw on the example of mandatory Measles vaccination to support our claim. We show that in this instance, while Measles is eradicated in the long run, individual anticipatory behaviors may cause major transition effects. As some individuals anticipate eradication, they do no vaccinate their children before mandatory vaccination comes into force. This leads to a transitional increase in prevalence and, consequently, to generational welfare differences. Somewhat ironically, anti-vaccinationists are among the ones benefiting the most from mandatory vaccination in this scenario. The transitional increase in prevalence can be avoided by implementing mandatory vaccination quickly after it has been announced.

While this study focuses on Measles vaccination decision, we use a framework that is relevant for all types of infectious diseases and anticipatory behaviors involving strategic interactions. Also, the effects we bring out are not conditional on considering an anti-vaccinationist subpopulation – free riding can also occur in an homogeneous population. Our study is based on numerical simulations, and on the restricting (yet relevant) assumption that individuals are rational and far-sighted. The use of numerical simulation methods is however clearly justified by the complexity of the problem, and we believe that one merit of our study is to display a use case for the numerical methods we described in Flaig et al. (2018). This approach is ultimately intended as a tool for public health professionals. Finally, we argue that our simulations allow to highlight effects whose magnitude calls for empirical investigations and possibly reconsideration of some public health policy recommendations. It has been demonstrated (Saint-Victor and Omer, 2013) that vaccination tends to decrease with prevalence, which may indicate free riding and “rational” behavior. Yet data is still missing to investigate the full extent of these phenomena and their welfare implications in the real world.

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Chapter 3

Vaccination as a cooperative behavior

This chapter is based on an article coauthored with N. Houy and P. Michel.

Abstract

We study voluntary Measles vaccination as a cooperative behavior. In this scenario, individuals form a coalition by agreeing to vaccinate their children and to retaliate against those who fail to do so. We rely on the model developed by Flaig et al. (2018a) that consists of a compartmental model coupled with a model of rational and far-sighted vaccination decision-making. This numerical approach overcomes the technical difficulty of including individual behavior in epidemiological models. We draw upon equilibrium and retaliation concepts borrowed from the theory of repeated games, even if individuals vaccinate only once in our framework. We bring out the vaccination cost and coalition size values for which cooperative vaccinating behavior is sustainable in different scenarios: (i) when there is no retaliation against individuals who refuse vaccination, (ii) when retaliation is mild, and (iii) when retaliation is harsh. It is well known that vaccination coverage tends to decrease near eradication prevalence levels. Interestingly, cooperation can be a powerful way to promote vaccine uptake where it would otherwise become insufficient due to low prevalence. Finally, we show that cooperation brings benefits in terms of reduced prevalence.

Keywords: Measles, voluntary vaccination, cooperation.

Measles is a highly contagious viral infectious disease. An efficient vaccine has been available since 1963 and a combination of vaccines protecting from Rubella, Mumps and Measles has been available since 1974. In the United States, in the decade preceding the introduction of the vaccine, virtually all children were infected before they reached 15 years of age (about 3 to 4 million people infected every year). An estimated 400 to 500 people died each year, 48,000 were hospitalized, and 1,000 developed encephalitis CDC (2018). Since 2000, the annual number of reported Measles infections in the US has been ranging from 37 people in 2004 to 667 people in 2014. However striking this decrease might be, eradication does not seem to be close. In fact, Measles outbreaks still regularly occur, mainly in pools of unvaccinated individuals (Amish communities in Ohio in 2014, or regularly in Romani camps in France, see INVS (2018a,b)), but not only (Salmon et al., 1999).

The last steps to meet vaccination coverage targets seem to be the hardest ones (Saint-Victor and Omer, 2013). Health authorities regularly insist that citizens should vaccinate more. Indeed, it is well known that vaccination is not only about protecting oneself. What is at stake, is also whether the population as a whole will be able to reach herd immunity, thus protecting those who may not have access to vaccination for a variety of reasons, and those who remained unimmunized because their immune system did not respond to the vaccine. Yet this externality is not, by definition, taken into account by perfectly rational and selfish individuals basing their vaccination decision on a private cost-benefit analysis. Consequently, the vaccination coverage resulting from private cost-benefit analyses is lower than what would be socially optimal.

Let us illustrate this point in the case of Measles with a short back-of-the-envelope computation. Assume a nonoptimistic yearly incidence of 667 cases in a population of 3×10^8 individuals, that is the highest incidence in the United States in the past few years. The average private cost of having Measles has been estimated to be about 7 quality-adjusted life days (QALD) by Thorrington et al. (2014). Considering a 3% discount rate, the present value of risking to be infected with Measles would be about $7 \times \frac{667}{3\times10^8} \times \frac{1}{3\%} \approx 5.2 \times 10^{-4}$ QALDs, *i.e.* 45 quality-adjusted life *seconds*! This computation is simplified and somewhat naive, but it still gives some important insights. Consider for instance that having a child vaccinated requires an adult to bring the child to a physician twice to receive two vaccine shots. This can hardly be deemed less costly than the expected cost of not being vaccinated.[1] Again, our computation is simplistic and does not take into account many aspects of the problem.[2] Yet we believe that the order of magnitude of our result will convince the reader that, at least in the case of Measles, the puzzle is not so much vaccine refusal as vaccination acceptance. We are not saying that it is not *collectively* profitable that individuals vaccinate.[3] Rather, we claim that calling to individuals' rationality for them to implement this optimal collective policy might be misguided. This is in line with the conclusions of the recent review by Brewer et al. (2017). In order to better inform policy makers, we hold that researchers should strive for a better understanding of the reasons underpinning Measles vaccination acceptance and the relatively high Measles vaccination coverages we can observe in most developed countries. While high, these vaccination coverages fall short of achieving herd immunity more often than not (see Hill et al. (2017) for instance), and Measles immunization remains a major public health issue. Many mutually non-exclusive reasons can be given for vaccination: behavioral explanations (risk attitude, beliefs), social norms, and the role of the media among others. In the current article, we investigate the role of cooperation in a theoretical framework with a simulation based approach.

[1] In real life, parents decide for their children and do not face the same costs. Assuming that parents are perfectly altruistic towards their children – and only towards them – makes all the computations of this article valid.

[2] One of our strongest assumptions is to ignore the fact that the vaccine against Measles is generally combined with vaccines against Mumps and Rubella, which should be an additional incentive to get vaccinated. Notice however that many anti-vaccination activists ask for vaccines to be administered independently. So in their case the combination of several vaccines seems to be more of a deterrent than an incentive.

[3] An enormous literature has shown the positive social benefit of vaccination against Measles, see Bester (2016) for a systematic review.

We believe that studying vaccination as a cooperative behavior is interesting from both theoretical and explanatory standpoints. For the latter, we will show in this article that cooperation can help explain the puzzle of vaccination acceptance described above. From a theoretical standpoint, we borrow *retaliation* (or punishment) concepts from the theory of repeated games. Vaccination decision-making is strategic in essence, which justifies a game theoretic approach. Formally, however, strategic interaction in vaccination is not repeated, since vaccination is usually scheduled at a given age and vaccination decision is made only once. Yet the concept of retaliation still makes sense in this context as an individual's utility – a player's payoff in our game – depends on future disease prevalence, that is on future players' vaccination decisions. This dynamic setting allows individuals to punish past bad behaviors.

The major difficulty in our investigation of cooperation in vaccinating behavior is the technical difficulty of solving the corresponding dynamical system. This system is indeed both backward and forward in time. In order to make their vaccination decision rationally, individuals must anticipate the future disease prevalence path which determines the risk of being infected. The spread of the disease depends in turn on past vaccination decisions. This two-ways dynamics can hardly be computed analytically and is hard to compute numerically.

In order to solve this problem, several approaches have been proposed. Some authors tackled the problem with a full consideration of the forward-backward dimension described above. Geoffard and Philipson (1996) and Chen and Cottrell (2009) studied SI epidemiological models, whereas Geoffard and Philipson (1997) and Laguzet and Turinici (2015) studied SIR models. Geoffard and Philipson (1996, 1997); Chen and Cottrell (2009) produced mainly qualitative descriptions of some features of the solution that can hardly be used in an applied context. Laguzet and Turinici (2015) overlooked vital dynamics. In the same stream of literature, Reluga and Galvani (2011) restricted themselves to the study of steady states.

An alternative stream of literature somehow decreases the complexity of the coupled system by disregarding the forward reasoning component in human behavior. Bauch et al. (2003) and Bauch and Earn (2004) sparked renewed interest in vaccination policy and individual choices with one period, static models. Further instances of one period models were provided by Reeling and Horan (2015), Code et al. (2007) and Shim et al. (2012a). In order to introduce dynamic decision-making in this framework, Bauch (2005) (followed by Reluga et al. (2006), d'Onofrio et al. (2011), Fu et al. (2011) and Yang et al. (2016)) proposed models with imitation behavior. Just as the spread of a transmittable disease when individual behavior is ignored, imitation only depends on past and current states of the epidemic: imitation dynamics goes forward in time. This outlook on the problem was also adopted by Fenichel et al. (2011). They assumed that individuals falsely believe that the current epidemiological state will persist (Voinson et al. (2015) added cognitive biases to this framework). Similarly, Buonomo et al. (2008), Epstein et al. (2008), Coelho and Codeco (2009), Funk et al. (2015) and Bhattacharyya et al. (2015) all modeled information and/or beliefs with forward dynamics in time.

In this article, we use the formal model and computational tools we developed previously

Flaig et al. (2018a,b) in order to analyze vaccination coverage in a cooperative setting. We define two levels of punishment and show the parameter values for which punishment threat sustains cooperation between individuals in a given subpopulation.

3.1 Model

Our model is made of the same two components as in Chapter 2. The first component is a usual SIR compartmental model with vaccination. It models the demographics and the spread of Measles assuming homogeneous mixing. Individuals can vaccinate at 14 months of age. Vaccination provides life-long immunity and has a 97% take-rate. There is no maternal immunity. Infection has an instantaneous 7 QALD cost. Birth and death rates are typical of a developed country.

The second component is a model of individual vaccination decision-making. At 14 months of age,[4] far-sighted individuals rationally anticipate the future prevalence of Measles, that is the risk of being infected during their life, and the corresponding expected cost. They then base their decision on a private cost-benefit analysis weighting the cost of vaccination against the expected cost of being infected. The vaccination decision of each individual modifies the future prevalence, thus influencing the payoff of all other players, including those yet to be born. This strategic interaction in vaccination decision-making justifies a game theoretic approach.

We consider two subpopulations – 1 and 2 – with different costs to vaccinate, c_1 and c_2 respectively. We call anti-vaccinationist the subpopulation with the highest cost to vaccinate.[5] α_1 is the share of subpopulation 1, and $\alpha_2 = 1 - \alpha_1$ is the share of subpopulation 2. We assume that individuals in subpopulation 1 can form a coalition by agreeing to cooperate and vaccinate at 14 months of age under the conditions described below. Individuals in population 2 always implement their best response to the vaccination decisions of all other individuals in both subpopulations. Notice that we make no assumption regarding the relative values of c_1 and c_2 at this point.

Our model is the same as that described by Equations (2.1)–(2.8) in Chapter 2, except that subpopulations 1 and 2 may switch role and represent alternatively vaccinationists or anti-vaccinationists depending on the simulation instance. Also, we do not use the usual sigmoid function because, in our study, we are especially interested in limit behaviors with 0% or 100% vaccination. The sigmoid may tend to a 0% or 100% behavior but never reaches it. Another solution would have been to define thresholds above (resp. below) which we assume 100% (resp. 0%) behavior. However, this would have required the introduction of an

[4]The assumption that children make their own decision is equivalent to considering perfectly altruistic parents making the decision of having their children vaccinated considering the latter's best interest (Ramsey, 1928). This assumption seems to be in line with observations in the case of the MMR vaccine (Brown et al., 2010).

[5]See Cojocaru et al. (2007); Manfredi et al. (2009); Shim et al. (2012b) for other instances of this modeling approach.

Notation	Value	Description
Epidemiology		
λ	2.8	Contact rate
γ_I	1/5	Rate of recovery
θ	97%	Vaccine efficacy
Decision-making		
u_{g}	1	Utility of being in good health
C	7	Total cost of being sick
c_1	variable	Vaccination cost of subpopulation 1
c_2	variable	Vaccination cost of subpopulation 2
α_1	variable	Proportion of individuals in subpopulation 1
α_2	$1-\alpha_1$	Proportion of individuals in subpopulation 2
δ	8.1×10^{-5}	Discount rate
ϵ	2×10^{-3}	Slope parameter of the function χ_ϵ
Vital dynamics		
ν	3.42×10^{-5}	Birth rate
μ	3.42×10^{-5}	Death rate
$1/l$	1/420	Aging rate

Table 3.1: Parameter values. Time unit: day. Costs and utility in QALD.

additional arbitrary parameter. Instead, we use the function

$$\chi_\epsilon : x \mapsto \begin{cases} 0 & \text{if } x \leq -\epsilon/2 \\ 1 & \text{if } x \geq \epsilon/2 \\ 1/2 + x/\epsilon & \text{otherwise} \end{cases}$$

as smoothed best response function.

