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Prevention of infectious diseases in the context of effective treatment: a game-theoretic approach

*La prévention des maladies infectieuses dans le contexte de traitements efficaces :
une approche par la théorie des jeux*

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Preface

This thesis was prepared at the Pierre Louis Institute of Epidemiology and Public Health (IPLESP – join unit of research and health UMRS 1136 of Sorbonne University (SU) & Inserm), within the team of Communicable diseases surveillance and modelling.

The first three years of PhD were funded through a doctoral contract from the French ministry of higher education and research, awarded through the Doctoral network in public health (RDSP), coordinated by the School of advanced studies in public health (EHESP). The fourth year of the PhD was funded by a research grant from the French research agency on AIDS and viral hepatitis (ANRS). During the last year of thesis, the PhD candidate held a research and teaching adjunct contract (ATER) at the Biology Faculty of SU and the Laboratory of Computational and Quantitative Biology (LCQB – join unit of research UMR 7238 SU & CNRS).

This thesis is devoted to public health issues in infectious disease epidemiology and individual behaviors regarding prevention, from the perspective of mathematical modeling. The approach is interdisciplinary, covering expertise from health-care providers about scientific communication, clinical trials processes and the implementation of public health interventions, next to epidemiological models of disease transmission and economics tools to model decision-making and data on individual behavior.

The completion of this thesis is contemporaneous with three major events of epidemiological interest. First, the resurgence of measles due to decline in vaccine coverage, after decades of successful mitigation. Second, the authorization and rollout of pre-exposure prophylaxis against HIV infection for at-risk individuals. Third, the emergence of the SARS-CoV-2 pandemic, which yielded broad implementation of non-pharmaceutical prevention interventions as well as the rollout of mass vaccination vaccination programs. These events highlight the pertinence and urgency to study epidemic control through

prevention interventions, accounting for the active participation of individuals.

This manuscript is structured as follows: [chapter 1](#) presents a general introduction to the subject of voluntary prevention of infectious diseases in a context where effective treatment exists, as well as the conceptual framework and modeling approaches that we used to study the subject. As part of my doctoral research, two scientific articles were produced ([Jijón et al., 2017](#); [Jijón et al., 2021](#)), which constitute the two main parts of this manuscript; [chapter 2](#) and [chapter 3](#) present these two articles, respectively. [Chapter 2](#) focuses on the modeling of voluntary vaccination against treatable childhood infectious diseases. [Chapter 3](#) focuses on the voluntary use of pre-exposure prophylaxis to avoid HIV infection among the population of men who have sex with men. Each of these two chapters includes a specific introduction, where the epidemiology of the public health issue that motivates our work is presented, as well as some additional material that was not included in the articles. [Chapter 4](#) presents a general discussion and conclusions.

An interdisciplinary note was written in the context of the RDSP, and is available in [Appendix A](#). This thesis is written in English; a detailed summary in French is provided in [Appendix B](#).

Abstract

Despite the current availability of effective preventive methods, controlling epidemics of preventable infectious diseases remains a key public health challenge. When facing an ongoing epidemic, individuals may decide to use prevention, or else to get treated in the case of acquiring the infection. Whereas treatment is generally well accepted by infected individuals, the acceptability of prevention may vary between individuals, which may lead to preventive behaviors that differ from the recommendations of the public health authorities.

My doctoral research concerns the mathematical modeling of infectious diseases transmission, taking into account the individuals' *prevention versus treatment dilemma*, the decision-making on whether or not to adopt prevention to avoid infection during an ongoing epidemic, in a context where efficient treatment is available. We aim to determine whether and under what conditions the voluntary adoption of prevention could avert an epidemic.

We propose a mathematical model that combines the disease transmission at the population level and the decision-making at the individual level. We model disease transmission using a compartmental model given by a system of ordinary differential equations. For the individual-level decision-making, we rely on a game-theoretic approach, which assumes that individuals solve the prevention versus treatment dilemma by choosing the strategy —to use prevention or not— that benefits them the most. The decision-making depends on the individuals' perception of their risk of infection, as well as on their perception of the relative cost of prevention versus treatment, which includes monetary and/or non-monetary aspects such as price, reimbursement policies, accessibility, social stigma, disease morbidity, undesired secondary effects, etc.

We explore two cases of the dilemma of prevention versus treatment. First, we address voluntary vaccination in the context of preventable and treatable childhood infectious diseases. In particular, we apply our methods and findings to the epidemiology of measles. Second, we study the voluntary adoption of pre-exposure prophylaxis to avoid HIV acquisition by the individuals who are most at risk of infection. In particular, we analyze the HIV epidemiology among one of the populations most at risk in France: men who have sex with men in the Paris region.

We obtain the probability that an individual voluntarily adopts prevention, as a function of the parameters of the prevention method (namely, effectiveness and cost). Our results suggest that epidemic elimination (i.e., the absence of new infections) is possible, provided that preventive methods are highly effective and that individuals perceive the relative cost of prevention

ABSTRACT

versus treatment to be low. However, epidemic elimination may be only temporary. Once the epidemic is averted, there is no long-term motivation to adopt prevention based in the individual's perception of the risk of infection. An important decrease in the number of infections may reveal less disease burden to individuals, who, in turn, perceive less benefit from prevention. In other words, epidemic elimination may induce a higher cost for prevention, as perceived by individuals. Hence, active efforts to maintain the cost of prevention low are required to preserve epidemic elimination in the long run.

Keywords. Behavioral epidemiology; Voluntary prevention; Epidemic elimination; Game theory; Compartmental model

Préface

Cette thèse a été réalisée au sein de l’Institut Pierre Louis d’Épidémiologie et de Santé Publique (IPLES – UMRS 1136 Sorbonne Université (SU) & Inserm), dans l’équipe Maladies transmissibles : surveillance et modélisation.

Les premières trois années de thèse ont été financées par un contrat doctoral du Ministère de l’enseignement supérieur et de la recherche, octroyé via le concours du Réseau Doctoral en Santé Publique (RDSP) coordonné par l’École des Hautes Études en Santé Publique (EHESP). La quatrième année de thèse a été financée par une allocation de recherche de l’Agence Nationale de Recherches sur le Sida et les Hépatites Virales (ANRS). La dernière année de thèse a eu lieu dans le cadre d’un contrat d’attaché temporaire d’enseignement et de recherche (ATER doctorant) au sein de la Faculté de Biologie de SU pour les activités d’enseignement et au sein du Laboratoire de Biologie Computationnelle et Quantitative (LCQB – UMR 7238 SU & CNRS) pour les activités de recherche.

Cette thèse étudie l’enjeu de santé publique concernant les épidémies de maladies infectieuses du point de vue de la modélisation mathématique, en tenant compte des comportements individuels en matière de prévention. Il était donc nécessaire d’utiliser des approches interdisciplinaires, allant des outils économiques pour modéliser la prise de décision et l’utilisation de données sur le comportement individuel, aux échanges avec les professionnels de la santé sur la communication scientifique, le déroulement d’essais cliniques et la mise en place d’interventions de santé publique.

Cette thèse a eu lieu pendant trois événements d’intérêt épidémiologique majeurs, qui mettent en évidence la pertinence et l’importance d’étudier l’impact potentiel des interventions de prévention sur les épidémies, en prenant en compte la participation active et volontaire des individus. Premièrement, la résurgence de cas de rougeole due à une diminution de la couverture vaccinale, après des décennies de contrôle. Deuxièmement, le déploiement de la prophylaxie pré-exposition

contre l'infection par le VIH et sa recommandation aux individus reconnaissant être à haut risque d'infection. Troisièmement, l'émergence de la pandémie du SARS-CoV-2, qui a donné lieu à l'implémentation d'interventions non pharmaceutiques ainsi qu'à des programmes de vaccination massive.

Cette thèse est une thèse sur articles. Elle est structurée comme suit : le [chapitre 1](#) présente une introduction générale du sujet de la prévention volontaire des maladies infectieuses dans le cadre où des traitements efficaces existent, ainsi que le cadre conceptuel et les approches de modélisation que nous avons utilisées pour étudier ce sujet. Dans le cadre de la thèse, deux articles scientifiques ont été rédigés ([Jijón et al., 2017](#); [Jijón et al., 2021](#)) et constituent les deux parties principales de ce manuscrit ; ainsi, le [chapitre 2](#) et le [chapitre 3](#) présentent respectivement ces deux travaux. Le [chapitre 2](#) est dédié à la vaccination volontaire contre les maladies infectieuses infantiles. Le [chapitre 3](#) est dédié à la modélisation de l'utilisation volontaire de la prophylaxie pré-exposition afin d'éviter l'acquisition du VIH, dans la population des hommes qui ont des rapports sexuels avec des hommes. Chacun de ces deux chapitres comprend une introduction spécifique, où l'épidémiologie du problème de santé publique qui motive notre travail est présentée, ainsi que du matériel supplémentaire qui n'a pas été inclus dans les articles. Le [chapitre 4](#) présente la discussion générale et les conclusions.

Une note interdisciplinaire a été préparée dans le cadre du RDSP, et est présentée dans l'[Appendice A](#). Cette thèse a été rédigée en anglais, et inclut un résumé détaillé en français dans l'[Appendice B](#).

Résumé

Malgré la disponibilité actuelle de méthodes préventives efficaces, le contrôle des épidémies de maladies infectieuses reste un défi majeur pour la santé publique. Face à une épidémie en cours, les individus peuvent décider d'utiliser la prévention ou de se faire traiter en cas d'infection. Alors que le traitement est généralement bien accepté par les individus infectés, l'acceptabilité de la prévention peut varier d'un individu à l'autre, ce qui peut conduire à des comportements préventifs qui diffèrent des recommandations des autorités de santé publique.

Mon sujet de thèse porte sur la modélisation mathématique de la transmission des maladies infectieuses, en prenant en compte le *dilemme de la prévention versus le traitement*, la prise de décision d'adopter ou non la prévention pour éviter l'infection, dans un contexte où un traitement efficace existe. L'objectif est de déterminer si la prévention volontaire pourrait prévenir une épidémie, et sous quelles conditions.

Nous proposons un modèle mathématique combinant la transmission de la maladie au niveau de la population et la prise de décision au niveau individuel. Nous modélisons la transmission de la maladie à l'aide d'un modèle compartimental donné par un système d'équations différentielles ordinaires. Pour la prise de décision au niveau individuel, nous utilisons une approche par la théorie des jeux, qui suppose que l'individu choisit la stratégie dont il bénéficie le plus, à long terme. La prise de décision dépend de la perception individuelle of the risque d'infection ainsi que la perception du coût relatif de la prevention versus le traitement, qui concerne des aspects monétaires et/ou non monétaires, comme le prix, les politiques de remboursement, l'accessibilité, le stigma social, la morbidité de la maladie, les effets secondaires indésirables, etc.

Deux cas de dilemme de prévention versus le traitement sont explorés. Premièrement, nous abordons la vaccination volontaire dans le contexte des maladies infectieuses infantiles évitables et pouvant être traitées. En particulier, nous appliquons nos méthodes et résultats à l'épidémie de la rougeole. Deuxièmement, nous étudions l'utilisation volontaire de la prophylaxie pré-exposition pour éviter l'acquisition du VIH par les individus à haut risque d'infection. En particulier, nous analysons l'épidémie du VIH parmi l'une des populations les plus à risque en France : les hommes qui ont des rapports sexuels avec les hommes en Île-de-France.

Nous avons obtenu la probabilité d'adopter volontairement la prévention, en fonction des paramètres de la méthode préventive (notamment, l'efficacité et le coût). Nos résultats suggèrent que l'élimination des épidémies (i.e., l'absence de nouvelles infections) est possible, à condition que les méthodes de prévention soient très efficaces et que les individus perçoivent le coût de la

prévention comme étant bas. Néanmoins, l'élimination de l'épidémie n'est que temporaire. Une fois l'épidémie éliminée, il n'y a plus de motivation à long terme pour adopter la prévention, basée sur la perception du risque d'infection. Une diminution importante du nombre d'infections peut amener les individus à ne plus percevoir les conséquences de l'infection et donc, à moins percevoir les avantages de la prévention. Autrement dit, l'élimination de l'épidémie peut amener aux individus à percevoir un coût de la prévention plus élevé. Par conséquent, des efforts pour maintenir le coût de la prévention bas sont nécessaires pour préserver l'élimination de l'épidémie à long terme.

Mots-clés. Épidémiologie comportementale ; Prévention volontaire ; Élimination épidémique ; La théorie des jeux ; Modèle compartimental.

Scientific production

Peer-reviewed articles

Jijón, S., Supervie, V., and Breban, R. (2017). Prevention of treatable infectious diseases: a game-theoretic approach. *Vaccine*, 37(40):5339–5345.
doi: [10.1016/j.vaccine.2017.08.040](https://doi.org/10.1016/j.vaccine.2017.08.040)

Submitted articles

Jijón, S., Supervie, V., and Breban, R. (2020). Can HIV epidemics among men who have sex with men be eliminated through participation to PrEP rollouts? [*Submitted to AIDS in January 2021; currently under peer-review*].