A description of the parameters with their values is given in Table 3.1.

We will study the sustainability of vaccination cooperation among subpopulation 1 with two different grim trigger strategies borrowed from the theory of repeated games (Friedman, 1971; Axelrod, 1984).

- The *mild* trigger strategy: if an individual does not cooperate/vaccinate, all individuals in the coalition (subpopulation 1) implement their best responses and fall back onto the subgame perfect Nash equilibrium strategy in the future.

- The *harsh* trigger strategy: if an individual does not cooperate/vaccinate, all individuals in the coalition (subpopulation 1) do not cooperate in the future (*i.e.* stop vaccinating).

In the following, we will say that vaccination cooperation is an equilibrium with mild (resp. harsh) threat if individuals in subpopulation 1 have no incentive to deviate from vaccinating when the mild (resp. harsh) trigger strategy is implemented.

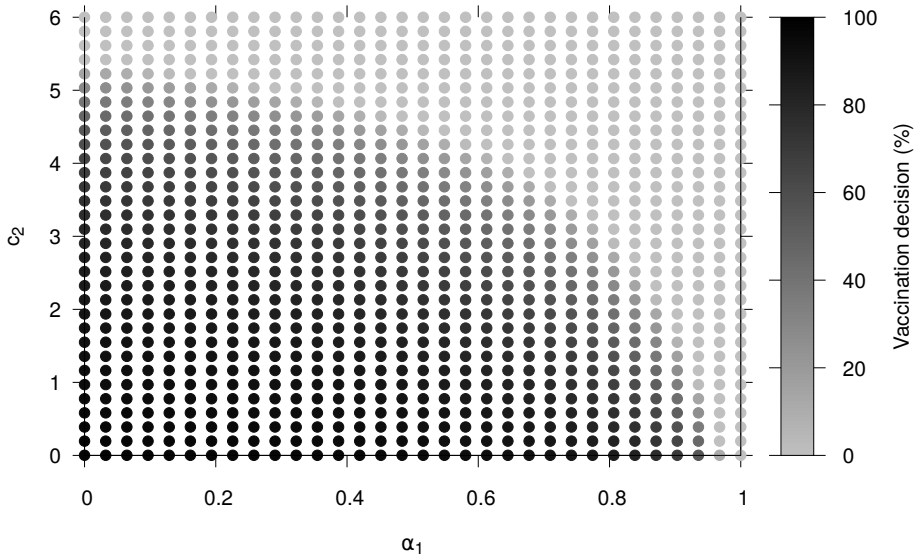


Figure 3.1: Steady state vaccination decision by individuals in subpopulation 2 when individuals in subpopulation 1 all vaccinate.

3.2 Results

When the subpopulation 1 coalition holds, vaccination decision by individuals in subpopulation 2 only depends on their own vaccination cost c_2 and on the share of each subpopulation in the total population. The steady state vaccination decision by individuals in subpopulation 2 in this scenario is shown in Figure 3.1. As expected, they tend to vaccinate less as their vaccination cost increases. Also, individuals in subpopulation 2 free ride on subpopulation 1 coalition: when the share of subpopulation 1 increases and the coalition holds, the risk of being infected decreases and subpopulation 2 can decrease its own vaccination coverage. In the following, all results will be for $c_2 = 3$.[6]

When the coalition holds in subpopulation 1, the best response of an individual in this subpopulation might be to free ride on others' vaccination. Figure 3.2 shows the steady state best response of a single individual in subpopulation 1, in the scenario where all individuals in subpopulation 1 vaccinate and there is no retaliation threat. That is, all individuals in subpopulation 1 will continue vaccinating even if one of them decides to not vaccinate. As we consider atomistic individuals, individuals in subpopulation 2 vaccinate as in Figure 3.1 (with $c_2 = 3$) when a single individual in subpopulation 1 deviates from the coalition. When the best response is to vaccinate for 100% of the individuals in subpopulation 1, the corresponding equilibrium is a subgame perfect Nash equilibrium (SPNE). Put differently, the coalition holds in subpopulation 1 because it is in each individual's best interest to vaccinate, even if there is no retaliation against free riders. In this case the coalition is sustainable without needing a collective cooperation mechanism.

SPNEs with all individuals in subpopulation 1 vaccinating are obtained for lower values of c_1, the vaccination cost of subpopulation 1. When c_1 is equal to c_2 (recall that $c_2 = 3$) the best

[6] We performed simulations for c_2 between 2×10^{-3} and 6 and obtained the same effects qualitatively.

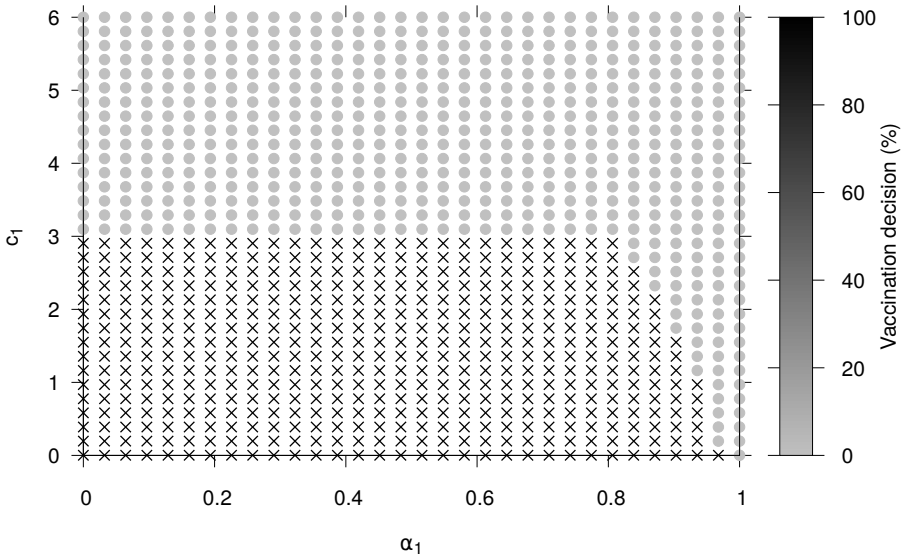


Figure 3.2: Steady state best response vaccination decision by a single individual in subpopulation 1 when all other individuals in subpopulation 1 always vaccinate (no threat). *Crosses:* points where the best response is to vaccinate for 100% of subpopulation 1. $c_2 = 3$.

response of an atomistic individual in subpopulation 1 is the same as that of an individual in subpopulation 2 shown in Figure 3.1. From $c_1 = c_2$, a small increase in c_1 makes it optimal for an individual in subpopulation 1 to free ride on subpopulation 2's vaccination. Notice that in this scenario the individuals in subpopulation 1, those who are forming a coalition, are actually anti-vaccinationists ($c_1 > c_2$).

We now turn to cooperation sustained by threats, mild and harsh, as defined above. It must be noted in the first place, that actually carrying out a threat is not necessarily optimal for individuals in subpopulation 1. Therefore, some cases where the coalition holds because (and only because) of a retaliation threat are not SPNEs. In the second place, notice that in order to determine if it is in the best interest of an individual in subpopulation 1 to deviate from the steady state coalition, we need to compare (i) his welfare if the coalition holds, with (ii) his welfare if he decides not to vaccinate and incurs mild or harsh retaliation. But welfare when retaliation is carried out depends on future prevalence, that is on all future vaccination decisions of subpopulation 2 in the case of harsh retaliation, and of both subpopulations in the case of mild retaliation. Technically, this requires solving a dynamic system out of steady state for each retaliation scenario, which is challenging in our case. We compute solutions as functional fixed points, see Flaig et al. (2018a,b) for more details.

Time dependent solutions when threats are carried out are illustrated in Figure 3.4. At time 0, 100% of the individuals in subpopulation 1 vaccinate as they are forming a coalition, and individuals in subpopulation 2 implement their best response strategy to this coalition, as displayed in Figure 3.1. The initial prevalence corresponds to these behaviors. Consider now the vaccination decision of an individual in subpopulation 1. If he vaccinates, the initial steady state coalition is sustained and he will face the corresponding prevalence (thin dashed lines in Figure 3.4). If he does not vaccinate, then either mild or harsh retaliation is carried

out by subpopulation 1 and he will have to face the corresponding prevalence (thin black lines in Figure 3.4).

Again, we must emphasize that there is no shortcut (e.g. restraining ourselves to steady state solutions) to results on the sustainability of a coalition in our case. We need full, time dependent, solutions. Indeed, when mild retaliation is carried out, prevalence (and then welfare) depends on the best response vaccination decisions of individuals in subpopulations 1 and 2, which in turn depends on their anticipation of future prevalence. The same holds when harsh retaliation is carried out, but only individuals in subpopulation 2 choose their optimal vaccination decision since harsh punishment consists in 0% of subpopulation 1 vaccinating.

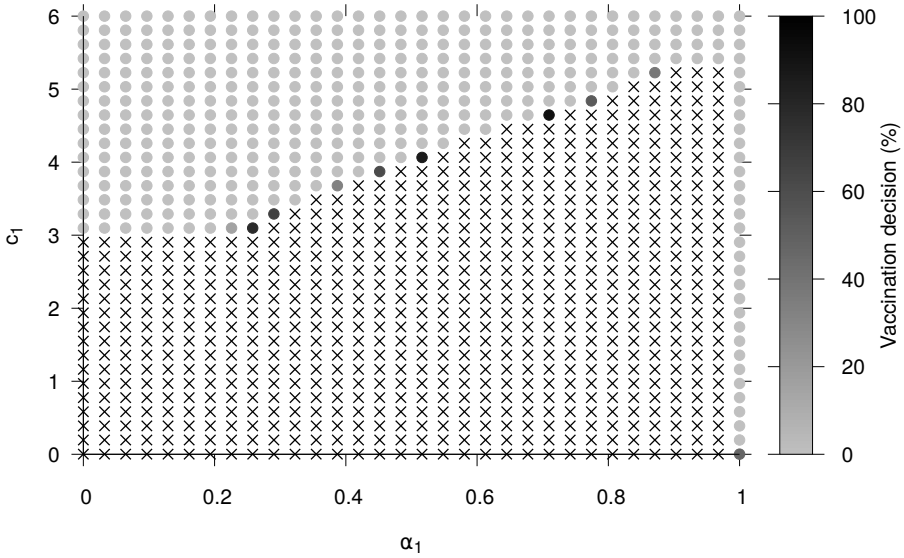
We solve for vaccination decisions and prevalence over time for different values of α_1 and c_1 in order to compute the best response of an individual in subpopulation 1 when mild and harsh trigger strategies are implemented. This allows us to highlight parameter values for which a coalition is sustainable thanks to the different trigger strategies. Our results are shown in Figure 3.3. These plots are to be compared with Figure 3.2. The parameter values for which we displayed full solutions in Figure 3.4 are such that it is optimal for an individual in subpopulation 1 to deviate when the mild trigger strategy is implemented, but it becomes optimal for him to vaccinate if the harsh trigger strategy is implemented.

We see in Figure 3.3 that trigger strategies sustain cooperation over wide ranges of parameter values. Also, the harsh trigger strategy performs slightly better than the mild trigger strategy. Retaliation threats are globally more effective when the share of subpopulation 1 is larger, as a larger share of individuals may carry out the threat. When α_1 is larger, it takes a higher vaccination cost c_1 for individuals in subpopulation 1 not to cooperate. However the mild trigger strategy becomes ineffective for α_1 close enough to 1. Recall that when the coalition holds, 100% of the individuals in subpopulation 1 vaccinate. When the share α_1 of subpopulation 1 is large enough, prevalence eradication levels are reached when the coalition holds. If the mild retaliation is carried out, individuals in subpopulation 1 vaccinate freely. Yet the prevalence is so low and α_1 so high that they can easily control the epidemic.