Other scientific contributions

Oral communications

Jijón, S., Molina, J.-M., Costagliola, D., Supervie, V., and Breban, R. Can HIV epidemics be eliminated through voluntary participation to PrEP rollouts?. EACS 2019 (Basel, Switzerland), November 6–9, 2019.

Abstract in EACS 2019 – Abstract book. *HIV Medicine*, 20(S9):35. DOI: 10.1111/hiv.12814.

Jijón, S., Prevención de enfermedades infecciosas en el contexto del tratamiento eficiente: un acercamiento por la teoría de juegos y una aplicación al VIH. [*Prevention of infectious diseases in the context of efficient treatment: a game-theoretic approach and an application*

to HIV epidemic]. Seminar organized by the MODEMAT Mathematical Modeling Centre (Quito, Ecuador), February 23, 2017.

Jijón, S. Can you prevent an epidemic by getting vaccinated?. Pint of Science Festival (Paris), May 21, 2019. [Vulgarization of science].

Poster communications

Jijón, S., Molina, J.-M., Costagliola, D., Supervie, V., and Breban, R. Can HIV epidemics be eliminated through voluntary participation to PrEP rollouts?. Presented at ANRS seminar, November 25–26, 2019.

Jijón, S., Supervie, V., and Breban, R. Prévention des maladies infectieuses : une approche par la théorie des jeux. Presented at the Université des Jeunes Chercheurs organized by Sidaction (Carry-le-Rouet, France), October 14–20, 2017, and at the ED 393 seminar (Saint-Malo, France), October 23–25, 2017.

Winner of the ED 393 Posters awards.

Jijón, S., Supervie, V., and Breban, R. Prevention of infectious diseases in the context of efficient treatment: a game-theoretic approach. Partial results presented at the ED 393 seminar (Saint-Malo, France), October 24–26, 2016.

Jijón, S., Supervie, V., and Breban, R. Prévention dans le contexte de traitement efficace : quel sera l'impact de la prophylaxie pré-exposition sur l'épidémie du VIH ? Presented at the ED 393 seminar (Saint-Malo, France), October 19–21, 2015.

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Acronyms and abbreviations

Acronyms

AIDS	Acquired immunodeficiency syndrome
ART	Anti-retroviral therapy
CDC	Centers for disease control and prevention
CI	Confidence interval
DFS	Disease-free state
ECDC	European centre for disease prevention and control
ES	Endemic state
GVAP	Global vaccine action plan
HIV	Human immunodeficiency virus
IdF	Île-de-France
MMR	Measles-Mumps-Rubella vaccine
MMWR	Morbidity and mortality weekly report from the CDC
MSM	Men who have sex with men
ODE	Ordinary differential equations
PrEP	Pre-exposure prophylaxis
STI(s)	Sexually-transmitted infection(s)
SDG	Sustainable Development Goals
TDF/FTC	Tenofovir disoproxil fumarate/Emtricitabine
UK	United Kingdom
US	United States
UNAIDS	Joint united nations program on HIV/AIDS
WHO	World health organization

Abbreviations

Eq(s). Equation(s)

Fig(s). Figure(s)

Ref(s). Reference(s)

ACCRONYMS AND ABBREVIATIONS

Glossary

Compliance. (Also called adherence). Behavior that follows the recommendations of a physician or other healthcare provider, or investigator in a research project ([Porta, 2013](#)).

Effectiveness (of prevention). Relative reduction in the number of infections, resulting from studies carried out under less than perfectly controlled conditions (more similar to typical behavior) ([CDC, 2006](#)).

Efficacy (of prevention). Relative reduction in the number of infections, resulting from studies carried out under ideal conditions (a.e., clinical trials) ([CDC, 2006](#)).

Eradication (of a disease). Termination of all transmission of infection by extermination of the infections agent through surveillance and globally coordinated efforts ([Porta, 2013](#)). Once the eradication status is achieved, control interventions are no longer necessary.

Herd immunity Immunity of a group or a community ([Porta, 2013](#)).

Incidence rate (force of infection, person-time incidence rate). Theoretical measure of the number of new cases that occur per unit of population-time. Mathematically defined as ([Porta, 2013](#))

$$\lim_{\Delta t \rightarrow 0} \frac{\text{Probability that a person well at time } t \text{ gets infected in the time interval } [t, t + \Delta]}{\Delta t}$$

which can be estimated by

$$\frac{\text{Number of new cases observed in the time interval } [t, t + \Delta]}{\text{Number of person-time units of experience observed in the time interval } [t, t + \Delta]}.$$

Incubation period. The interval of time between the infection and the first symptoms of disease ([Porta, 2013](#)).

Prevalence. Proportion of infected individuals at a specified time or period ([Porta, 2013](#)).

Prevention. Actions that prevent disease transmission and/or infection ([Porta, 2013](#)).

Prophylaxis. Preventive healthcare ([Porta, 2013](#)).

Chapter 1

General introduction

1.1 The prevention of infectious diseases

The prevention of infectious diseases has greatly improved, not only as a result of the development
5 of safe, highly-effective preventive methods, but also thanks to regional and global public health programs aiming for infectious diseases' elimination. During the last decade, the World Health Organization (WHO) developed the Global Vaccine Action Plan (GVAP) 2011–2020, aiming to ensure individuals to live free from vaccine-preventable diseases (WHO, 2020). As a result, vaccine coverage among children and vaccine development have shown a remarkable progress,
10 but many of the objectives remained unmet (WHO, 2020). Disease-specific programs were also developed to fight infectious diseases' epidemics. For instance, the Global Measles and Rubella Strategic Plan 2012–2020 (WHO, 2012), and the Fast Track to end AIDS epidemic (UNAIDS, 2011).

Nowadays, disease-prevention interventions are included in the WHO's 17 Sustainable Development Goals; specifically, in the 3rd goal: "To ensure healthy lives and promote well-being for all at all ages" (WHO, 2020a). The objectives concerning communicable diseases include to end, by 2030, the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases, as well as to end preventable deaths of newborns and children under 5 years of age (WHO, 2020a). The currently ongoing Immunization Agenda 2030, the successor of the GVAP 2011–2020, continues
20 to place immunization in the core of national strategies for primary health care and universal

health coverage ([WHO, 2019](#)). In parallel, a global program to end sexually transmitted diseases by 2030 is ongoing, aiming, for instance, to the elimination of cervical cancer through vaccination interventions against human papillomavirus ([WHO, 2016a](#)). The Fast Track initiative to end the AIDS epidemic is still ongoing, setting more ambitious and inclusive targets ([UNAIDS, 2014](#)).

25 Global preventive interventions have successfully impacted epidemics. Immunization alone can now prevent more than 20 life-threatening diseases ([WHO, 2019](#)). Between 2000 and 2018, vaccination against measles prevented an estimated 23 million deaths ([WHO, 2019b](#)); during the same period, the number of new HIV infections fell by 39%, thanks to preventive interventions ([WHO, 2019a](#)). The number of cases of poliomyelitis (commonly known as polio) 30 have decreased from an estimated 350 000 cases in 1988, to 33 reported cases in 2018 ([WHO, 2019d](#)). Meningococcal meningitis' incidence has decreased by 58% in a relatively short period of time ([WHO, 2019c](#)). Mass immunization programs achieved the eradication of smallpox in 1980¹ ([CDC, 2001](#)). Preventive interventions have decreased the overall number of new infections worldwide ([Global Public Health Achievements Team, 2011](#)) and placed some communicable diseases (such as measles and poliomyelitis) in the path towards elimination ([Global Public Health Achievements Team, 2011](#)).

1.1.1 Declaring epidemic elimination

Global (respectively, regional) epidemic elimination refers to the end of an epidemic as a public health concern, through a high or a complete reduction of the infectious disease transmission worldwide (respectively, in the region), during a period of active surveillance ([Porta, 2013; Nishiura, 2016](#)). Disease elimination does not imply the complete termination of disease transmission, nor the elimination of the infectious agent, as opposed to disease *eradication* ([Porta, 2013](#)).

Therefore, global programs aiming to disease elimination set specific targets to be met in a 45 certain amount of time and thus, declaring disease elimination may depend on the specific infectious disease and the context. Table 1.1 shows some disease-specific targets, currently included in WHO programs aiming regional and/or global elimination. The classical approach of the WHO to declare the end of an epidemic is to observe a significant period of time (for instance,

¹During the pre-vaccination era, the mortality rate due to smallpox infection were about 30% ([CDC, 2001](#)).

twice as long as the empirical maximum of the incubation period) passed after the last reported
50 case ([Nishiura, 2016](#)). However, the case-free period approach to determine disease elimination may depend highly on the sample size, be inappropriate for diseases with high proportions of asymptomatic cases ([Nishiura, 2016](#)), and depend greatly on prevention coverage ([Eichner and Dietz, 1996](#)). Other, rather heuristic ways to determine the end of an epidemic may also be used, depending on specific settings. For instance, the declaration of the elimination of the Middle
55 East respiratory syndrome (MERS) in Korea was made after the removal of movement restriction for the last quarantined case ([Nishiura, 2016](#)).

These kind of difficulties may be overcome using mathematical models to estimate the end of an epidemic. For instance, modeling studies have found that asymptomatic cases of poliomyelitis infection may still occur with a probability lower than 1%, after 5 years of having no symptomatic
60 cases within a 200 000 population ([Eichner and Dietz, 1996](#)). In addition, mathematical modeling may provide estimates of unobserved variables and parameters, as well as identify the criteria to be met to end an epidemic; thus being useful to set public health targets for epidemic elimination.

Infectious disease	Main targets	Target year	Ref.
HIV	<ul style="list-style-type: none"> • 90% reduction of transmissions, compared to 2010 • 95% of infected people to know their HIV status • 95% of diagnosed people to be on treatment • 95% of people on treatment to have suppressed viral load 	2030	(UNAIDS, 2014)
Measles	<ul style="list-style-type: none"> • Absence of cases for at least 3 years • Regional high vaccination coverage 	2020 ^{a,b}	(WHO, 2018a)
Poliomyelitis	<ul style="list-style-type: none"> • Absence of cases for at least 3 years • No circulation of wild strain 		(Eichner and Dietz, 1996)
Rubella	<ul style="list-style-type: none"> • Regional 95% reduction in the number of cases • Absence of cases for at least 3 years • Regional high vaccination coverage 	2020 ^b	(WHO, 2018a)
Yellow fever	<ul style="list-style-type: none"> • Reduce outbreaks to zero 	2026	(WHO, 2019)

Table 1.1 – Targets of some recent, global programs aiming to end infectious diseases

Some recently disease-specific targets set within the WHO programs aiming to end epidemics.

^a The American region was certified as having eliminated measles in 2016, after high vaccination coverage efforts, but lost its certification in 2018, after observing several outbreaks. Measles is currently endemic in all regions (WHO, 2020).

^b Unmet targets.

1.2 The prevention versus treatment dilemma

“An ounce of prevention is worth a pound of cure”, goes the popular saying. Yet, the individuals’
65 preference for prevention over treatment may not be guaranteed. Some studies have indeed found
a preference for prevention ([Bosworth et al., 2010](#); [Mortimer and Segal, 2008](#)), while others have
found a preference for treatment ([Corso et al., 2002](#); [Schwappach, 2002](#)) or not a significant
preference ([Ubel et al., 1998](#)). Preference has also been found to vary widely according, for
instance, to age and health state ([Luyten et al., 2015](#)) and to the perceived urgency of the
70 intervention ([Meertens et al., 2013](#)).

In high-income settings, individuals may face some difficulties and discomfort when adopting new behaviors and thus, individuals’ attitudes towards prevention may differ from the public health authorities’ recommendations. Therefore, when facing the risk of an epidemic, in a context where efficient treatment is available, individuals who find themselves at risk of infection
75 may engage in a *prevention versus treatment dilemma*, and make the decision between adopting prevention or not, and be treated in case of infection.

The adoption of prevention thus depends mainly on the individuals’ perception of its benefits and inconveniences versus those of treatment, as well as their perception on their own risk of infection. Public health authorities and healthcare providers may play an essential role shaping
80 these perceptions. For instance, by sharing information about epidemics and disease burden, as well as providing information on the available preventive and therapeutic tools, and increasing their availability and access.

Voluntary prevention is defined as the preventive methods adopted voluntarily by individuals to avoid infection. That is, by willingly following the recommendations of public health
85 authorities’ — in contrast to mandatory² prevention. To evaluate the impact of voluntary prevention on the epidemic dynamics, it is thus essential to account for individuals’ resolution of the prevention versus treatment dilemma. Here, we focus in the role of the individual-level decision-making, facing epidemic threat in a context where efficient preventive and therapeutic methods are available, from the epidemiological and mathematical modeling perspective.

²Required by law or community rules.

90 1.3 Mathematical and behavioral epidemiology of infectious diseases

Mathematical modeling of infectious diseases was used to assist public health decision-making for the first time in 1760³, when Daniel Bernoulli (1700–1782) studied smallpox and recommended universal inoculation to prevent smallpox-related mortality: "...it has been noticed that, on the 95 one hand, the more natural smallpox spreads, the more dangerous it is; and, on the other, that inoculation carried out at the height of an epidemic is not by any means as reliable as if it were done quite outside any epidemic" (Bernoulli, 1766; Blower and Bernoulli, 2004). Bernoulli's recommendation was based on his estimation of the number of lives saved by universal inoculation against smallpox (Blower and Bernoulli, 2004). The model proposed by Bernoulli consisted in 100 analyzing surveillance data consisting in the yearly number of individuals who had been infected, the number of deaths due to smallpox infection, etc. Then, he compared the number of smallpox deaths before and after the adoption of inoculation amid the population (Blower and Bernoulli, 2004; Dietz and Heesterbeek, 2002). In his paper, Bernoulli also acknowledged that individuals could be interested in being inoculated because of the benefits it offered at the individual level 105 (such as avoiding lethal infection), versus those offered at the population level (such as increasing the average life expectancy).

Since the 18th century, different kinds of models have been developed to describe epidemic dynamics (Brauer, 2017). Mathematical models are useful to understand the transmission mechanisms behind surveillance data, to estimate the values of parameters that cannot be directly 110 measured, to predict disease epidemiology and to select intervention designs aiming to control the epidemic and or the disease burden (Valleron, 2000). Mathematical epidemiology has thus become a powerful tool for public health decision-making and epidemic control (Valleron, 2000).

Behavioral epidemiology is a relatively recent branch of mathematical epidemiology that studies the interplay between the human behavior and the course of an epidemic (Manfredi and 115 D'Onofrio, 2013; Verelst et al., 2016; Wang et al., 2016). Behavioral epidemiology accounts for the role of human behavior as a key component of epidemic spread and the implementation of public health policies. For instance, by taking into account the changes in individual behavior as a response to epidemic dynamics and epidemic threats, as well as the individual attitudes

³The paper was first presented at the Royal Academy of Sciences in Paris in 1760 and then published in 1766.

towards the available preventive methods.

120 From the modeling perspective, the issue of voluntary prevention and its impact on the epidemic has been addressed using hybrid models that combine mathematical models describing the disease transmission at the population level, with models describing the individual's adoption of preventive methods to avoid being infected (Verelst et al., 2016). The infectious disease transmission has been modeled using mostly deterministic compartmental models⁴ and individual-based
125 models (which allow to consider some stochasticity). The adoption of prevention has been modeled, for instance, by a change in the individual's susceptibility to the infection (such as being immunized), a change in the model parameters (such as reducing disease transmissibility) or a change in the contact structure (such as reducing the number of contacts with other individuals, which is known as *social distancing*); see (Verelst et al., 2016). Traditionally, hybrid models
130 studying social distancing use the individual-based models for the disease transmission, while those studying vaccination use compartmental models (Verelst et al., 2016).

In behavioral epidemiology, individuals are assumed to translate the information about epidemic dynamics into behavioral changes; i.e., acknowledging their risk of infection and making informed decisions. The information about the epidemic has been previously modeled as epidemiological indicators —assumed to be provided to individuals by public health authorities—, as well as subjective perceptions and/or rumors (Verelst et al., 2016). The interaction between the epidemiological information and the change in behavior has been modeled, for instance, as a threshold that triggers the prevention adoption, or as a dynamic parameter which affects and is affected by prevention adoption (Verelst et al., 2016). Some models have used the risk of
135 infection perceived by individuals to explicitly address the prevention versus treatment dilemma (see section 1.3.3).

1.3.1 Modeling disease transmission using deterministic compartmental models

Deterministic compartmental models have been widely used to model disease transmission
145 among large populations (Brauer, 2017). These models are defined by a system of ordinary differential equations (ODE), whose state variables represent the number or proportion of indi-

⁴As opposed to stochastic models (that can also be compartmental), which can be particularly useful to model disease transmission among small populations.

viduals in each compartment, and whose parameters represent the rates of transition from one compartment to another (Hethcote, 2000); for instance, from susceptible to infected, then to infectious or contagious, to recovered, dead, and so on. The transition of individuals from being 150 susceptible to being infected, is often modeled by the *force of infection* (or infection rate), which depends on the disease transmission mechanisms, such as the contacts between uninfected and infectious individuals, and their probabilities to occur.

Classical compartmental models are usually named by acronyms obtained from merging the initials of the compartment variables. For instance, a model considering only susceptible, 155 infected and recovered individuals is called an *SIR* model. The Bernoulli's paper mentioned in the previous section can be represented by an *SI* model (Dietz and Heesterbeek, 2002). Figure 1.1 depicts a paradigm example of a classical compartmental model accounting for newborns immunization. Susceptible individuals (S) get infected (I) and then, recover (R). Considering 160 an imperfect preventive method allows to model individuals getting infected despite having been previously immunized⁵. To keep track of immunized individuals, the immunity induced by a preventive method is included in the model by adding, for instance, a compartment representing the proportion of newborns who are immunized (M). The classical *SIR* thus becomes a *MSIR* model.

⁵On the contrary, in the case where perfect immunity is considered, immunized individuals are directly removed from the population — to the Recovered compartment.

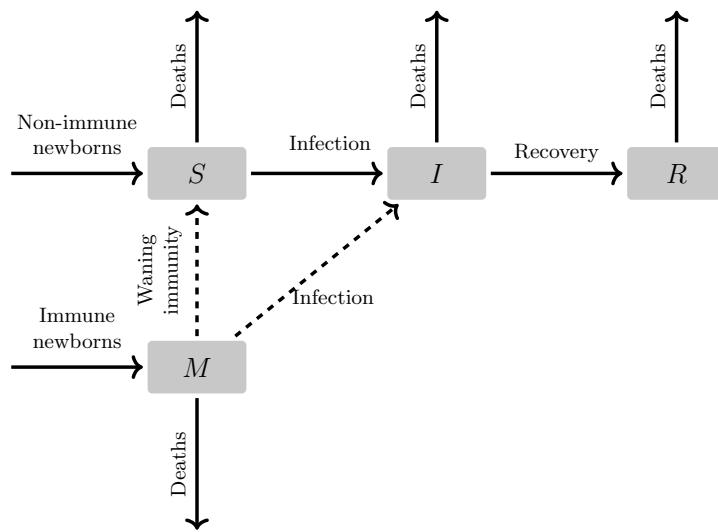


Figure 1.1 – Conceptual compartmental model with prevention

Flow diagram of a classical *SIR*-type compartmental model, describing the transmission of an infectious agent and disease progression, among a population by modeling individuals' transitions through different states, during their lifetimes. Some of the newborns may be immunized (*M*) against the infectious disease or not. Susceptible (*S*) individuals get infected (*I*) and then recover (*R*). Depending on the level of protection offered by the preventive method, immunized individuals may get infected, nevertheless, and/or immunity may wane with time (dashed arrows). Individuals leave the population by dying.

More complex compartmental models can include population stratification by disease progression (e.g., acute infection, chronic or asymptomatic period), kind of case resolutions (e.g., removal, recovery, death), demographics (e.g., age, sex), exposure to the disease (e.g., risk of infection, number of contacts), use of preventive and/or therapeutic tools, etc. (Hethcote, 2000).

1.3.2 The basic and the effective reproduction numbers

The *basic reproduction number*, noted R_0 , is defined as the expected number of secondary cases produced by a single infectious individual, during the entire infectious period, in a fully susceptible population (Anderson and May, 1991; Heesterbeek, 2002). The *effective reproduction number* —also called the replacement number— is defined as the expected number of secondary cases produced by an infectious individual, at a given time or in a given context; for instance, once the population is subject to interventions such as prevention and treatment (Ridenhour et al., 2018; van den Driessche and Watmough, 2008, 2002; Hethcote, 2000). In other words, the

effective reproduction number represents the number of secondary infections occurring at a time t , whereas the basic reproduction number represents a theoretical number of secondary cases occurring in the absence of previous infections and interventions, and thus, independent of time.

The basic and the effective reproduction numbers reflect epidemic severity, and thus are
180 useful to study the impact of preventive methods on epidemic dynamics: a large basic reproduction number corresponds to a fast epidemic spread throughout the population; a decrease in the effective reproduction number reflects epidemic mitigation.

The basic and the effective reproduction numbers can be estimated using mathematical models (Ridenhour et al., 2018; Guerra et al., 2017). In particular, they can be computed from
185 deterministic compartmental models, and thus be expressed as functions of the ODE system parameters (Heffernan et al., 2005; van den Driessche and Watmough, 2002, 2008). Notably, there exists a relation between the reproduction numbers and the behavior of the ODE system at the equilibrium (van den Driessche and Watmough, 2002). ODE systems defining classical compartmental models for disease transmission, similar to the model depicted in fig. 1.1, often
190 have two equilibria: a disease-free state (DFS), where there are no new infections, and an endemic state (ES), where the epidemic persists (Hethcote, 2000; van den Driessche and Watmough, 2002). A reproduction number is a threshold parameter for the ODE system equilibria: there is a transcritical bifurcation (that is, an exchange in the stability of the equilibria) for the ODE system when the reproduction number equals to 1. When the reproduction number is lower
195 than 1, the ODE system reaches the DFS and thus the epidemic is eliminated in the long run; otherwise, the ODE system will reach the ES (Hethcote, 2000; van den Driessche and Watmough, 2002). See fig. 1.2 for a conceptual visualization of the transcritical bifurcation.

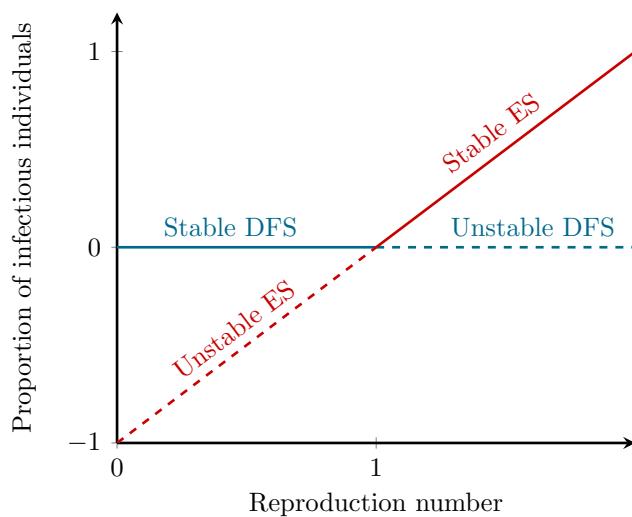


Figure 1.2 – Conceptual visualization of the bifurcation diagram for an ODE system

Classical ODE systems describing disease transmission usually have two equilibria: the disease-free state (DFS, depicted in blue), where there are no new infections, and the endemic state (ES, depicted in red), where the epidemic persists. A change in stability of the equilibria occurs when the reproduction number equals to 1 (depicted by the transition from a solid to a dashed line). Note that negative populations (red, dashed line), while correspond to some the solutions of the ODE system mathematically, have no biological interpretation.

Herd immunity: a public health target

Prevention-induced *herd* or *community immunity* refers to the situation in which susceptible
200 individuals are indirectly protected against infection, due to a sufficiently large proportion of the population adopting the preventive method against the pathogen. As a result, disease transmission is greatly reduced and the population is said to be immune as a group; the epidemic is expected to be eliminated in the long run (i.e., the DFS is reached) (Porta, 2013; Fine et al., 2011; CDC, 2006; Anderson, 1992).

205 From the modeling perspective, the proportion of individuals required to adopt prevention, for the community to reach herd immunity, is obtained from the level of prevention coverage (i.e., the proportion of the population that has adopted the preventive method) required for the effective reproduction number to be below 1. The larger the basic reproduction number, the larger the prevention coverage required to eliminate the epidemic.

210 Public health authorities usually set the target for prevention interventions depending on
the prevention coverage threshold that gives herd immunity. However, as discussed in [section 1.2](#),
different public sentiments and strategies towards the prevention versus treatment may yield a
sub-optimal prevention coverage (i.e., lower than the prevention coverage threshold). Hence, it
is key for public health authorities to know whether voluntary prevention coverage can deliver the
215 level needed for herd immunity.

1.3.3 Modeling the decision-making about prevention adoption

Among the mathematical models accounting for behavioral change, game-theoretic approaches
have been used to address the individual's decision-making facing the prevention versus treatment
dilemma ([Bauch et al., 2013](#); [Verelst et al., 2016](#); [Wang et al., 2016](#); [Chang et al., 2020](#)). Game
220 theory is a mathematical discipline that allows to model rational individual's decision-making
and selection of strategies through the assessment of risk and payoff. The individuals' decisions
are modeled by finding the equilibrium set of strategies; that is, the strategies that individuals
benefit the most from, in the long run ([Manfredi and D'Onofrio, 2013](#)). In particular, the
prevention versus treatment dilemma may be modeled by the comparison of the payoff expected
225 for adopting the strategy of using prevention, with that of adopting the strategy of being treated
in the case of infection.