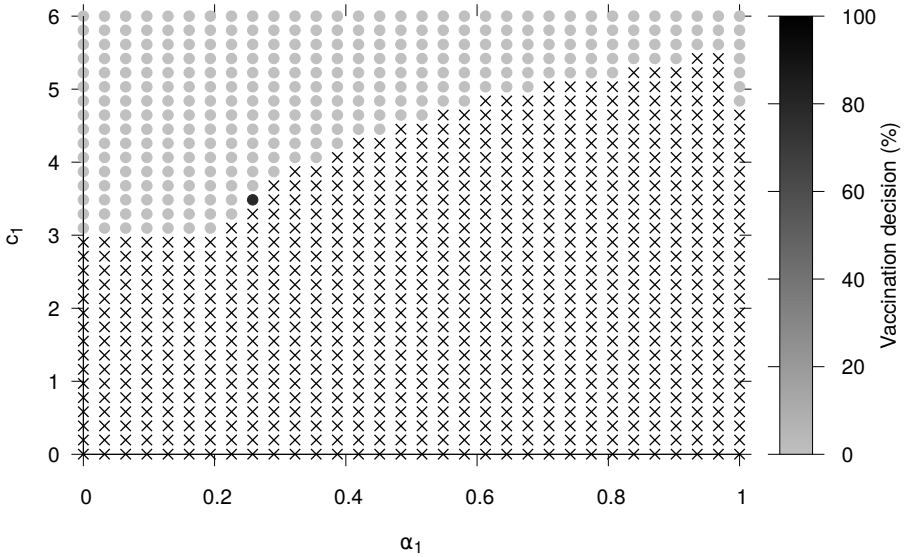
One question remains unanswered: does cooperation bring any benefit in terms of prevalence reduction? In Figure 3.5, we show the prevalence levels resulting from the equilibria shown in Figure 3.3. Because prevalence is a function of time, we display at each point:

- if vaccination is an equilibrium sustained by the appropriate trigger strategy (crosses in Figure 3.3), the steady state prevalence with individuals in subpopulation 1 vaccinating and individuals in subpopulation 2 playing their best response strategy,
- if vaccination is not an equilibrium sustained by the appropriate trigger strategy (dots in Figure 3.3), the steady state prevalence with all individuals playing their best response strategy (mild trigger strategy, Figure 3.5a) or individuals in subpopulation 1 never vaccinating and individuals in subpopulation 2 playing their best response strategy (harsh trigger strategy, Figure 3.5b).

When the coalition does not hold, and whatever the implemented trigger strategy, the prevalence levels observed when all individuals in subpopulation 1 do not vaccinate (harsh

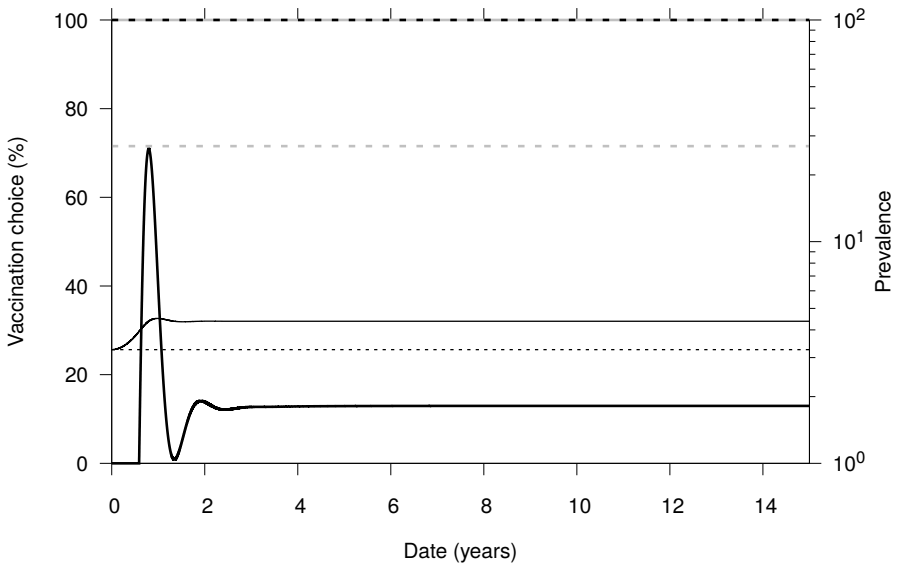


(a) Mild trigger strategy.

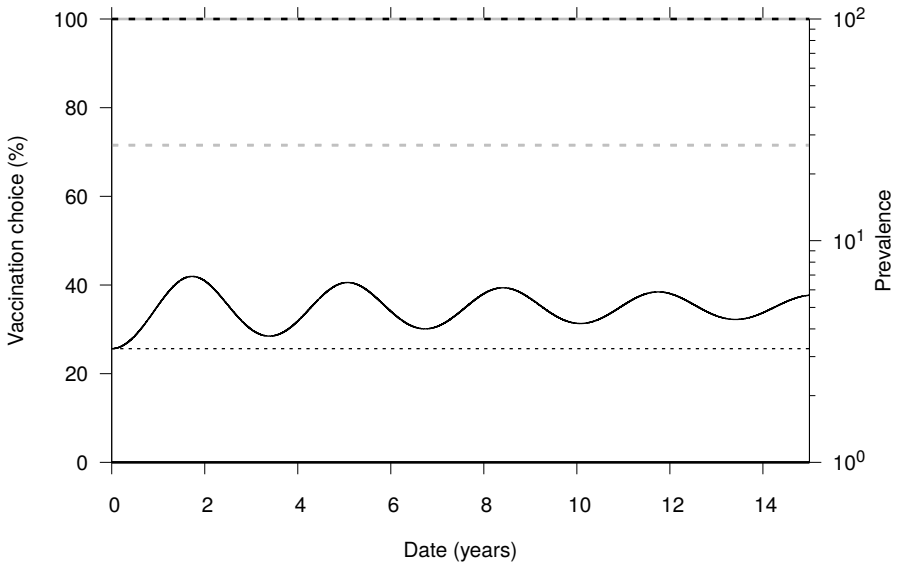


(b) Harsh trigger strategy.

Figure 3.3: Best response vaccination decision by an individual of subpopulation 1 when the mild *(upper panel)* and harsh *(lower panel)* trigger strategies are implemented. *Crosses:* points where the best response is to vaccinate for 100% of subpopulation 1. $c_2 = 3$.



(a) Mild trigger strategy.



(b) Harsh trigger strategy.

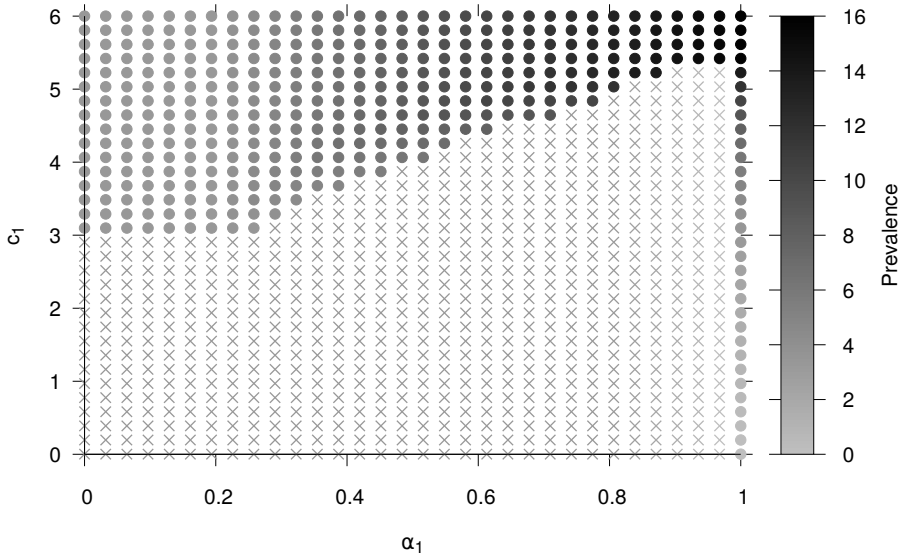
Figure 3.4: Solutions when mild *(upper panel)* and harsh *(lower panel)* retaliations are carried out with $\alpha_1 = 30\%$, $c_1 = 3.5$, and $c_2 = 3$. *Thick black (left axis):* best response vaccination decision of subpopulation 1. *Thick gray (left axis):* best response vaccination decision of subpopulation 2. *Thin black (right axis):* instantaneous prevalence per 10^5 individuals. *Dashed:* initial steady state with sustained coalition.

punishment) or when they apply their best response (mild punishment) are close. And this is quite not surprising because this configuration occurs for high costs c_1 and hence, the best response of individuals in subpopulations 1 is to not vaccinate anyhow. However, when a coalition holds, it obviously leads to much lower prevalence levels whenever α_1 is significant or not. Figure 3.5 illustrates the importance of having cooperation sustained in order to meet public health objectives.

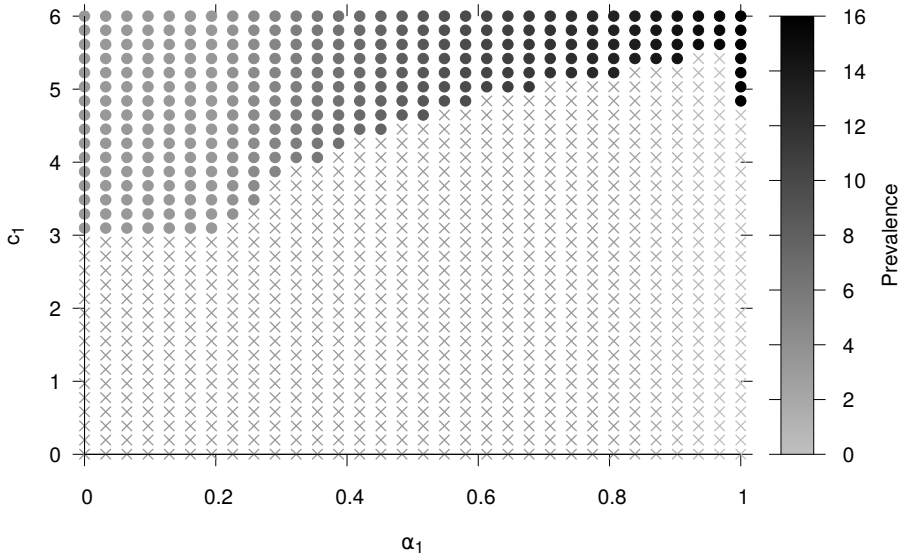
3.3 Conclusion

The starting point for this article is the observation that *individual* tradeoffs between the private costs and benefits of vaccination are unlikely to explain observed immunization levels. We then undertake an investigation of vaccination as a cooperative behavior. We use the model previously developed by Flaig et al. (2018a,b) and retaliation concepts borrowed from repeated games theory. Our contribution is technical and theoretical. First, we overcome the technical difficulty of including forward-looking voluntary vaccinating behaviors in an epidemiological model. Modeling such behaviors is unavoidable in our case. Second, we apply concepts from repeated games theory even though all players vaccinate only once. This is justified by the fact that vaccination decisions have an impact on individuals who have already made their decision, and on those who will have to decide later. Hence, the concepts of retaliation threat and of credibility of a threat do make sense in our framework. We showed results for two different kinds of threat.

We believe that cooperation can be an explanation for the relatively high levels of vaccination coverage in developed countries, where there is no supply constraints but vaccination is offered on a voluntary basis. If it is the case, it is crucial to understand this aspect when designing public policies to achieve collective objectives. However, cooperation, because it is at least in part a forward-looking behavior, is hard to include in an epidemiological framework. We hope that this article, by providing an appropriate theoretical framework, will be a first step toward a better understanding of cooperative vaccination choice.



(a) Mild trigger strategy.



(b) Harsh trigger strategy.

Figure 3.5: Long term (steady state) prevalence per 10^5 individuals resulting from the equilibria displayed in Figure 3.3. *Crosses:* points where the best response is to vaccinate for 100% of subpopulation 1. $c_2 = 3$.

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Conclusion

This thesis tackled the issue of including individual vaccination decisions in epidemiological models. This issue consists firstly in a technical challenge. The coupled equations governing the spread of the disease and vaccination decision-making are difficult to solve. This is especially true of models that are meant to be actionable, that is models relying on reasonably realistic epidemiological assumptions. The notion of what is reasonable is of course contingent on the modeled disease, but also on the questions addressed with the model. This leads us to a second question that followed naturally from the technical difficulty: is solving the equations even worth the trouble? And particularly in the field of health economics, does including individual decision-making alter usual economic evaluations? More speculative questions also arose along the way. While our approach focuses primarily on individual decisions, a simple calculation shows that individual decisions based on costs and benefits alone hardly account for the relatively high (though often insufficient) observed vaccination coverages. Vaccination acceptance, rather than refusal, seemed to require closer inquiry.