Minimization of perceived cost

$$\text{Total cost} = \quad (1.1)$$

Most studies using game-theoretic models for individual decision-making have used deter-
ministic, compartmental models to describe the epidemic dynamics at the population level ([Bauch
230 et al., 2003](#); [Bauch and Earn, 2004](#); [Breban et al., 2006](#); [D'Onofrio et al., 2007](#); [Vardavas et al.,
2007](#); [Galvani et al., 2007](#); [Breban, 2011](#); [Liu et al., 2012](#)). These hybrid models have been used
to address, for instance, vaccination facing a biochemical attack ([Bauch et al., 2003](#)), volun-
tary vaccination during a public scare of vaccination against childhood infectious disease ([Bauch
and Earn, 2004](#)) and recurrent decision-making on preventing seasonal infections such as in-
235 fluenza ([Breban et al., 2006](#); [Galvani et al., 2007](#)). The risk of infection perceived by individuals

has been defined, for instance, by a free parameter taking different values (Bauch and Earn, 2004), by epidemiological indicators reflecting the current epidemiological situation (Bauch et al., 2003; D’Onofrio et al., 2007; Breban, 2011; Liu et al., 2012) or considering the past experience of individuals facing the epidemic (Breban et al., 2006; Vardavas et al., 2007; D’Onofrio et al., 2007). Prevention has been considered to offer perfect immunity (Bauch et al., 2003; Bauch and Earn, 2004; D’Onofrio et al., 2007) or short-term immunity, thus requiring recurrent decision-making (Breban et al., 2006).

These modeling studies have concluded that the level of prevention coverage achieved through selfish individual-level decisions (i.e., decisions motivated by the individual’s own interest) may differ from the level of prevention coverage needed to achieve herd immunity (Bauch et al., 2003; Bauch and Earn, 2004; Breban et al., 2006; Galvani et al., 2007; Breban, 2011), unless incentives are offered (Vardavas et al., 2007; Liu et al., 2012). However, as discussed in section 1.2, mass vaccination has resulted in epidemic elimination —globally, regionally or at least temporarily—, owing to vaccination campaigns facilitating vaccine adoption on nation-wide scales. Therefore, the impact of voluntary prevention on epidemic dynamics, and whether it can eliminate epidemics or not, remains to be studied.

1.4 General objectives of my doctoral research

The main objective of my doctoral research project was to build mathematical models for infectious disease transmission at the population-level, accounting for the individual-level decision-making on whether or not to adopt available preventive methods to avoid the infection, in a context where effective treatment exists. We aimed to evaluate the impact of the voluntary adoption of prevention on the epidemic dynamics. In particular, our purpose was to determine whether and under what conditions could voluntary prevention avert epidemics.

Two applications were explored. The first part of my thesis focuses on voluntary vaccination against treatable childhood infectious diseases; see chapter 2. This first project was designed for analytical results. The second part of my thesis focuses on the voluntary use of pre-exposure prophylaxis by men who have sex with men and who are at high risk of infection, in the current context of the HIV epidemic, where highly effective antiretroviral therapies are available; see chapter 3. Due to the complexity of the HIV transmission model, the model was studied

265 using numerical simulations.

1.5 General description of our methods

1.5.1 The mathematical model

We coupled two components to build a mathematical model describing the interplay between epidemic dynamics and voluntary prevention: one for the infectious disease transmission at the 270 population level and one for the decision-making on whether or not to use prevention, at the individual level. See [fig. 1.3](#) for a graphical depiction of our hybrid model. Details on the models specifically developed for each of the two applications are found in the following chapters.

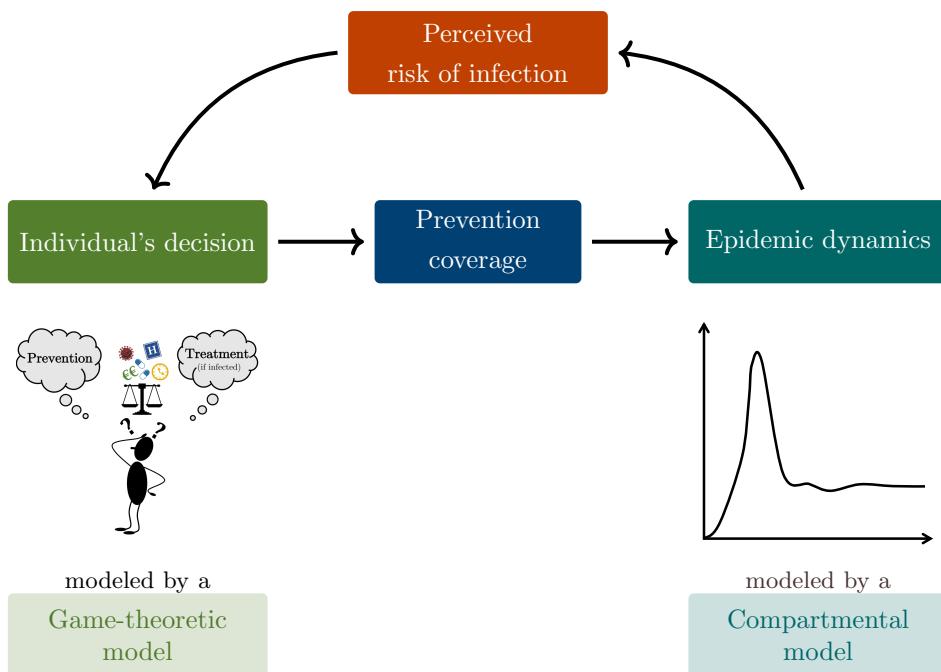


Figure 1.3 – Diagram of our hybrid model

When facing an ongoing epidemic, individuals address the prevention versus treatment dilemma by evaluating their risk of infection, its consequences, the availability of both preventive and therapeutic tools, and the related benefits and constraints. Therefore, the individuals' decision on whether or not to adopt a prevention method to avoid the infection may be biased, yet closely related to the course of the epidemic. Indeed, the risk of infection depends on the disease's prevalence, which in turn depends on the efficacy and coverage of the preventive and therapeutic methods. Hence, each individual's decision may be indirectly influenced by others' decisions, since the sum of all decisions determines the voluntary prevention coverage, which impacts the course of the epidemic.

Modeling disease transmission at the population level

To describe disease transmission within a population, we use a deterministic compartmental model, defined by a system of ODEs, which represents the individuals' infection and disease progression (Hethcote, 2000; Jacquez et al., 1988). In addition, we consider a compartment representing individuals adopting prevention. We do not consider that prevention is 100% effective and thus, individuals adopting prevention can nevertheless be infected. Therefore, our model explicitly accounts for two parameters regarding prevention: coverage and effectiveness.

We use the ODE system to compute epidemiological indicators such as the incidence rate, the

disease prevalence, the number of diagnoses, etc., which can be expressed explicitly as functions of the prevention parameters. By computing these epidemiological indicators at the endemic state of the system⁶, we observe the behavior of the epidemic in the long run, which will be useful for the decision-making component of the model (see below).

285 We compute the effective reproduction number from the ODE system, following the methods developed by [van den Driessche and Watmough \(2002\)](#). We also express the effective reproduction number as a function of the prevention parameters, and we obtain the basic reproduction number by setting the prevention coverage equal to 0. In other words, the basic reproduction number reflects the epidemic's severity in the case where no prevention method is available.

290 As mentioned in [section 1.3.2](#), the effective reproduction number is used to study the impact of the preventive methods on the epidemic. We say that the epidemic is *eliminated* or *averted* by the prevention method if the effective reproduction number —a function of the prevention parameters— is below 1. If the effective reproduction number is inferior to the basic reproduction number, we say that the epidemic is *controlled* by the preventive method, since a reduction in 295 the effective reproduction number is reflected in a reduction in the epidemic's incidence.

We first use the effective reproduction number to determine the conditions under which disease elimination or disease persistence occur, in the long run, regardless of individual behavior. In particular, a threshold for the prevention coverage leading to epidemic elimination can be determined. Then, the introduction of the decision-making component allows to study whether 300 and under what conditions this theoretical threshold for epidemic elimination could be reached voluntarily.

Modeling decision-making at the individual level

To describe the individual's decision-making, we rely on a game-theoretical approach: a non-cooperative single-player game, where an individual is assumed to act in his own interest. We 305 assume that individuals address the prevention versus treatment dilemma by evaluating their risk of infection and by weighing the benefits and inconveniences of the preventive method versus those of treatment, which include monetary and non monetary aspects, such as price, undesired secondary effects, difficulties in access, disease morbidity, etc. In a game-theoretic framework,

⁶The existence of the endemic and the disease-free equilibria is studied in detail by [Hethcote \(2000\)](#) for the vaccination model and by [Jacquez et al. \(1988\)](#) for the PrEP model.

these factors are known as *costs*.

310 The fundamental tool for modeling decision-making is the individual's expected *utility*, which summarizes the individual's perception of the costs to pay for choosing one of two strategies before their risk of infection: to adopt prevention, or not (and be treated upon infection). Game theory postulates that rational decision-making can be mathematically modeled by maximizing the utility. In other words, the aim of using a game theoretic approach is to find the individuals' 315 strategies that benefit them the most, in the long run.

We formally define utility as a function of the endemic risk of infection and the *relative cost of prevention versus treatment*, perceived by individuals. We consider that individuals may acknowledge official estimations of the epidemiological indicators (which can be obtained, for instance, from the transmission model, and communicated to the public by health authorities, 320 healthcare providers, scientific journalists, associations, etc.), but may also make their decision based on a misperception of their risk of infection. The relative cost remains a rather qualitative parameter that indicates how more beneficial is prevention perceived, over treatment.

The prevention coverage that maximizes the individual's expected utility gives the probability for an individual to voluntarily adopt prevention, as a function of the model parameters. 325 Hence, we obtain the *voluntary prevention coverage*, the prevention coverage reached voluntarily by the individuals who perceive themselves as being at risk of infection. We study the voluntary prevention coverage in terms of the preventive method's parameters: effectiveness and the relative cost of prevention versus treatment. In particular, we look for the conditions for which the voluntary prevention coverage can yield epidemic control and/or elimination, through the 330 reduction of the effective reproduction number.

Chapter 2

Voluntary vaccination against treatable childhood infectious diseases

2.1 Introduction

335 2.1.1 Vaccines against childhood infectious diseases

Vaccines are used to stimulate the individuals' immune system to fight infectious diseases, providing individuals with acquired immunity against the disease — in contrast to naturally-acquired immunity, which occurs after infection and recovery. The development of highly-effective vaccines inducing long-lasting immunity has changed the course of many epidemics ([Global Public](#)

[340 Health Achievements Team, 2011](#)). As a result, most countries have established vaccination programs, with vaccination schedules varying between countries and regions. Childhood immunization schedules (i.e., vaccines to be administered before the age of 5, or when children start attending school) currently recommended by the WHO and local public health authorities include vaccines against: measles, bacterial meningitis, mumps, poliomyelitis, and rubella ([CDC, 2015c; Ministère des Solidarités et de la Santé, 2019](#)).

Some of these infectious diseases have reached — or been close to reach — elimination status, at least regionally, thanks to high levels of vaccine coverage; see table [2.1](#). For instance, vaccination made the eradication of smallpox possible in 1980 ([WHO, 1980; CDC, 2001](#)). Im-

munization programs reduced the number of polio cases by 99% since 1988, worldwide. Polio
350 was declared eliminated from the Americas in 1994, from the Western Pacific region in 2000
and from the European region in 2002. As for 2019, polio remained endemic in only 3 countries
(WHO, 2019d). The combined measles-mumps-rubella (MMR) vaccine was first licensed
for use in the US in 1971 and was recommended worldwide once safety and high effectiveness of
the three-vaccine combination were demonstrated in different settings (Strebel et al., 2013). The
355 remarkable reduction of diseases cases inspired the worldwide priority goal to eliminate rubella
and measles by 2020 (Andrus et al., 2011; WHO, 2020b), which remains to be achieved.

As discussed in the previous chapter, epidemic control requires safe, highly-effective vaccines,
as well as high levels of vaccine coverage. However, despite the large evidence of vaccine-induced
reduction in the number of infections and the public health authorities' recommendations about
360 vaccination, parents still hesitate to vaccinate their children (Larson et al., 2016). Therefore, the
coverage of vaccines against childhood infectious diseases remains suboptimal in many settings
(that is, below the elimination threshold, the threshold to obtain herd immunity; cf. table 2.1)
and disease outbreaks still occur.

Infectious disease	R_0	Year of licence	Vaccine effectiveness	Herd immunity threshold	Vaccine coverage (year)
Diphtheria	4–5 (Anderson and May, 1991)	1930s (CDC, 2015c)	95% ^a (CDC, 2015c)	80%–85% (Anderson and May, 1990)	85% ^d (2019) (WHO, 2020a)
Measles	8–18 (Anderson and May, 1991)	1963 (CDC, 2015c)	>95% ^b (Plotkin et al., 2012)	92%–95% (Anderson and May, 1990)	64% (2016) (WHO, 2018b)
Polio	5–7 (Anderson and May, 1991)	1955 (Plotkin et al., 2012)	99% ^c (CDC, 2015c)	80%–85% (Anderson and May, 1990)	86% ^c (2019) (WHO, 2020a)
Rubella	6–16 (Anderson and May, 1991)	1969 (CDC, 2015c)	~100% (Plotkin et al., 2012)	85%–87% (Anderson and May, 1990)	71% (2019) (WHO, 2020a)
Smallpox	3–10 (Plotkin et al., 2012)	1796 (WHO, 2016b)	95% (CDC, 2015a)	66%–70% (Plotkin et al., 2012)	*

Table 2.1 – Key data on vaccination against some preventable childhood infectious diseases, worldwide.

Basic reproduction number (R_0), year of vaccine development (or year of first use as preventive method), vaccine effectiveness, vaccine coverage required to reach herd immunity and vaccine coverage reached worldwide.

^aAfter four spaced doses between 2 and 18 months old.

^bAfter two shortly separated doses.

^cAfter three doses of inactivated poliovirus vaccine.

^dCorresponding to three doses.

*Eradication declared in 1980 (WHO, 1980). Smallpox eradication was reached through massive inoculation programs, initially aiming to reach at least 80% in 1966, then aiming to reach a 100% coverage (Plotkin et al., 2012).

2.1.2 Vaccine hesitancy

365 Vaccine hesitancy is defined by the WHO as the “delay in acceptance or refusal of vaccines despite availability of vaccine services” ([WHO, 2014](#)). In 2019, the WHO listed vaccine hesitancy among the ten threats to global health ([WHO, 2019](#)). The underlying causes for vaccine hesitancy vary widely, from misinformation, to undesired effects, safety concerns, healthcare system mistrust, social pressure, religious convictions, etc. ([Brown et al., 2010](#); [Dubé et al., 2013](#); [Larson et al., 2014](#); [Dubé et al., 2018](#); [Quinn et al., 2019](#)).

370 A large-scale survey on confidence in immunization conducted in 2015 found that, while the state of vaccine confidence is overall high worldwide, there are regions where vaccine hesitancy remains a public health challenge ([Larson et al., 2016](#)); see [fig. 2.1](#). Seven of the ten least confident countries were identified in the European region. France was identified as the country 375 having the lowest confidence in vaccine safety, between the 67 countries included in the survey. Indeed, 45.2% of French respondents reported mistrust in vaccine safety (of note, the global average was 13%) ([Larson et al., 2016](#)).

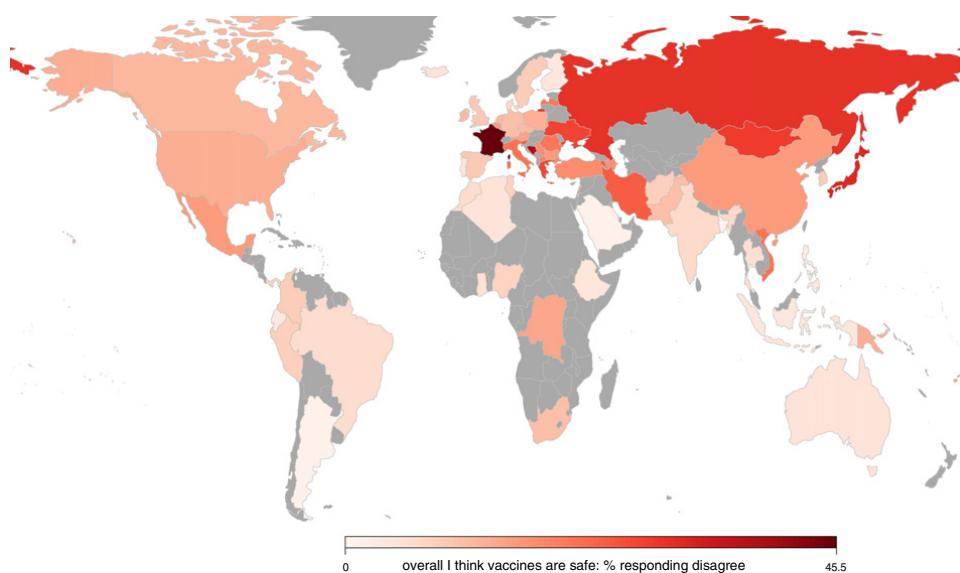


Figure 2.1 – Immunization confidence, worldwide

World map of the percentage of negative responses (“tend to disagree” or “strongly agree”) to the survey the statement “overall I think vaccines are safe”. Figure adapted from Ref. ([Larson et al., 2016](#)).

Childhood-vaccine hesitancy may result in a decline in vaccination coverage, which may reach sub-optimal levels and lead to outbreaks of infectious diseases otherwise controlled, such

380 as measles (Strebel et al., 2013). Indeed, as of 2017, twelve countries of the European Union (EU) had reported a decrease in the MMR vaccine coverage (Larson et al., 2018). Parents declining MMR vaccination for their children have declared to mistrust vaccines' safety and effectiveness, as well as believing that the diseases they prevent are mild and uncommon (Brown et al., 2010). Hence, measles vaccination coverage and incidence are considered as tracers of the strength of 385 immunization programs for the 2030 SDG (WHO, 2019).

2.1.3 The measles epidemic

Measles infection, treatment and prevention

Measles is a highly contagious airborne disease. Its clinical course goes as follows. The median incubation period varies from 10 to 13 days after exposure (CDC, 2015b; Strebel et al., 2013), 390 after which symptoms appear. A rash appears around 14 days after exposure, spreading from the head to the rest of the body in a few days. Other symptoms include high fever, conjunctivitis and coughing. Individuals infected with measles are considered to be infectious from 4 days before to 4 days after the rash onset. After infection, individuals acquire lifelong immunity. Newborns may be passively immunized through maternal antibodies, which protects them during the first 395 months of life (Strebel et al., 2013).

In high-income settings, the most common complications of measles infection include: otitis (7%–9%), pneumonia (1%–6%, mostly among children younger than 5 years), encephalitis (1 per 1 000–2 000 measles cases, mostly among adults older than 20 years) and death (1–3 per 1 000 measles cases, where 60% of fatalities are caused by pneumonia) (Strebel et al., 2013).

400 Treatments for measles do not cure the disease, but may help reducing the symptoms, the disease duration and the probability of developing complications. Treatments include the administration of vitamin A (recommended for children with acute measles), dehydration treatment, and the prescription of Ribavirin and Interferon, which are antivirals mostly recommended to treat cases with complications or immunocompromised individuals (Strebel et al., 2013).

405 The first vaccine against measles¹, consisting of the attenuated virus, was licensed in the US in 1963. Around 19 million doses were administrated in the US from 1963 to 1975. Other

¹Called the *Edmonston B* vaccine.

attenuated vaccines have been developed and are currently used around the world (Strebel et al., 2013). The measles vaccine is currently administered through the MMR vaccine, by subcutaneous injections. The MMR vaccine provides immunity similar to that of natural infection; that is, 410 lifelong immunity.

MMR vaccine is currently recommended to be administrated in two doses. As of 2018, all countries included the first dose of MMR or other measles-containing vaccines (MCV) to the vaccine schedule, whereas only 89% included the second dose (Peck et al., 2017). In most countries, the first dose is to be administered at 12 to 15 months old, and the second dose at the 415 age of 4 to 6, before entering school. Studies have found that a high proportion of the individuals who have not had an immune response to the first dose, will respond to the second dose. Hence, the second dose is not considered a booster, but rather a way to ensure immunological response among a greater proportion of the population. MMR vaccine effectiveness has been estimated at more than 95% (Strebel et al., 2013).

420 Adverse effects induced by the MMR vaccine are mild. During the 6 to 12 days following vaccination, some vaccinees may experience fever (5% to 15% vaccinees) and rash (5% of the vaccinees). These adverse effects are more common after the first dose, rather than after the second dose, since most vaccinees do have an immune response following the first MMR administration (Strebel et al., 2013).

425 Measles epidemiology

Before the introduction of the measles vaccines, virtually everybody got infected, mostly before the age of 10 (Strebel et al., 2013). The rate of secondary cases among susceptible individuals has been estimated at 90% or greater. Around 2.6 million deaths were caused by measles each year, worldwide (WHO, 2019b). The proportion of the population that needs to be vaccinated 430 in order to reach herd immunity has been estimated at 92% to 95% (Strebel et al., 2013).

The success of smallpox eradication had raised hopes of eliminating measles in the 80s (Hopkins et al., 1982). In 1997, the WHO, the Pan American Health Organization (PAHO) and the Centers of Disease Control (CDC) established the goal of eradicating measles from the Pan American region by 2010 (Services, 1997). Intensive two-dose vaccination campaigns lead to 435 measles no longer being endemic in the region in 2002, since transmission was interrupted in

many countries (Sever et al., 2011; De Quadros, 2004). Single-dose vaccinations have demonstrated to be effective, as well, especially when mass vaccination campaigns are successfully implemented (Sever et al., 2011). Some countries tried to establish a single-dose administration of measles vaccine, but outbreaks persisted and the two-doses program was reestablished to ensure high levels of immunity at the population level (Strebel et al., 2013).

Despite these successes, measles reemerged in the American region in 2003, with some reported cases that were attributed to virus reintroduction and failure in implementing the recommendations on vaccination strategies (Services, 1997; De Quadros, 2004; Andrus et al., 2011). Still, measles epidemic remained relatively controlled in the region, which raised expectations to eliminate measles globally by 2015 (De Quadros, 2004).

Measles has periodically reemerged in many countries, worldwide, including high-income countries, mostly due to a decrease in MCV vaccine coverage. Large outbreaks have been reported during the period 2008–2012 in countries like Italy, France and the UK (Amendola et al., 2015; Antona et al., 2013; Keenan et al., 2017; Bechini et al., 2019). More recently, as of 2018, the coverage level of the first dose of MCV was 86%, whereas for the second dose it was 69%, worldwide (Peck et al., 2017) — way below the 95% threshold for measles vaccine coverage to yield epidemic elimination. In the European region, the coverage was of 95% and 91%, respectively (Peck et al., 2017). By the end of the first half of 2019, the European region had reported the highest number of measles cases in the last decade (WHO, 2019; ECDC, April 2019). In particular, around 2600 cases were reported in France alone (WHO, 2020); see fig. 2.2 for a visualization of the measles epidemiology and MMR vaccine coverage in France, during the last decade. French coverage of MMR vaccination remained below the recommended thresholds, which provoked the reemergence of measles outbreaks in the French territory.

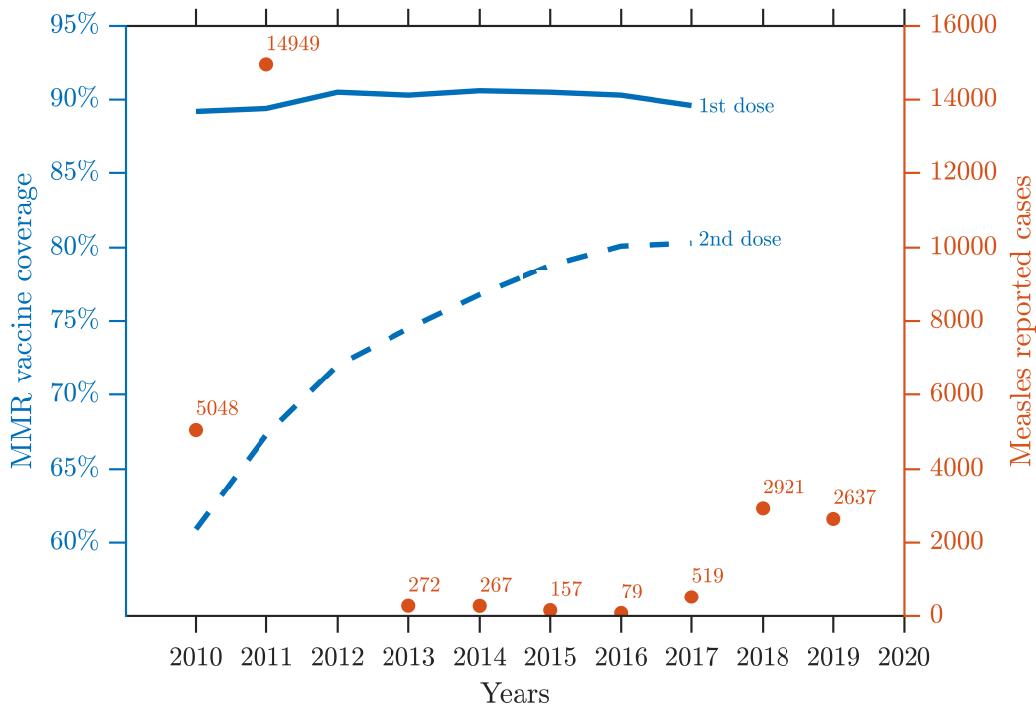


Figure 2.2 – MMR vaccine coverage and measles cases in France

In blue, the coverage for the first (solid line) and the second recommended doses (dashed line) of MMR vaccine, among 2-year-old children, for the period 2010–2017 ([France, 2019](#)). In red, the reported cases of measles in France, for the period 2010–2019 ([WHO, 2020](#)); N.B. no data was reported to the WHO in 2012. The coverage of the first recommended dose of MMR has been stable, around 89%, while the coverage of the second dose increases, but remains below 80%. These low vaccine coverages do not allow epidemic elimination. Indeed, large outbreaks occurred during the period 2010–2011, and again from 2018 on ([WHO, 2020](#)).