Arguably, vaccination decision-making is essentially strategic *and* anticipatory. This requires to solve for dynamic prevalence paths and vaccination decisions under the assumption that individual are rational and far-sighted. We met this technical challenge by expressing vaccination decision as a functional fixed point, and by solving with a fixed point iteration algorithm. We showed the versatility of this approach in Chapter 1 with a Measles-like model including some complicating features: vital dynamics and waning vaccine efficacy. For illustration, we also showed the qualitative differences between the results of our model and the results of the corresponding model of adaptive behavior.

We then dwelled on the example of mandatory Measles vaccination to show that fully accounting for individual strategic decision-making can alter the results of cost-effectiveness analyses (Chapter 2). To do this, we took the same perspective that can be found in economic analyses of public health policies. Namely we used a fairly simple compartmental model, and we based our analysis on a comparison of costs and benefits where the individual private cost of being sick with Measles was found in the health economics literature. We also performed a welfare analysis based on a comparison with a benchmark steady state scenario, which is a common procedure. We found that individual strategic behavior can cause large welfare transfers between generations. Importantly, these welfare transfers are not only large, they are non-negligible by the very standards of usual economic evaluation methods.

Many factors beyond individual costs and benefits can account for vaccination behavior.

This thesis (Chapter 3) investigates cooperation, that is coalitions of vaccinating individuals, as a possible explanation of vaccination behavior. In a brief theoretical discussion, we explained why and how concepts of retaliation usually found in repeated games can readily be used in the context of vaccination. We focused on two types of retaliation that we found relevant, and we showed in each case that retaliation threats can sustain vaccination. Investigating cooperation and retaliation, however, is only possible where full time dependent solutions to the vaccination decision problem can be computed. This provided a more theoretical use case for our modeling approach and solution method.

In vaccination games, payoffs and vaccination decisions depend on the full path of prevalence. Prevalence, however, depends itself on vaccination decisions. This feedback loop is of course well-known and has largely been studied. The work presented in this thesis originates from a gap in this literature. Since the equations corresponding to the feedback loop are difficult to solve, authors have usually relied on simplifying assumptions or restricted themselves e.g. to steady state solutions. This thesis adds to the literature on vaccination games with an approach allowing to solve for dynamic prevalence and vaccination decision paths. So our first contribution to the literature is technical in the sense that we overcome technical difficulties irrespective of whether doing so has any practical use.

The technical difficulty of solving dynamic vaccination games might well account for another literature gap, namely in the related health economics literature. In addition to being difficult to model, strategic individual behavior is usually assumed to yield only negligible effects in economic evaluations. As a consequence, it is as a rule overlooked without further investigations. Here, our contribution to the literature is both theoretical and technical. On the theoretical side, we show with an example that individual behavior cannot be disregarded *a priori* in economic evaluations. This result challenges assumptions commonly found in the literature. On the technical side, we provide tools to include individual strategic behavior in economics evaluations. This is perhaps the main takeaway of this thesis: while solving a difficult problem is of little interest in itself, our approach is of practical use and is meant to be applied in further studies.

In the same spirit but on a much more speculative level, we also contributed to the understanding of vaccination behavior. The literature on this topic consists mostly of empirical studies based on questionnaires. Our work opens up game theoretic modeling possibilities as it allows to consider how vaccinating individuals might retaliate against those who refuse vaccination. Again, we brought a theoretical argument – that retaliation makes sense in the context of vaccination – and our modeling approach provided a tool to carry out the ensuing analysis.

Our work will appeal primarily to public health practitioners, health economists, and more generally to health system participants interested in cost-effectiveness analyses. They will find a discussion of why strategic anticipatory behavior must in some case be considered in economic evaluations. More importantly, they will find tools to do so. Economic evaluation is the field of application where we can expect our work to have the most implications. Indeed, most improvements on cost-effectiveness analyses attempt to capture ever

more specific features of a disease, or to measure individual costs and benefits ever more precisely. We took another direction by adding a noticeably basic assumption to economic evaluations: that of individual strategic anticipatory behavior. Doing so, however, allows to discern effects that would otherwise remain hidden. Moreover, while this thesis focuses on Measles vaccination decision-making, other applications might be found where individual anticipations and strategic behavior can be expected to carry weight.

This thesis will also be of interest for researchers in other disciplines. Game theorists will find a method to solve dynamic vaccination games along with illustrative use cases. In particular, they will find new perspectives to investigate cooperative behavior in vaccination. As for theoretical epidemiologists, this thesis will mostly provide them with further illustrations of the implications of individual behaviors in epidemiology.

Let us conclude with some caveats regarding the work presented here and with directions for future research. Stating the obvious, we must emphasize once again that our work is based on numerical simulations. As much as we tended to describe our results as real life scenarios for brevity and clarity in the text, these results are only provisional until confronted with empirical facts. Empirical investigations were left outside the scope of this thesis, but they remain necessary if we are not to lose sight of reality.

The assumption that vaccination decision is based on individual cost-benefit analyses is less restrictive than it may seem since the welfare of others can in principle be included in private utilities. The assumption of rationality, however, is more restrictive but it remains a standard way to produce internally consistent benchmarks. In the applications of our work to economic evaluations, our point was to consider strategic interactions in standard frameworks, and certainly not to challenge the whole of these otherwise well-established methods.

The same argument goes for the use Nash equilibria. We presented results in terms of Nash equilibria without examining how such equilibria might be reached. This question is essential in the fields of ecology and evolutionary game theory, and borrowing concepts from these disciplines might prove fruitful in the future. To a very limited extent, this is what we did in Chapter 3. As for the stability of our solutions, our investigations are restricted to robustness checks (especially on the slope parameter of the smoothed best response function) without in depth formal discussion of the properties of the dynamical system.

This is brings us to the lack of some mathematical foundations in our work. We gave rationales to interpret the smoothed best response as an approximation for mixed strategy best responses. Yet doing this formally would require two mathematical proofs that do not appear in this thesis as we focused on producing operational results. First, showing that for all sequence of slope parameters going to infinity, the corresponding sequence of solutions of the dynamical system converges to a unique limit. This requires to consider several candidate modes of convergence, among which pointwise convergence and uniform convergence. Second, showing that this limit is a mixed strategy Nash equilibrium. This being said, the smoothed best response can also be interpreted in terms of the aggregate of noisy best responses, which is a standard interpretation in economics and computational social sciences.

Discussing results in terms of mixed strategies is especially meaningful for engaging with

researchers working on mean field game approaches. Some of them have recently developed models that share several qualities with ours: they are versatile, they allow to compute full dynamic solutions of the vaccination game, and they do not rely on simplifying assumptions. Having in mind that simulations only make sense if they are run over a range of parameter values, our preference will go to the faster method (for a given and relevant solution quality). The performance of the solution method used in this thesis varies a lot from one problem instance to another. It typically took from few seconds up to several hours to compute a single solution. Determining what method falls behind or outperforms the other might demand systematic comparisons in each application case. Yet some investigations on the properties of our solution method, for instance proving convergence formally, remain to be done analytically.

Finally, while our approach opens up many modeling possibilities, it will not always be relevant. It only applies to strategic *and* anticipatory behavior. That is, to situations where the payoffs and decisions of each individual depend on the decisions of all other individuals, and at the same time where events and decisions unfold over a period of time. If individuals can reasonably be described as passive, then the case falls outside the scope of game theory (and even economics). For instance, individuals might passively go from one health status to another and anticipate it. This anticipation would however not have strategic implications. If individuals have the ability to adapt to others' decisions but cannot influence others' payoffs, then the interaction is still not strategic. If there is a strategic interaction but all individuals decide at the same time, then a static one period game will be sufficient to describe the situation. The tool we developed in this thesis calls for careful justification when put to use.

Appendices

Appendix A

Theoretical supplement to Chapter 1

A.1 Alternative formulation of the problem

In Equations A.1a–A.2d, we provide an alternative formulation of Equations 1.1a–1.2d making the construction of the model more apparent.

$$\begin{aligned} s^\epsilon(t+dt) =& s^\epsilon(t)\left[1-\alpha\chi_\epsilon(V_V^\epsilon(t+dt)-V_S^\epsilon(t+dt)-c)dt-\lambda\frac{i^\epsilon(t)}{n^\epsilon(t)}dt-\mu dt\right] \\ &+\nu n^\epsilon(t)dt+\gamma_V v^\epsilon(t)dt \end{aligned} \tag{A.1a}$$

$$i^\epsilon(t+dt) = i^\epsilon(t)\left(1-\gamma_I dt+\lambda\frac{s^\epsilon(t)}{n^\epsilon(t)}dt-\mu dt\right) \tag{A.1b}$$

$$v^\epsilon(t+dt) = v^\epsilon(t)(1-\gamma_V dt-\mu dt)+\alpha s^\epsilon(t)\chi_\epsilon(V_V^\epsilon(t+dt)-V_S^\epsilon(t+dt)-c)dt \tag{A.1c}$$

$$r^\epsilon(t+dt) = r^\epsilon(t)(1-\mu dt)+\gamma_I i^\epsilon(t)dt \tag{A.1d}$$

$$\begin{aligned} V_S^\epsilon(t) =& u_g dt+(1-\delta dt)\left\{\lambda\frac{i^\epsilon(t)}{n^\epsilon(t)}V_I^\epsilon(t+dt)dt+\alpha\xi_\epsilon(V_V^\epsilon(t+dt)-V_S^\epsilon(t+dt)-c)dt\right. \\ &\left.+\left(1-\mu dt-\lambda\frac{i^\epsilon(t)}{n^\epsilon(t)}dt\right)V_S^\epsilon(t+dt)\right\} \end{aligned} \tag{A.2a}$$

$$V_I^\epsilon(t) = u_b dt+(1-\delta dt)\left\{\gamma_I V_R^\epsilon(t+dt)dt+(1-\mu dt-\gamma_I dt)V_I(t+dt)\right\} \tag{A.2b}$$

$$V_V^\epsilon(t) = u_g dt+(1-\delta dt)\left\{\gamma_V V_S^\epsilon(t+dt)dt+(1-\mu dt-\gamma_V dt)V_V^\epsilon(t+dt)\right\} \tag{A.2c}$$

$$V_R^\epsilon(t) = u_g dt+(1-\delta dt)(1-\mu dt)V_R^\epsilon(t+dt) \tag{A.2d}$$

for t in $[0,T]$.

A.2 Proof of Theorem 1

This proof was derived by P. Michel.

Without loss of generality, Equations 1.1a–1.2d can be normalized by introducing

$$\Delta^\epsilon_{VS}(t) = V^\epsilon_V(t) - V^\epsilon_S(t), \quad \Delta^\epsilon_{IR}(t) = V^\epsilon_I(t) - V^\epsilon_R(t), \quad \Delta^\epsilon_{IS}(t) = V^\epsilon_I(t) - V^\epsilon_S(t),$$
$$\overline{s^\epsilon}(t) = s^\epsilon(t)/n^\epsilon(t), \quad \overline{i^\epsilon}(t) = i^\epsilon(t)/n^\epsilon(t), \quad \overline{v^\epsilon}(t) = v^\epsilon(t)/n^\epsilon(t), \quad \overline{r^\epsilon}(t) = r^\epsilon(t)/n^\epsilon(t).$$

For all t in $[0, T]$ we get

$$\frac{d}{dt}\overline{s^\epsilon}(t) = -\,\overline{s^\epsilon}(t)\left(\alpha\chi_\epsilon(\Delta^\epsilon_{VS}(t) - c) + \lambda\overline{i^\epsilon}(t) + \nu\right) + \nu + \gamma_V\overline{v^\epsilon}(t) \tag{A.3a}$$

$$\frac{d}{dt}\overline{i^\epsilon}(t) = -\,\overline{i^\epsilon}(t)\left(\gamma_I - \lambda\overline{s^\epsilon}(t) + \nu\right) \tag{A.3b}$$

$$\frac{d}{dt}\overline{v^\epsilon}(t) = -\,\overline{v^\epsilon}(t)\left(\gamma_V + \nu\right) + \alpha\overline{s^\epsilon}(t)\chi_\epsilon(\Delta^\epsilon_{VS}(t) - c) \tag{A.3c}$$

$$\frac{d}{dt}\overline{r^\epsilon}(t) = -\,\overline{r^\epsilon}(t)\nu + \gamma_I\overline{i^\epsilon}(t) \tag{A.3d}$$

and

$$-\frac{d}{dt}\Delta^\epsilon_{VS}(t) = -\,(\delta + \mu + \gamma_V)\Delta^\epsilon_{VS}(t) - \alpha\xi_\epsilon(\Delta^\epsilon_{VS}(t) - c) - \lambda\overline{i^\epsilon}(t)\Delta^\epsilon_{IS}(t) \tag{A.4a}$$

$$-\frac{d}{dt}\Delta^\epsilon_{IS}(t) = (u_b - u_g) - (\delta + \mu + \lambda\overline{i^\epsilon}(t))\Delta^\epsilon_{IS}(t) - \alpha\xi_\epsilon(\Delta^\epsilon_{VS}(t) - c) - \gamma_I\Delta^\epsilon_{IR}(t) \tag{A.4b}$$

$$-\frac{d}{dt}\Delta^\epsilon_{IR}(t) = (u_b - u_g) - (\delta + \mu + \gamma_I)\Delta_{IR}(t) \tag{A.4c}$$