2.2 Objectives

- 460 The objective of the first part of my PhD was to reassess the impact of voluntary vaccination on treatable childhood disease transmission. First, we aimed to build a model combining game theory with an infectious disease transmission model, in order to study the epidemic dynamics as a result of the individual-level decision-making on whether or not to adopt vaccination against childhood infectious diseases. Then, we aimed to determine whether and how could voluntary
- 465 vaccination avert the epidemic.

In particular, we intended to apply our results to the epidemiology of an infectious disease preventable by vaccination, allowing to discuss the possibility of epidemic elimination. We thus chose to apply our results to the epidemiology of measles.

2.3 Published article

- 470 A scientific article titled “Prevention of treatable infectious diseases: a game-theoretic approach” (Jijón et al., 2017) was published in the journal *Vaccine*. The complete article is available from page ??.

2.3.1 Description of the article

A brief overview of the literature regarding the modeling of infectious diseases and voluntary vaccination is found in the introduction. We propose a model combining game theory with an infectious disease transmission model, in order to study the epidemic dynamics as a result of the individual-level decision-making on whether or not to adopt vaccination against childhood infectious diseases. A flow chart representing the compartmental model for the disease transmission at the population level is depicted in fig. 2.3, in the Additional material section of this chapter. We present in detail the methods used to compute the voluntary vaccination coverage and to determine the conditions ensuring epidemic elimination. An application of the model to the epidemiology of measles is provided. The paper includes a discussion on public policies that may be implemented in high-income settings in order to increase vaccine adoption.

2.3.2 Results statement

- 485 Adding the decision-making model to the classical disease-transmission model provides an estimate of the vaccination coverage that can be reached voluntarily, as a function of the relative cost of vaccination versus treatment, perceived by individuals. Therefore, the relative cost became the parameter to be tuned to increase vaccination coverage.

Our model provides lower bound estimates for the vaccine efficacy and the duration of vaccine-induced immunity, as well an upper bound for the relative cost of vaccine versus treat-

ment, in the context of epidemics controlled by vaccination. These parameters are expressed as functions of the basic reproduction number, i.e., the epidemic severity before the introduction of preventive methods.

According to our findings, voluntary-vaccination programs can successfully avert epidemics if
495 vaccines are highly efficient, the vaccine-induced immunity is long-lasting and they are delivered at low perceived cost. However, epidemic elimination may only be temporary (cf. [fig. 2.4](#) in the [Additional material](#)) and active efforts from public health authorities are needed to maintain the perceived cost of vaccination low.

Application to measles

500 We applied our methods to the epidemiology of measles. Our findings suggest that measles elimination was possible thanks to the very long-lasting immunity induced by the MMR vaccine, as well as to the relative cost of vaccination versus treatment which was certainly perceived as low during the mass-vaccination programs of the 90's.

However, a decrease in vaccine coverage has been observed in several high-income countries.
505 We conclude that reducing the cost of vaccination perceived by individuals in the current context, where measles disease and its sequelae have been less witnessed, may help reaching epidemic elimination through voluntary vaccination, and maintaining elimination status in the long run. For instance, by maintaining the population informed about measles epidemiology in the pre-vaccination era, the disease burden and measles-vaccine high-performance.

510 2.4 Additional material

2.4.1 Additional figures

Disease transmission flow diagram

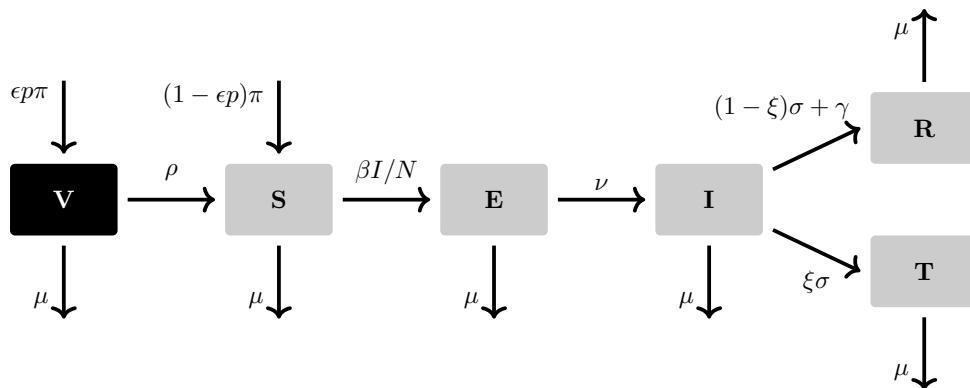


Figure 2.3 – Flow diagram for the compartmental model of vaccination against childhood infectious diseases

This flowchart depicts to the ODE system (1) of the article. Newborns can get vaccinated (V) or remain susceptible (S). Recently infected individuals (E) pass through a latent stage of infection. Then, they become infectious (I) and can recover naturally (R) or get on treatment (T). N denotes the total population. We use p for vaccine coverage, ϵ for vaccine efficacy and ρ for the rate of vaccine-induced immunity waning. The parameter π stands for the inflow of newborns, μ for the disease-unrelated death rate, β for disease transmissibility, ν for the progression through the latent stage, σ is the rate at which individuals start treatment and γ is the natural recovery rate. Treatment efficacy is noted ξ .

Bifurcation diagram

Fig. 2.4 is a variation of fig. 1 of the article which allows to visualize the stability of the ODE system equilibria and the loss of stability of the DFS when the decision model is coupled to the transmission model.

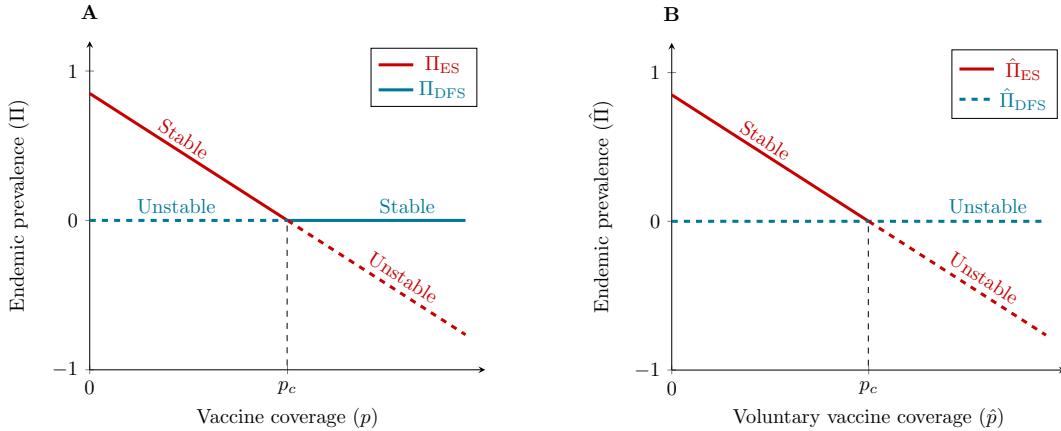


Figure 2.4 – Bifurcation diagram for the endemic prevalence

The disease-free state (DFS) and the endemic state (ES) are depicted in blue and red, respectively. A change in the stability of the system's equilibria occurs when the vaccine coverage reaches the critical value p_c (i.e., when the effective reproduction number equals to 1), which is depicted by the transition from a solid to a dashed line. (A) The bifurcation diagram for the endemic prevalence, for the model without the individual-level decision-making component. (B) The bifurcation diagram for the endemic prevalence induced by voluntary prevention, $\hat{\Pi} \equiv \Pi(\hat{p})$. The stability of the DFS for $\hat{p} \geq p_c$ is lost when the game is coupled to the compartmental model: there exists no equilibrium coverage for voluntary vaccination once the epidemic has been averted.

2.5 Further discussion

2.5.1 A note on mandatory vaccination

Here, we discuss briefly the results of implementing mandatory vaccination, as an alternative to allowing individuals to decide whether or not to adopt recommended immunization programs.

Some countries have witnessed infectious diseases reemergence and have established manda-

tory vaccination as a result. As of 2018, vaccination against measles was mandatory in 9 European countries. In 2019, France had added 8 mandatory vaccines to a list of 3, and Italy had established 10 mandatory vaccines (Bechini et al., 2019). The most common strategies to 525 enforce vaccination have been implementing monetary fines to parents who do not vaccinate their children, excluding unvaccinated children from school (Drew, 2019; Bechini et al., 2019) and withholding public financial child support (Drew, 2019; Australian Government Department of Health, 2015).

Italy, France and Australia have witnessed an increase in MMR vaccine coverage following 530 mandate establishment. However, it is not clear whether this coverage level will last in the future. In addition, mandatory vaccination may not always accomplish the objective of increasing vaccination coverage. For instance, in California, in the US, the number of unvaccinated children that were home-schooled quadrupled between September 2016 and August 2019 (Drew, 2019).

Hence, mandatory vaccination may not solve the issues that lead to non-vaccination and 535 may increase health disparities between individuals. Experts thus believe that mandatory vaccination should be a temporary measure only (Bechini et al., 2019). Instead of mandates enforcing vaccination, increasing vaccination coverage through the voluntary participation of individuals would require allocating resources towards facilitating access to vaccination and information campaigns to address vaccine hesitancy (Drew, 2019; Bechini et al., 2019). These arguments 540 highlight the importance of addressing the individuals' decision-making on vaccination adoption and the pertinence of our results.

Chapter 3

Voluntary use of pre-exposure prophylaxis to prevent HIV infection among men who have sex with men⁵⁴⁵

3.1 Introduction

3.1.1 The HIV epidemic

HIV infection, diagnosis and treatment

Human immunodeficiency virus (HIV) is a retrovirus that attacks the human immune system, by targeting the CD4+ T immune cells (or simply CD4 cells), which are white cells that help killer cells by signaling the presence of the infectious pathogen. HIV uses CD4 cells to replicate itself, destroying them in the process. HIV is a sexually transmitted infection (STI), which may spread through seminal, rectal and vaginal fluids as well as through blood and breast milk ([CDC](#)).

The natural stages of the HIV infection (i.e., when the infection is not treated) go as follows.

- ⁵⁵⁵ A recently infected individual goes through an acute stage of infection, where the virus replicates at a high rate, and the individual may experience flu-like symptoms. The acute stage of infection

lasts a few weeks. Then, for several years, the chronic¹, often asymptomatic, stage of infection takes place. During the chronic stage of infection, both CD4 cells count and viral load are relatively stable. The last stage of the HIV infection is the acquired immune deficiency syndrome (AIDS), where the count of CD4 cells rapidly decreases along with rapid increment of the viral load. In the AIDS stage, the individual's immune system is severely compromised and thus, opportunistic infections (such as tuberculosis, pneumonia, etc.) occur and lead to AIDS-related death. AIDS may last a few years (CDC). Fig. 3.1 depicts the natural dynamics of CD4 cells count and viral load, during the HIV stages.

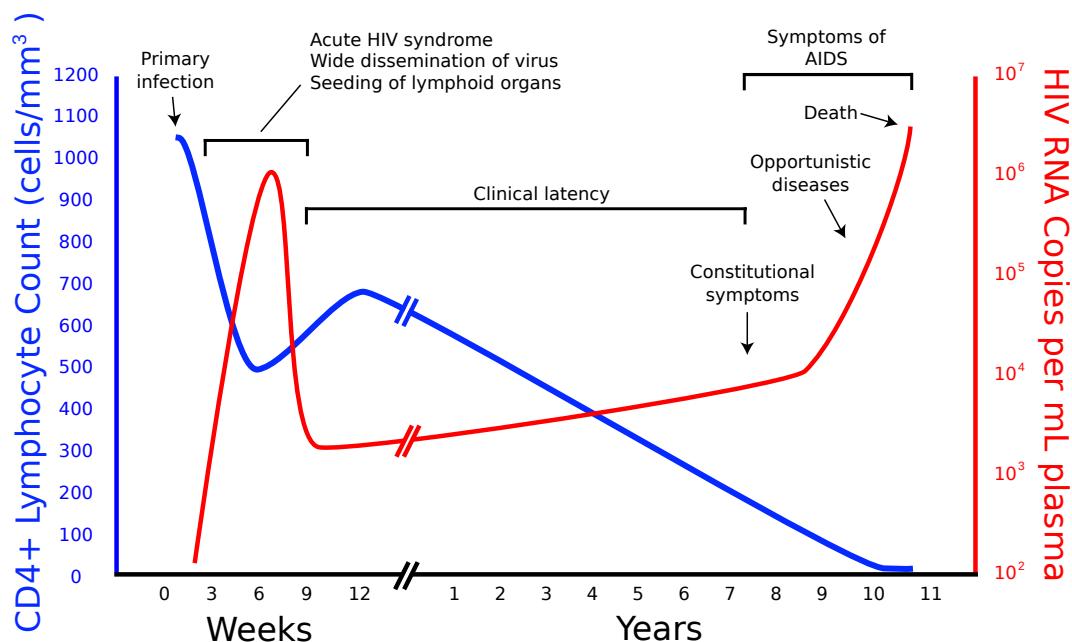


Figure 3.1 – The HIV infection progression

Average CD4+ T cell count (blue) and HIV viral load (red) during the course of an untreated HIV infection. Image source: ([Sigve](#)) (no copyright).

HIV infection may be diagnosed 10 to 90 days after exposure to HIV, depending on the testing method used (CDC). To date, there is no cure for HIV. However, effective antiretroviral therapy (ART) inhibiting viral replication has been developed to treat HIV infection, stopping its progression. Multiple types of ART disrupting with different stages of the HIV life cycle are currently available. This has allowed to combine two or three different drugs, which is called combination ART, to prevent the emergence of drug resistance, which may result from the rapid mutation capacity of HIV (WHO, 2016a).

The WHO currently recommends HIV infected individuals to start ART immediately after

¹Also referred to as the *latent* phase.

diagnosis, and to take ART for life (WHO, 2016a). An infected individual successfully undergoing ART is able to decrease the viral load until being undetectable to HIV tests, which is called *viral suppression*. It has been shown in clinical trials that an individual with undetectable viral load does not transmit HIV (AJ et al., 2016). Moreover, the life expectancy for infected individuals taking ART can be almost the same as the life expectancy of uninfected individuals, especially in high-income settings (Trickey et al., 2017). Hence, thanks to effective ART, the number of infections, AIDS-related diseases and deaths has been greatly reduced globally (WHO, 2016a).

580 The HIV epidemiology, worldwide

The first patients with —what would later be known as— AIDS were observed in 1981 (Barré-Sinoussi et al., 2013). HIV was first isolated in 1983, and identified as its causal pathogen in 1984 (Gallo and Montagnier, 2003). The peak of the epidemic was observed in the late 90's. Nowadays, despite great efforts to prevent and treat HIV infection, the epidemic continues to spread globally (UNAIDS, 2018; Roser and Ritchie, 2020); see fig. 3.2. As of 2019, about 38 million people around the globe were living with HIV, and 32 million have died from AIDS-related illnesses since the start of the epidemic (UNAIDS, 2019b).

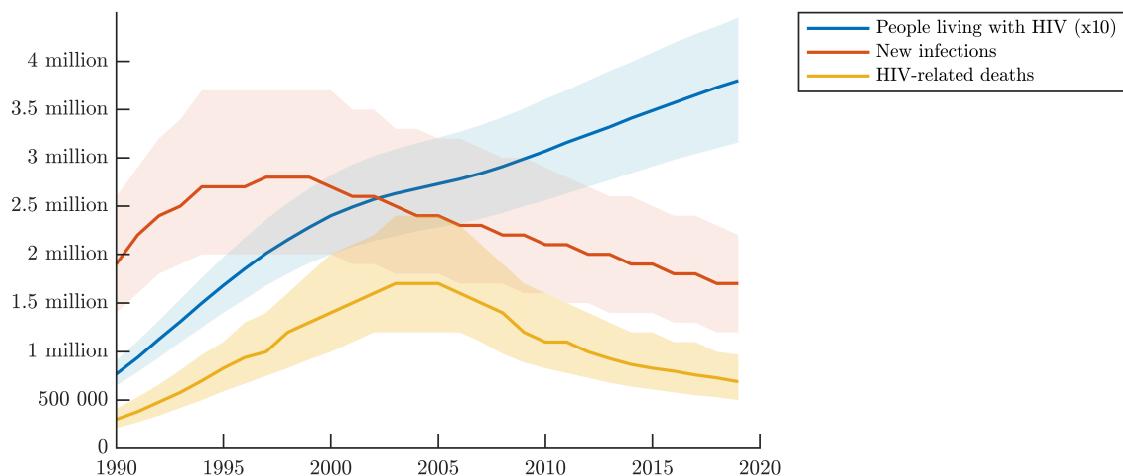


Figure 3.2 – HIV/AIDS epidemiological indicators, worldwide

Total number of people living with HIV (the data was divided by 10 to fit the same figure with the other measures; i.e., in 2019, there were ~ 38 million people living with HIV), number of new HIV infections and number of HIV-related deaths, from 1990 to 2019, worldwide. Source: UNAIDS HIV estimates (UNAIDS, 2020).

In most high-income settings, the HIV epidemic continues to expand among men who have sex with men (MSM) (UNAIDS, 2018; WHO, 2016b; Beyer et al., 2012). The high transmission of HIV among MSM may be explained by biological factors, such as the high probability of HIV transmission through receptive anal intercourse, as well as by behavioral factors, such as unprotected sexual intercourses, large number of casual partners and using recreational drugs (Beyer et al., 2012).

The prevention of HIV infection

Prevention interventions have proven to be successful to reach risk reduction among MSM, by sharing information on HIV/AIDS risk, promoting safer sex and changes in social behavior, etc. (Johnson et al., 2002). The prevention methods against HIV include, among others: abstinence, condom use (Chen et al., 2017), seroadaptation² (practices aiming to reduce contamination among serodiscordant sexual partners, such as seropositioning and serosorting) (McFarland et al., 2011; Velter et al., 2015) and, more recently, the use of ART as prevention (in the form of pre- and post-exposure prophylaxis) (WHO, 2016a).

3.1.2 Pre-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) consists of the use of ART by uninfected individuals before possible exposure to HIV. The first commercialized version of PrEP consists of the combination of two antiretrovirals, Emtricitabine (FTC) and Tenofovir disoproxil fumarate (TDC), sold under the registered name Truvada®, and currently available in generic form. FTC/TDC pills may be taken continuously (i.e., taken every day) or *on demand* (i.e., taken right before and after possible exposure to HIV) (Desai et al., 2018; Siguier and Molina, 2018).

Hopes are that the use of PrEP may curb the HIV epidemic among MSM. Recent studies have estimated a reduction in the number of new HIV infections at the population level after PrEP rollout among high-risk MSM that may place some settings in the path towards HIV epidemic elimination (Palk et al., 2018; Grulich et al., 2018; Brown et al., 2018).

²The term *seroadaptation* refers to the adaptation of sexual behaviors due to serological status awareness. Similarly, *seropositive* (respectively, *seronegative*) refers to an individual infected (respectively, uninfected) with HIV.

Efficacy of PrEP

The first randomized, double blind, clinical trial conducted among MSM to study the efficacy of PrEP was the *iPrevex* study, which showed a moderate relative risk reduction of 44%, through daily use of TDF-FTC (versus placebo) (Siguier and Molina, 2018; Grant et al., 2010). However, the results suggested that compliance was a major factor for efficacy: the risk reduction increased to 92% when considering only the subgroup of individuals with detectable TDF-FTC concentrations (Grant et al., 2010).

The efficacy of daily oral PrEP was also studied among serodiscordant heterosexual couples in the *Partners* study, which found a TDF-FTC PrEP efficacy of 84% for men and 66% for women, and in the *TDF-2* study, where the efficacy was estimated at 62.2% (Siguier and Molina, 2018). Among heterosexual women, two studies found no efficacy of PrEP, due to the low compliance of the participants (Siguier and Molina, 2018). An efficacy of 49% was estimated at a study among injecting drug users (Siguier and Molina, 2018).

Two recent trials conducted on high-risk MSM showed that PrEP has an effectiveness of 86%; *PROUD*, a study comparing daily PrEP uptake versus the deferred (by 1 year) adoption of daily PrEP (McCormack et al., 2016), and *Ipergay* (Molina and Earn, 2015), a randomized double blind trial comparing on-demand PrEP uptake versus placebo. Both the placebo arm of *Ipergay* and the deferred arm of *PROUD* were discontinued anticipatedly, in light of the high efficacy of PrEP (Siguier and Molina, 2018). The open-label follow-up of the participants of the *Ipergay* trial showed a 97% reduction in the incidence (Siguier and Molina, 2018; Molina et al., 2017). In addition, two cohort studies observed no HIV infections among MSM taking PrEP under good compliance (Siguier and Molina, 2018; Desai et al., 2018). These results place PrEP, next to condom use, among the most effective HIV prevention methods for MSM.

Therefore, the WHO currently recommends PrEP as a prevention method for MSM at high risk of HIV infection (WHO, 2015, 2016b,a). Individual-level PrEP eligibility criteria for MSM include, for instance, having unprotected anal intercourses with casual partners and/or partners with positive or unknown serostatus (WHO, 2015). PrEP uptake recommendations include providing PrEP together with other HIV prevention options (notably, condom use), performing HIV tests every 3 months, regularly testing for other STIs and monitoring renal functions (WHO, 2016a)

Price of PrEP and cost-effectiveness analyses

The price payed by PrEP users varies widely between countries where PrEP is available. In the US, the price of PrEP may be about 1 400€ to 1 800€ per month, while in countries like France and Sweden, PrEP is offered for free to individuals, since it is completely covered or reimbursed by the social security system. In addition, the availability of generic TDF/FTC molecules has led to a reduction in the price of PrEP paid by individuals in countries like Germany, Ireland, Switzerland and Poland ([Salzman, 2019](#)).

Cost-effectiveness analyses have shown that a PrEP rollout among MSM at high risk of infection is cost-effective in comparison to other interventions ([Durand-Zaleski et al., 2018](#); [Revill and Dwyer, 2017](#); [Cambiano et al., 2017](#); [Nichols et al., 2016](#); [Ouellet et al., 2015](#); [Desai et al., 2008](#)), but may remain expensive nevertheless ([Juusola et al., 2013](#); [Gomez et al., 2012](#)). Moreover, cost-effectiveness analyses have shown to be highly sensitive to the price of PrEP ([Coleman and Prins, 2017](#)). This exhibits the need of reducing PrEP price, which remains a key barrier to broadly provide PrEP through public health programs ([ECDC, 2016](#)).

PrEP availability and accessibility

As of June 2018, only 35 countries had at least one public policy implemented regarding PrEP rollout; most of them (15 countries) in the European region ([Hodges-Mameletzis et al., 2018](#)). Global efforts thus remain far from the WHO recommendations to scale up PrEP programs among high-risk populations ([WHO, 2016b](#)).

PrEP acceptability among MSM

As with other prevention methods, PrEP effectiveness is associated with persistence and adherence, which highlights the importance of MSM accepting to adopt and keep using PrEP as long as their risk of HIV infection remains high, and use it correctly. It is thus important for individuals to have a fair perception of their risk of HIV infection, the consequences of acquiring HIV infection and all the implications of a PrEP uptake to make informed decisions on whether or not to adopt PrEP as a prevention method against HIV infection.

On the one hand, the MSM community has shown to be highly aware on their risk of infec-

tion, which has resulted in the practice of risk-reduction strategies (McFarland et al., 2011; Velter et al., 2015). Paradoxically, these preventive practices may mislead individuals into believing their sexual behaviors are not risky enough (Golub, 2014), so additional prevention measures such as PrEP may not be adopted (Young et al., 2014). On the other hand, MSM have also shown to be highly aware of PrEP (Frankis et al., 2016; Grov et al., 2016) and PrEP has shown to be well-accepted (if available) among MSM who identify themselves at high risk of infection (Frankis et al., 2016; Ferrer et al., 2016; Taylor et al., 2014; Aghaizu et al., 2013).

Still, PrEP acceptability among MSM has been recently estimated at a moderate level of about 58% (Peng et al., 2018). Acceptability may be affected not only by the price of the molecule, but also by other non-monetary barriers, all the extra efforts and discomfort that the individuals on PrEP may confront; for instance: difficulties regarding PrEP uptake and accessibility, pill burden, difficulties in managing adherence, fear of acquiring other sexually transmitted infections due to drop in condom use (Young et al., 2014; Taylor et al., 2014; Pérez-Figueroa et al., 2015; Holt et al., 2018; Desai et al., 2018; Sidebottom et al., 2018), difficulties understanding PrEP effectiveness (Underhill et al., 2016), lack of tolerability (Siguier and Molina, 2018), alcohol-PrEP interactive toxicity beliefs (Kalichman and Eaton, 2017) and social stigma and discrimination (Young et al., 2014; Pérez-Figueroa et al., 2015; Arnold and Steward, 2016).