By definition, $\overline{s^\epsilon}(t) + \overline{i^\epsilon}(t) + \overline{r^\epsilon}(t) + \overline{v^\epsilon}(t) = 1$. Hence we can write Equations A.3a–A.4c as fixed-point problem

$$(\overline{s^\epsilon}(t), \overline{i^\epsilon}(t), \overline{v^\epsilon}(t), \Delta^\epsilon_{VS}(t), \Delta^\epsilon_{IS}(t), \Delta^\epsilon_{IR}(t)) = \Phi(\overline{s^\epsilon}(t), \overline{i^\epsilon}(t), \overline{v^\epsilon}(t), \Delta^\epsilon_{VS}(t), \Delta^\epsilon_{IS}(t), \Delta^\epsilon_{IR}(t)).$$

After some computation on the integral version of Equations A.3a–A.4c, we have

$$\sup_{[0,t]}\|\Phi(u) - \Phi(v)\|(t) \leq C_\epsilon(t)\sup_{[0,t]}\|u - v\|(t),$$

where

$$C_\epsilon(t) \leq t\,\max\begin{bmatrix} \alpha(1 + \frac{1}{4\epsilon}) + 2\lambda + \nu + \gamma_V, \\ \gamma_I + 2\lambda + \nu, \\ \gamma_V + \nu + \alpha(1 + \frac{1}{4\epsilon}), \\ \delta + \mu + \gamma_V + 3\alpha + \lambda, \\ \delta + \mu + 2\lambda + 3\alpha + \gamma_I \end{bmatrix}.$$

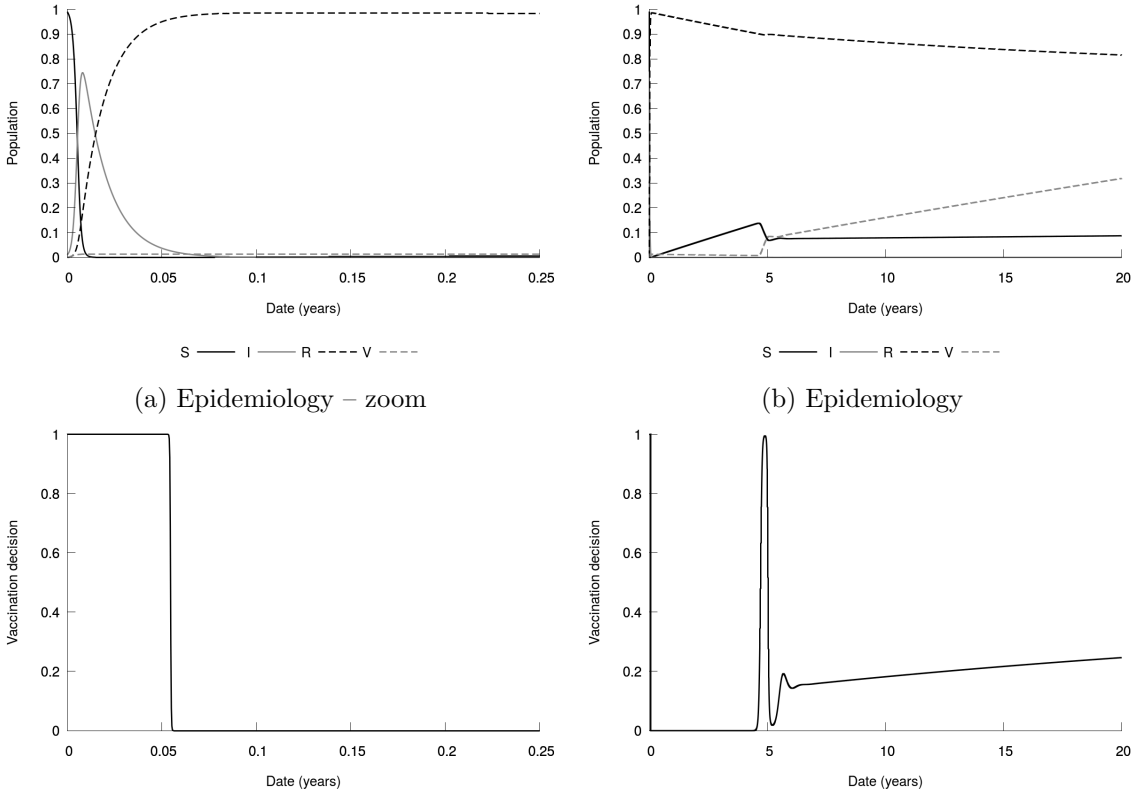
Let $M = C_\epsilon(T) + 1$. Then

$$\sup_{t\in[0,T]} \|(\Phi(u) - \Phi(v))e^{-Mt}\|(t) \leq \frac{C_\epsilon(T)}{M}\left(1 - e^{-MT}\right) \sup_{t\in[0,T]} \|(u - v)e^{-Mt}\|(t).$$

Hence, by contraction mapping theorem on $C^0([0,T])$, there exists a unique solution to Equations A.3a–A.4c and hence to Equations 1.1a–1.2d.

Appendix B

Robustness checks and sensitivity analysis for Chapter 1



(a) Epidemiology – zoom

(b) Epidemiology

(c) Vaccination decision – zoom

(d) Vaccination decision

Figure B.1: Epidemiological results and vaccination decisions with $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$.

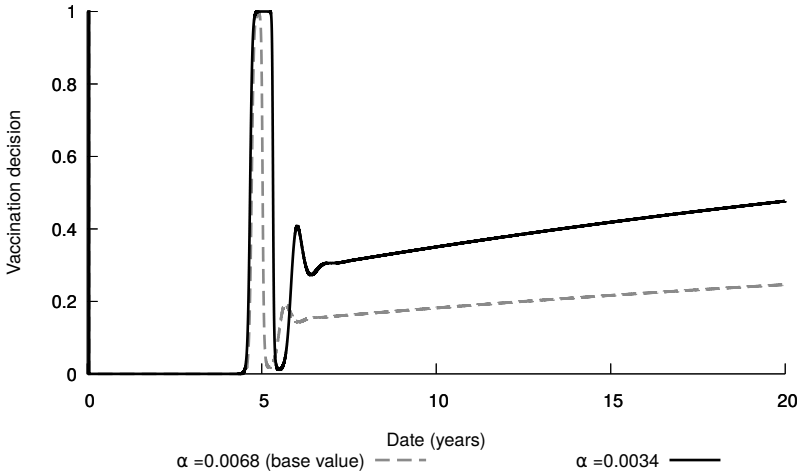
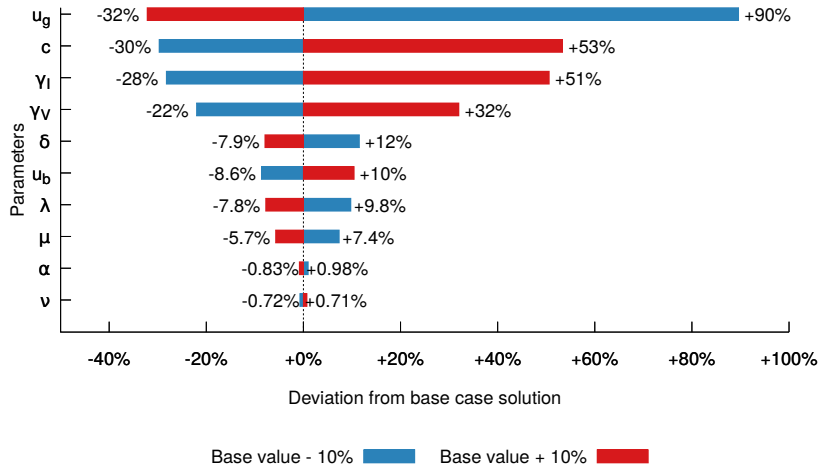
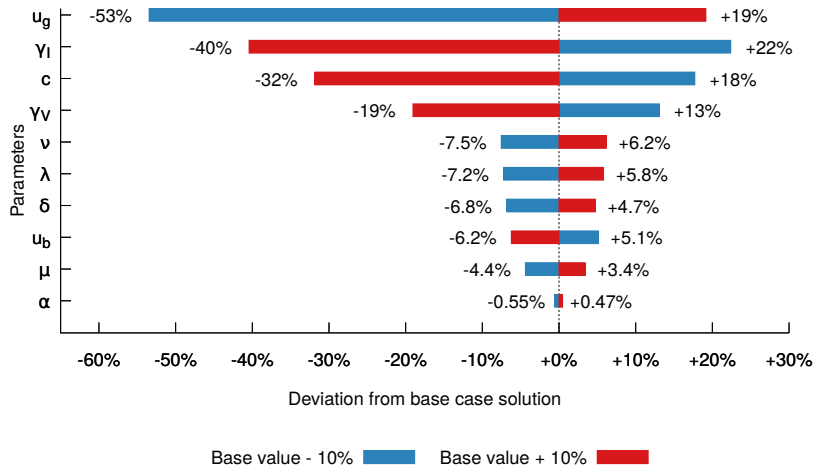


Figure B.2: Sensitivity to α of the long term vaccination decision in our base case model for $\epsilon = 1/20$.

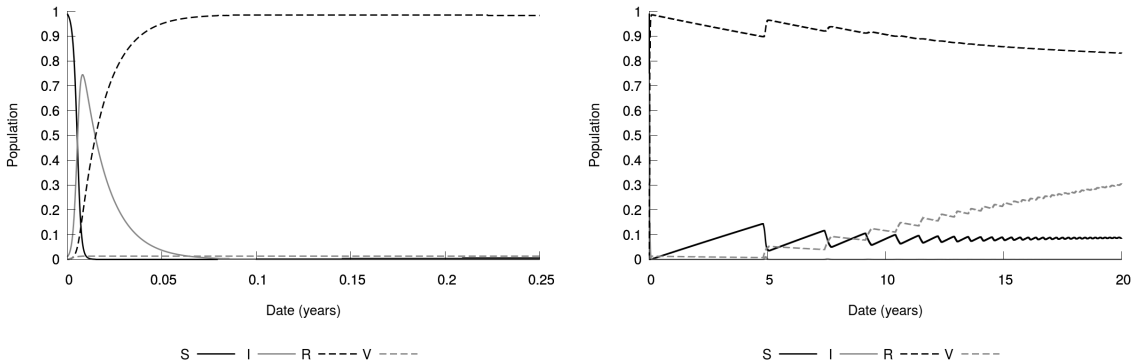


(a) Stationary i/n sensitivity



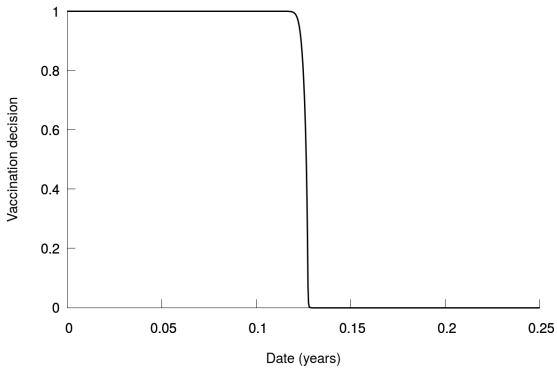
(b) Stationary v/n sensitivity

Figure B.3: Sensitivity analysis of the steady state values of i/n and v/n in our base case model for $\epsilon = 1/20$, and a $\pm 10\%$ variation of each parameter.

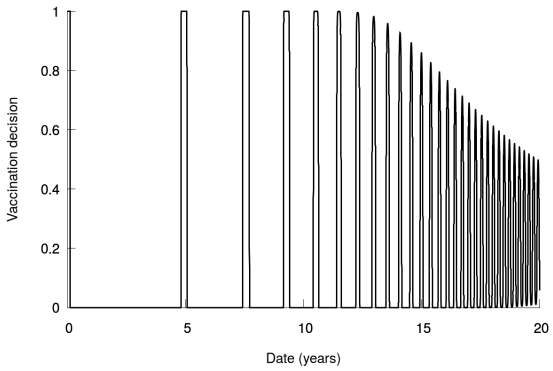


(a) Epidemiology – zoom

(b) Epidemiology



(c) Vaccination decision – zoom

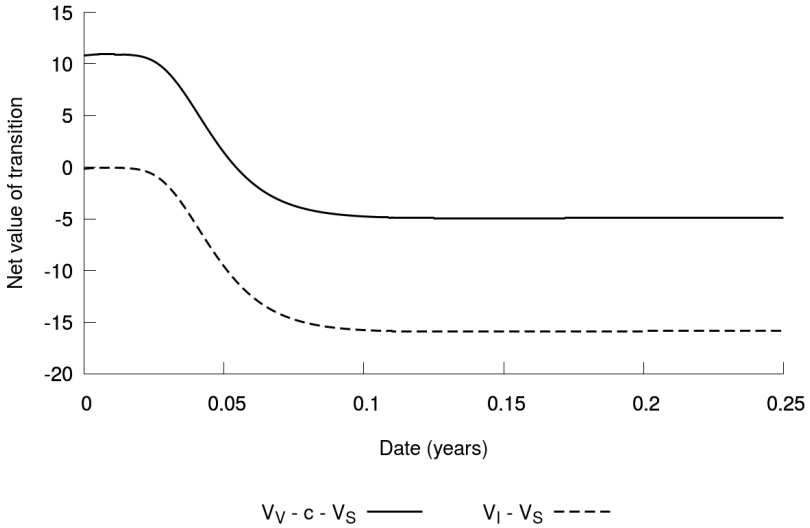


(d) Vaccination decision

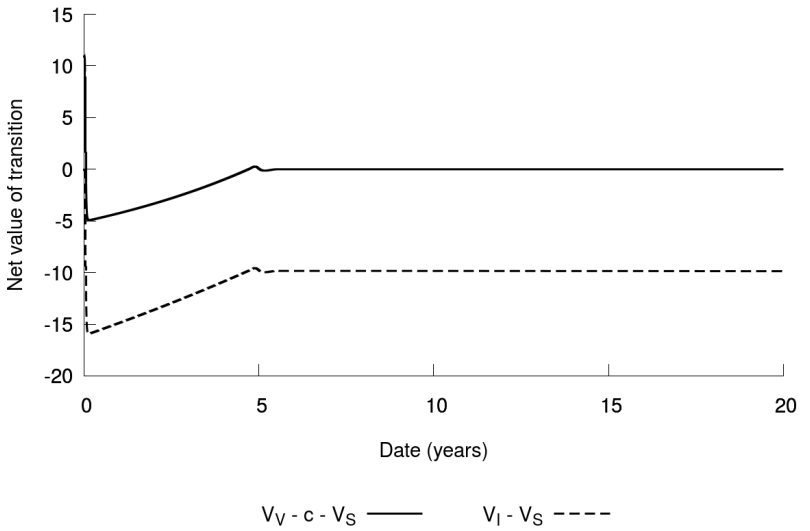
Figure B.4: Epidemiological results and vaccination decisions with $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$ – Individuals with adaptive behavior.

Appendix C

Additional results to Chapter 1

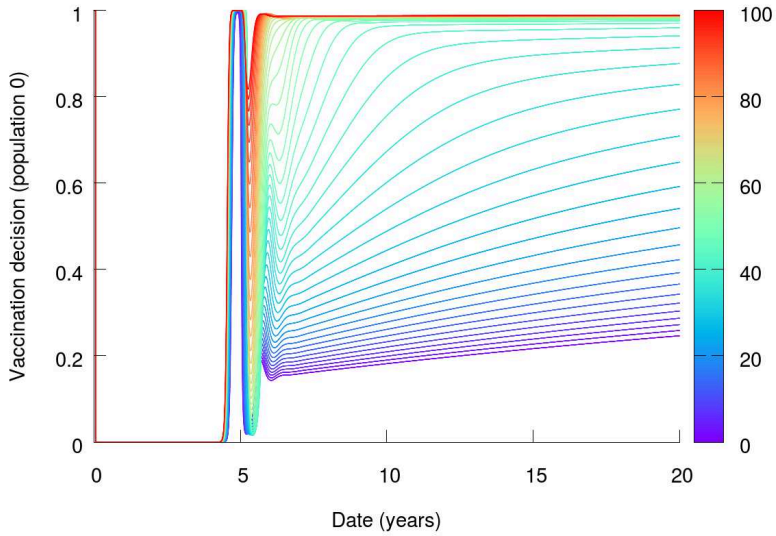


(a) First quarter of the epidemic

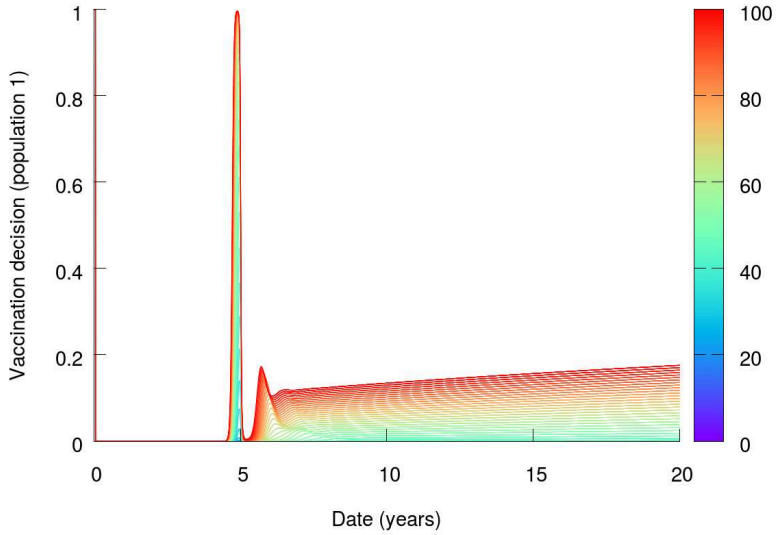


(b) First 20 years of the epidemic

Figure C.1: Net value of health status transition for vaccination cost $c = 10$, $\epsilon = 1/600$, and $n^{\epsilon}(0) = 1$.

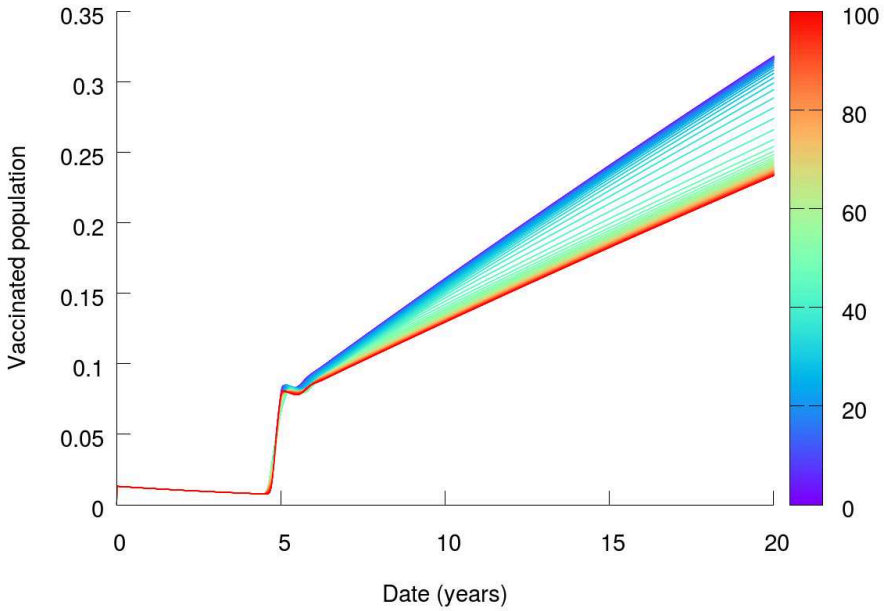


(a) Population 0

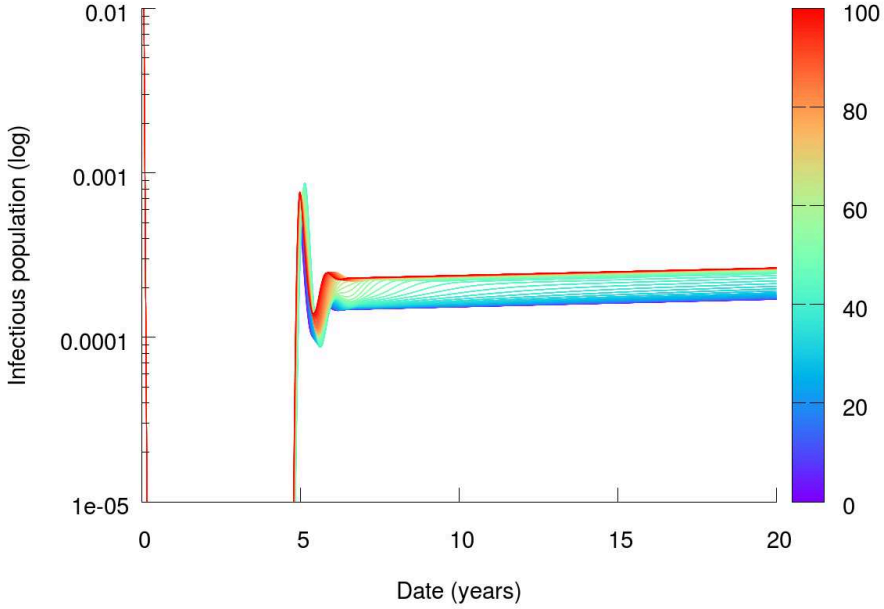


(b) Population 1

Figure C.2: Vaccination decisions for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 11$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.

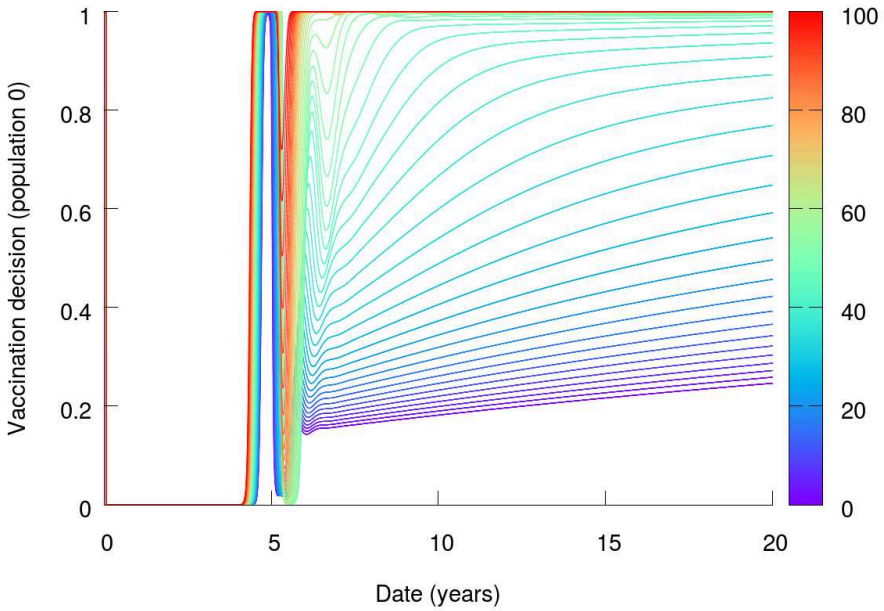


(a) Total number of vaccinated individuals in both populations

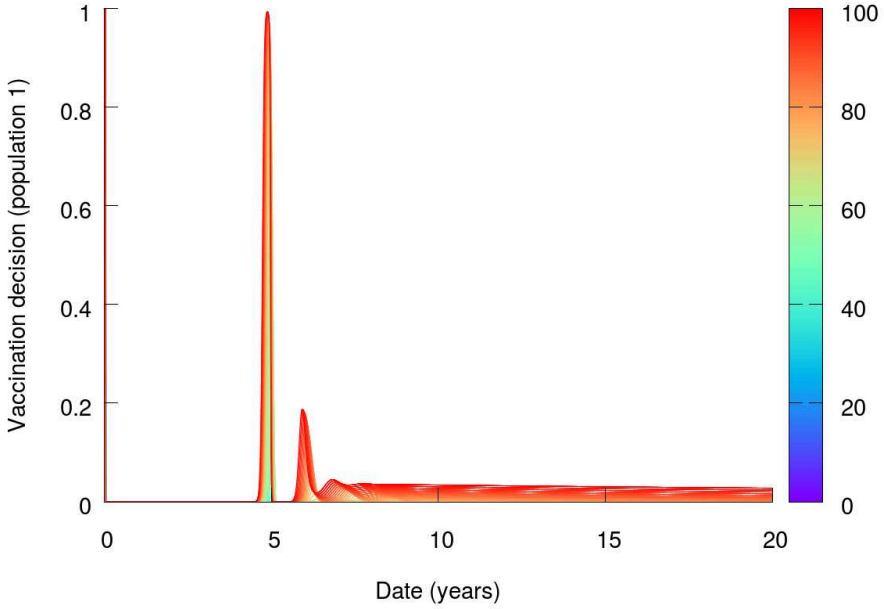


(b) Total number of infectious individuals in both populations

Figure C.3: Epidemiological results for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 11$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.

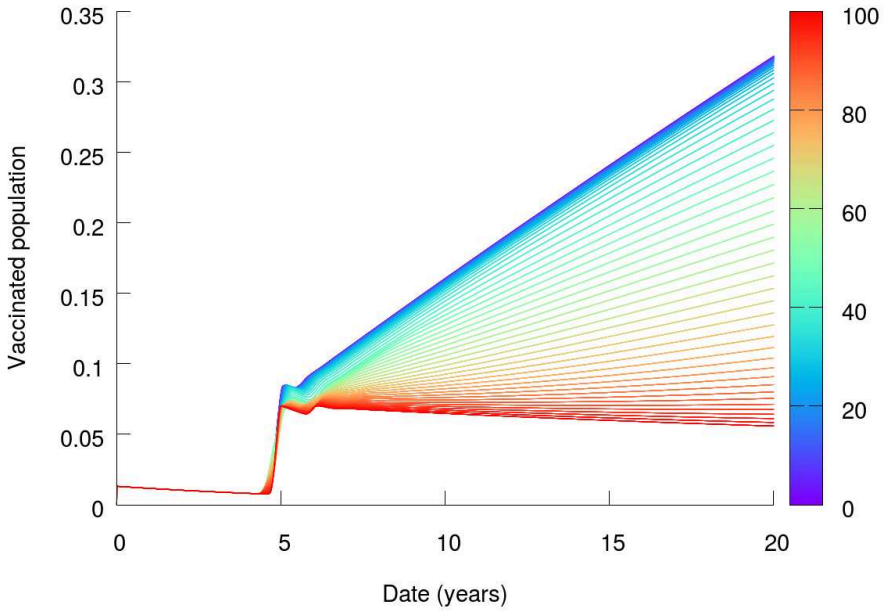


(a) Population 0

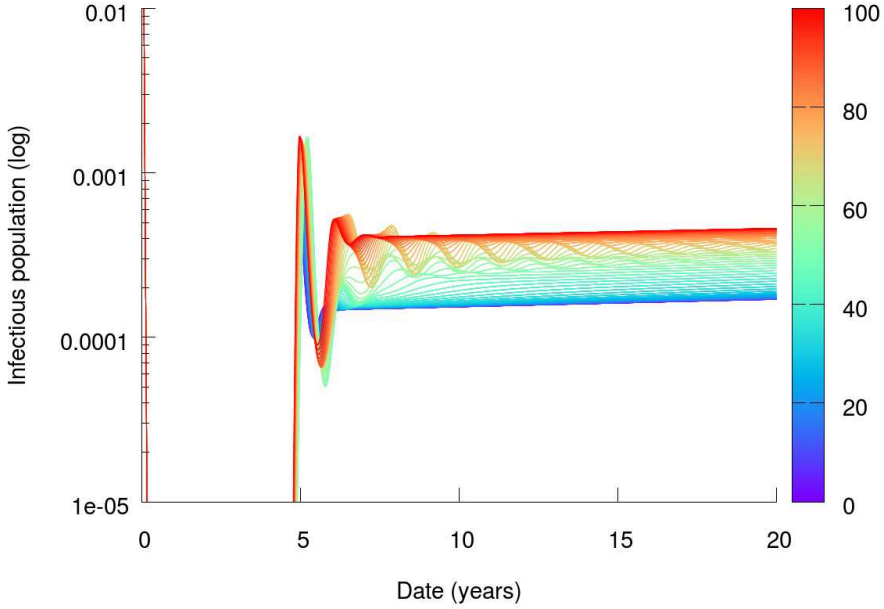


(b) Population 1

Figure C.4: Vaccination decisions for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 12$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.

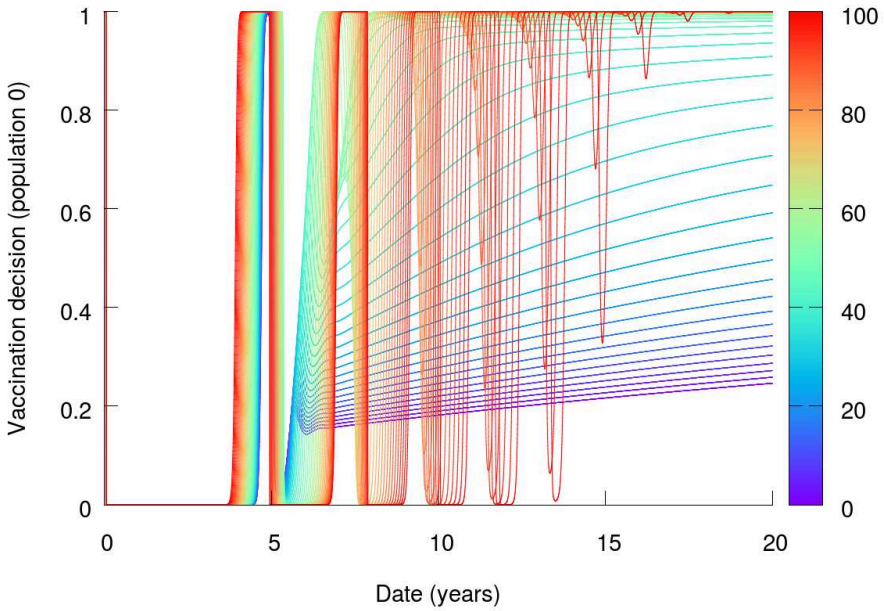


(a) Total number of vaccinated individuals in both populations

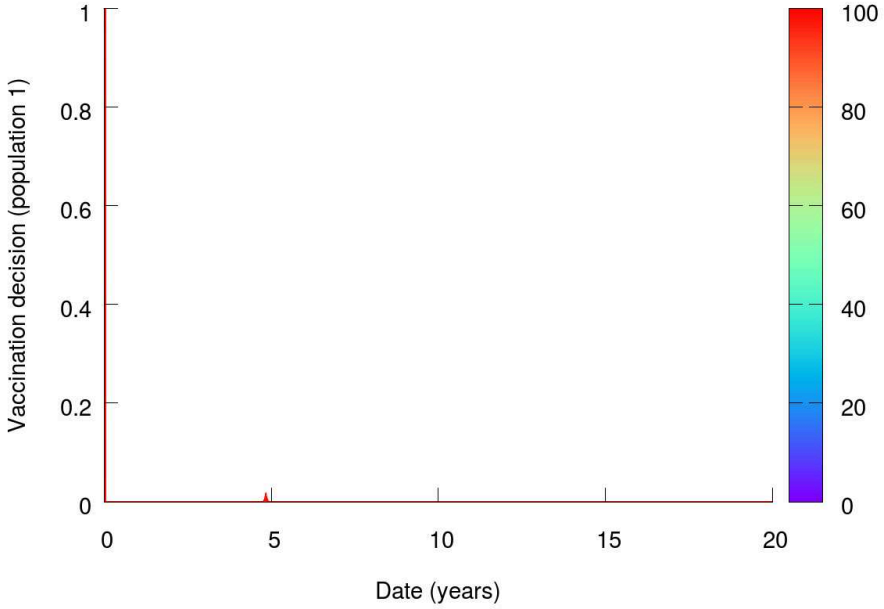


(b) Total number of infectious individuals in both populations

Figure C.5: Epidemiological results for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 12$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.

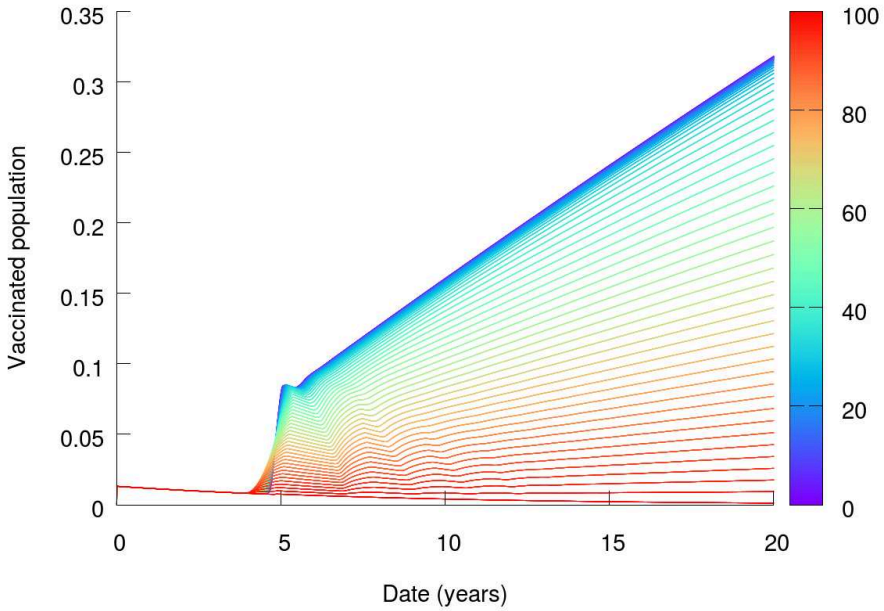


(a) Population 0

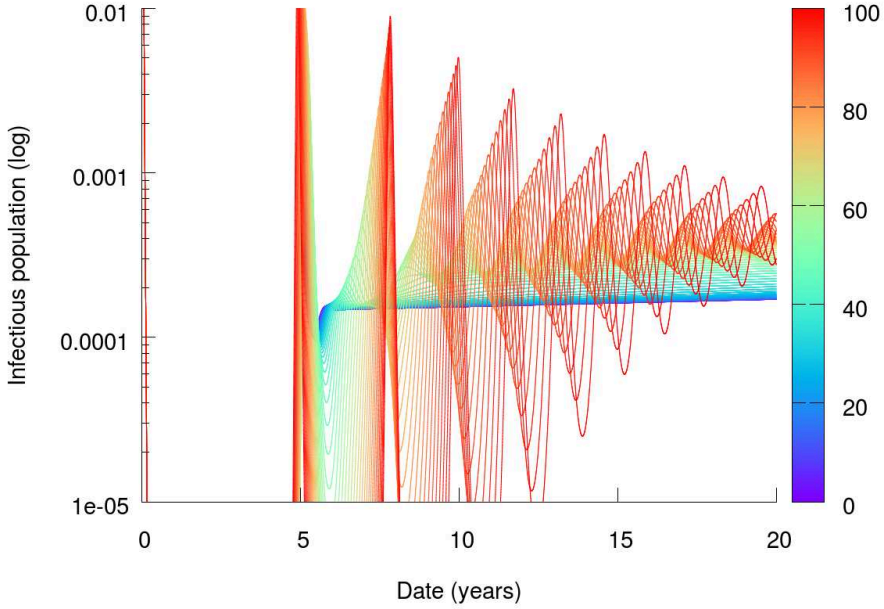


(b) Population 1

Figure C.6: Vaccination decisions for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 15$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.



(a) Total number of vaccinated individuals in both populations



(b) Total number of infectious individuals in both populations

Figure C.7: Epidemiological results for two perfectly mixed populations with different costs to vaccinate. *Population 0:* $c = 10$. *Population 1:* $c = 15$. $\epsilon = 1/20$ and $n^{\epsilon}(0) = 1$. Color scale indicates the proportion of individuals in Population 1.

Appendix D

Mandatory vaccination: results for $\alpha_{\mathsf{av}} = 1\%$

In this appendix, we provide results for $\alpha_{\text{av}} = 1\%$ as a robustness check. We also performed simulations for α_{av} as high as 12% but there was little qualitative difference with the case $\alpha_{\text{av}} = 4\%$ presented in the main text.

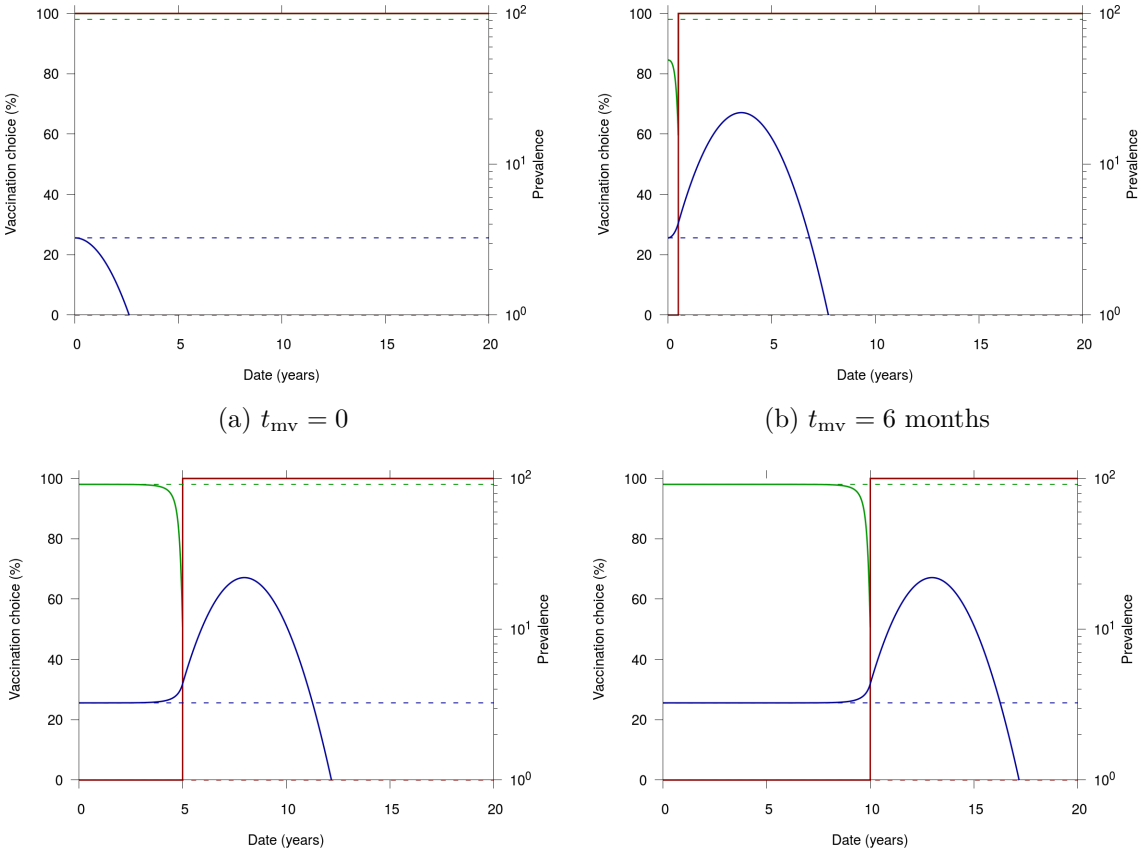
For $\alpha_{\text{av}} = 1\%$, calibration to a 250 cases per year per 6×10^7 individuals yields $c_{\text{v}} = 8.08 \times 10^{-3}$ and $c_{\text{av}} = 1.14 \times 10^{-2}$. Vaccination costs are higher than for $\alpha_{\text{av}} = 4\%$ (Table 2.1).

Due to higher vaccination costs, less than 100% of the vaccinationists and 0% of the anti-vaccinationists vaccinate initially (Figure D.1). For the same reason, vaccination by vaccinationists drops significantly before mandatory vaccination date t_{mv}. As a consequence, prevalence increases faster and is significant for a wider range of t_{mv} values (Figures D.1 and D.2c).

When vaccination is mandatory, both subpopulations have to pay a substantially higher cost than for $\alpha_{\text{av}} = 4\%$, which reduces their welfare (Figure D.3). In the case of anti-vaccinationists (Figure D.3b), the herd immunity externality does not compensate for this higher vaccination cost.

In Figure D.4, the value of being susceptible at time 0, when mandatory vaccination is announced, only increases as mandatory vaccination date t_{mv} gets very close from 0. This is because prevalence increases significantly even for relatively small values of t_{mv}. The spike in prevalence offsets the benefits of eradication if mandatory vaccination comes into force more than a few months after announcement.

The value of being susceptible and less than 14 months (green and red curves on Figure D.4) is low or negative as children have a high probability of turning 14 months after t_{mv}. If they do, they have to pay their high vaccination cost. Their value increases as the probability of turning 14 months after t_{mv} decreases.



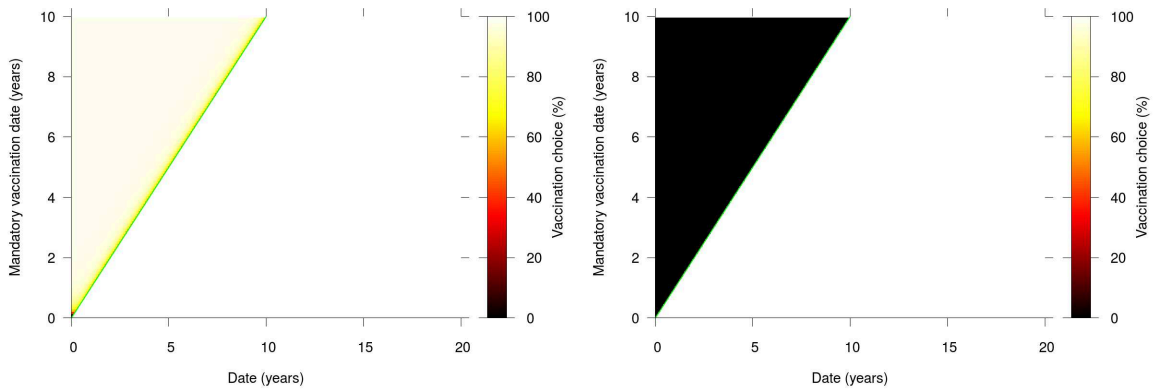
(a) $t_{\mathrm{mv}} = 0$

(b) $t_{\mathrm{mv}} = 6$ months

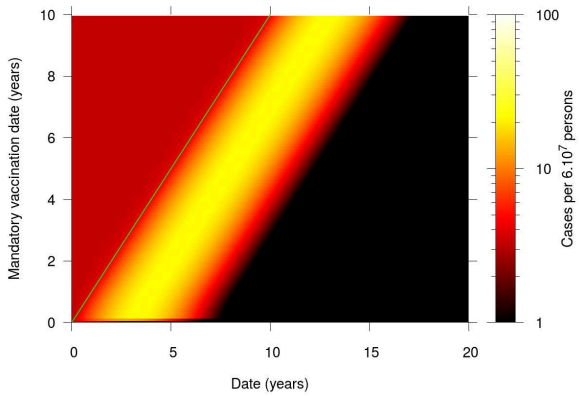
(c) $t_{\mathrm{mv}} = 5$ years

(d) $t_{\mathrm{mv}} = 10$ years

Figure D.1: Prevalence and vaccination decisions for $\alpha_{\mathrm{av}} = 1\%$. *Green (left axis):* vaccination decision by vaccinationists. *Red (left axis):* vaccination decision by anti-vaccinationists. *Blue (right axis):* instantaneous prevalence per 6×10^7 persons. *Dashed:* initial state.

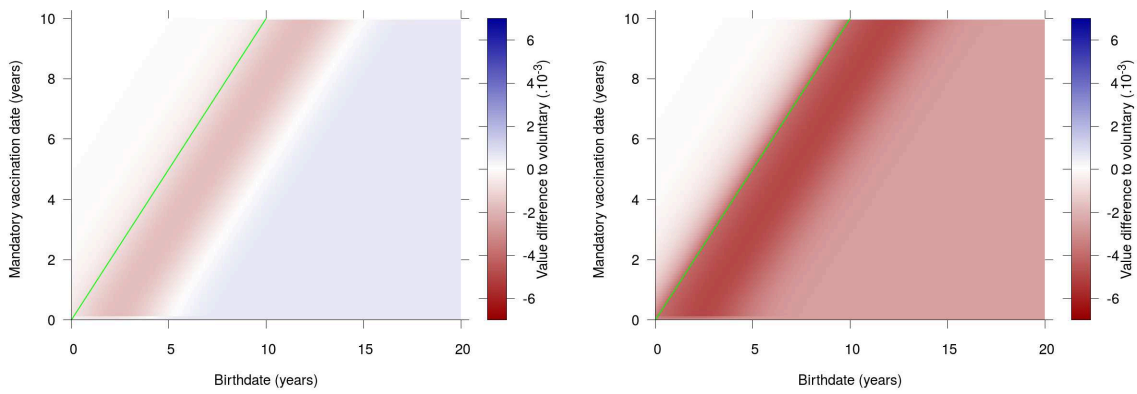


(a) Vaccination decision by vaccinationists (b) Vaccination decision by anti-vaccinationists



(c) Instantaneous prevalence

Figure D.2: Vaccination decisions and prevalence for a mandatory vaccination date (t_{mv}) between 0 and 10 years for $\alpha_{\text{av}} = 1\%$. *Green:* date $t = t_{\text{mv}}$.



(a) Vaccinationists (b) Anti-vaccinationists

Figure D.3: Value difference between mandatory vaccination scenario and benchmark scenario for children born after time 0 for $\alpha_{\text{av}} = 1\%$. *Green:* birthdate $t = t_{\text{mv}}$.

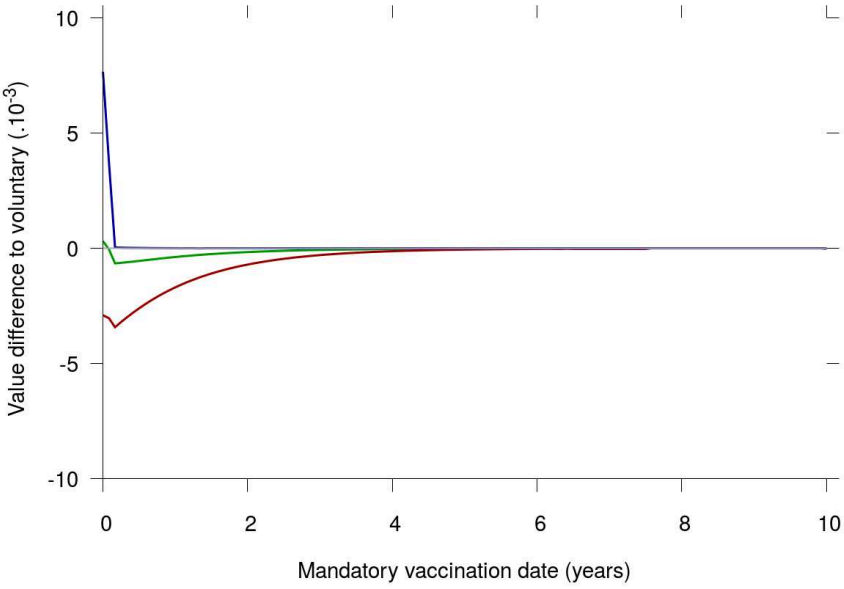


Figure D.4: Value difference at time 0 for susceptible children born before time 0 for $\alpha_{\mathrm{av}} = 1\%$. *Blue:* individuals older than 14 months. *Green:* vaccinationists younger than 14 months. *Red:* anti-vaccinationists younger than 14 months.

A simulation based approach to vaccination behavior

We tackle the issue of including individual vaccination decisions in epidemiological models. We draw on the example of Measles vaccination, and we focus on strategic interactions and anticipatory behavior. We contribute to a fuller account of such behaviors by developing a modeling approach intended as a tool for practitioners and theorists.

In Chapter 1, we show how the interplay between individual anticipatory vaccination decisions and the otherwise biological dynamics of a disease may lead to the emergence of recurrent patterns. We consider a Measles-like outbreak, rational and far-sighted individuals, vital dynamics, and waning vaccine efficacy. This chapter illustrates the versatility of our approach. For comparison, we provide results for individuals with adaptive behavior.

In Chapter 2, we investigate the effect of anticipatory behavior in a scenario where Measles vaccination becomes mandatory. When mandatory vaccination is announced in advance, we show that individuals may alter their vaccination behavior, thus causing an increase in prevalence before Measles is ultimately eradicated. These transition effects lead to non negligible welfare differences between generations. We consider an anti-vaccinationist subpopulation with a higher vaccination cost, and exhibit scenarios where anti-vaccinationists are among those who benefit the most from mandatory vaccination.

In Chapter 3, we discuss whether coalitions of vaccinating individuals can account for the relatively high vaccination coverages observed in developed countries. We explain why and how retaliation concepts usually found in repeated games can be used in the context of vaccination, even though individuals vaccinate only once. This allows us to model how vaccinating individuals might retaliate against those who refuse vaccination. We show that retaliation threats can sustain vaccination where it would otherwise be suboptimal for individuals.

Keywords: vaccination, game theory, epidemics, forward-backward system, backward induction, cost-effectiveness analysis, mandatory vaccination, cooperation, Measles