3.1.3 The HIV epidemiology and PrEP rollout in France

In France, like in most high-income settings, the number of new HIV infections remains remarkably high in some subpopulations. Between 6 000 and 7 000 new HIV infections are estimated to occur each year at the national level (Marty et al., 2018). These numbers have remained rather stable since 2011 (Siguier and Molina, 2018; Santé Publique France, 2019). More than 40% of the new HIV infections occur among people living in Île-de-France (ÎdF)—the Paris region, while only 19% of the French population lives in this region (Marty et al., 2018).

About 43% of the new HIV infections occur among MSM (Siguier and Molina, 2018), while MSM represent less than 2% of the general population (Bajos and Bozon, 2008)—1.6% when defining MSM as men who had at least one sexual intercourse with another man in the past twelve months and 4% when defining MSM as men who had at least one sexual intercourse with another man in their lifetimes (Marty et al., 2018). By far, MSM are the most affected by HIV in

France, with HIV incidence rates ($\sim 1\%$) more than 60-fold higher than the national level (Marty et al., 2018). The incidence rate among high-risk MSM living in ÎdF has been estimated as high as 9% in the *Ipergay* trial (Molina et al., 2018).

PrEP rollout in France

PrEP was authorized by French health authorities in 2016 (Siguier and Molina, 2018) and is currently recommended for MSM at high risk of HIV infection (ANRS, 2015; ANSM, 2017; Siguier and Molina, 2018; Haute Autorité de Santé). MSM need to meet at least one of the following criteria, to be prescribed PrEP:

- i) To have had unprotected, i.e., condomless sexual intercourses with at least 2 different partners in the last 6 months;
- ii) To have had STI events in the last 12 months;
- 710 iii) To have had at least one post-exposure treatment for HIV in the last 12 months;
- iv) Drug use during sexual intercourse.

In France, the recommendation to use PrEP in its registered form (Truvada[®]) was made in November 2015. Full PrEP reimbursement (both for Truvada and generics) by the French Social Security system was implemented in January 2016 (ANSM, 2017). PrEP has also shown to be cost saving in the French context (Durand-Zaleski et al., 2018).

About 13 900 MSM initiated PrEP in ÎdF between January 2016 and June 2020 (EPI-PHARE, 2020), with a marked growing trend; cf. fig. 3.3. Still, there remains a gap between PrEP eligibility and PrEP adoption. A recent study found that there is a high number of missed opportunities of PrEP prescription (that is, cases of MSM recently diagnosed with HIV that 720 would have been eligible to a PrEP prescription) (Lions et al., 2019).

Among on-PrEP MSM in the Paris region, some evidence of risk compensation (drop in condom use) has been observed (Molina et al., 2018). Also, a 30-month dropout rate of $\sim 32\%$ (Costagliola et al., 2019), which reveals the need of understanding and addressing PrEP persistence.

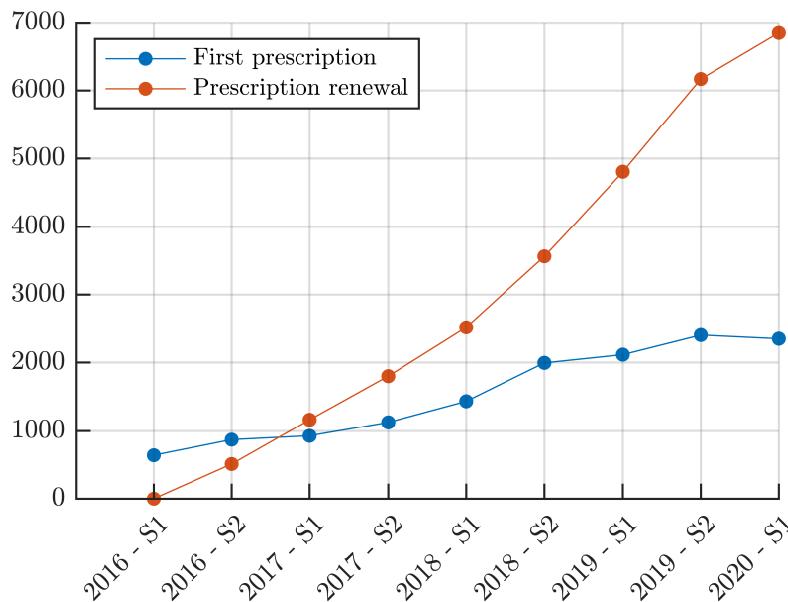


Figure 3.3 – PrEP users in Île-de-France, by semester, by year

Number of first PrEP prescriptions (i.e., people starting PrEP; in blue) and PrEP prescription renewals (in red) in the Paris region, by semester (S1 and S2) from January 1st, 2016 to June 30th, 2020. The data suggested that the great majority of PrEP users in the region were MSM. The total number of first prescriptions since PrEP rollout in the region was $\sim 13\,900$ while only $\sim 6\,850$ prescription renewals were established the first semester of 2020. On average, 85% of PrEP users got a prescription renewal the following year. Source: [EPI-PHARE \(2019, 2020\)](#)³.

725 3.1.4 Worldwide efforts to end AIDS and the path towards ending the HIV epidemic

Ending AIDS has become a global objective. Specific strategies and objectives have been set during the past decade ([UNAIDS, 2011, 2014](#)). Nowadays, the initiative to end AIDS as a public health threat by 2030 is part of the Sustainable Development Goals. One essential direction 730 adopted towards ending AIDS has been HIV prevention through the combination of behavioral and biomedical approaches ([UNAIDS, 2011, 2014](#)). In particular, the WHO has published recom-

³Scientific group of the French Agency of Medicine and Health Products Safety (ANSM) analyzing the data collected by the French System of Health Data (SNDS).

mendations targeting the populations most at risk of HIV infection⁴, which include MSM ([WHO, 2016b](#)). Another strategy to end AIDS is through the scaling up of diagnosis, treatment and care. The UNAIDS 90–90–90 initiative was launched in 2015, aiming for 90% of infected individuals to be aware of their serostatus, 90% of diagnosed individuals to receive sustained ART and 90% of treated individuals to reach viral suppression, by 2020 ([UNAIDS, 2017](#)). In 2016, the objectives were extended to 95%–95%–95% by 2030, targeting to achieve a 90% reduction in HIV incidence compared with 2010 levels ([UNAIDS, 2014](#)). The reduction in the number of in **TERMINAR**

3.1.5 Mathematical modeling of the HIV epidemic and PrEP uptake among MSM

Mathematical modeling has been extensively used to describe the HIV epidemic dynamics ([Jacquez et al., 1988; Castillo-Chavez, 1989](#)). In particular, it has been used to describe HIV transmission among MSM and to evaluate the impact of preventive interventions on the epidemic's dynamics ([Gumel et al., 2006; Gomez et al., 2012; Punyacharoensin et al., 2011; Eaton et al., 2012; Cremin et al., 2013; Punyacharoensin et al., 2016; Kim et al., 2014; Robineau et al., 2017; Palk et al., 2018; LeVasseur et al., 2018](#)). For instance, deterministic approaches using compartmental models have been implemented to describe the HIV transmission at the population level ([Supervie et al., 2010; Punyacharoensin et al., 2011; Gomez et al., 2012; Juusola et al., 2013; Kim et al., 2014; Punyacharoensin et al., 2016; Palk et al., 2018; Rozhnova et al., 2018](#)).

The heterogeneity of the risk of HIV infection among MSM has been modeled by considering structured mixing, where the population is stratified by risk of infection and the probabilities of sexual contacts between individuals are assumed to be non-random ([Jacquez et al., 1988, 1989; Gupta et al., 1989; Sattenspiel et al., 1990](#)). The risk categories have been defined according to the individuals sexual behavior: by explicitly defining the probabilities of HIV transmission in terms of the number of sexual contacts the individuals may sustain, the probability of having sexual contacts with individuals in other risk-categories and the inherent probability of HIV-transmission.⁵ Hence, an individual at high-risk (respectively, low-risk) of infection would be assumed to have a high (respectively, low) number of sexual contacts.

⁴Also called *key populations*, among which an HIV incidence greater than 3 per 100 person-years has been observed ([WHO, 2015](#)).

⁵Sexual behavior is also referred to in the literature as *sexual activity*. Sexual contacts may be defined, for instance, by sex acts or sexual partnerships ([Jacquez et al., 1988](#)).

There are two main kinds of non-random structured mixing that have been used to model
760 HIV-transmission dynamics: i) *proportional mixing*, where sexual contacts are assumed to be proportional to the number of individuals in each risk-category; and ii) *preferred mixing*,⁶ where a fraction of the individuals is assumed to mix preferentially with other individuals in the same risk-category, and the rest of the contacts are proportional (Jacquez et al., 1988). The higher the heterogeneity, the lower the prevalence at the endemic state (where there are no changes in the epidemic dynamics) and, in the case that extremely risky behaviors are considered, two peaks may be observed in the epidemic dynamics (Punyacharoen et al., 2011).

Modeling studies have evaluated the impact of a PrEP rollout on the HIV epidemic among MSM, predicting a remarkable reduction in the number of new HIV infections (Gomez et al., 2012; Kim et al., 2014; Punyacharoen et al., 2016; Jenness et al., 2016; Robineau et al., 2017;
770 Rozhnova et al., 2018; Palk et al., 2018; Rozhnova et al., 2019). In particular, recent mathematical models have studied HIV epidemic elimination through PrEP rollouts among MSM (Rozhnova et al., 2018; Scott et al., 2018; Hansson et al., 2020). These models assume that PrEP coverage can reach any value and, in particular, high values, which may not be granted in the real world. Therefore, it is unclear whether and how PrEP coverage levels, which are required to substantially
775 impact or eliminate HIV epidemics, can be reached and maintained, in the long term.

The subject of HIV elimination through healthcare interventions has also been addressed by modeling studies. For instance, by defining HIV elimination as the effective reproduction number being below 1, along with an incidence under 1 yearly case by 1000 individuals, a 2009 study found that testing the whole population yearly and treating immediately all seropositive
780 individuals may result in epidemic elimination within 10 years (Granich et al., 2009). Another study found that, to reach less than 1 yearly case by 1000 among MSM in the UK, would require a 90% of recently infected individuals to be diagnosed and treated in the year following infection (Phillips et al., 2013). A more recent study estimated that, reaching the 95–95–95 target, along with high adoption of preventive methods like PrEP and condom coverage among
785 MSM, would only ensure an 80% reduction in incidence by 2030 (Scott et al., 2018). Regarding PrEP interventions, a recent study found that HIV elimination would require 82% PrEP coverage among high-risk MSM during 5 years to reach HIV elimination (Rozhnova et al., 2018).

To the best of our knowledge, no modeling study has addressed the individual-level decision-

⁶Also referred to as *assortative mixing*.

making on whether or not to adopt a prevention method—namely, PrEP—to avoid HIV infection
790 and thus evaluated the impact of voluntary adoption of PrEP on the HIV epidemic.

3.2 Objectives

The main objective of the second part of my PhD was to model HIV transmission within the population of MSM, taking into account the individual-level decision-making on whether or not to adopt PrEP as a prevention method against HIV, in the current therapeutic context. To
795 that end, we built a mathematical model describing the HIV transmission at the population level, coupled with a model accounting for the individual-level dilemma of prevention versus treatment regarding PrEP. In particular, we aimed to address this issue for one of the most at risk populations in mainland France: MSM in ÎdF.

We aimed to obtain a mathematical characterization of the probability for a typical individual to adopt PrEP on his own, which would yield the voluntary PrEP coverage at the population level. Moreover, we expected to obtain the PrEP coverage as a function of the risk of HIV infection, the PrEP parameters and the HIV epidemic's intrinsic parameters (unlike previous studies, in which values are predetermined for the prevention coverage ([Gomez et al., 2012](#); [Punyacharoen et al., 2016](#); [Robineau et al., 2017](#); [Rozhnova et al., 2018](#)) or full PrEP coverage is
805 assumed ([Kim et al., 2014](#))).

Finally, we aimed to evaluate the impact of PrEP on the HIV epidemic among MSM, when PrEP is taken voluntarily by those who find themselves most at risk. Moreover, we intended to determine whether and under what conditions could the voluntary PrEP coverage control and, eventually, eliminate the epidemic.

810 3.3 Article submitted for publication

A scientific article presenting our findings, titled “Can HIV epidemics among men who have sex with men be eliminated through participation to PrEP rollouts?” ([Jijón et al., 2021](#)), was submitted for publication to the *AIDS* journal in January 2021, and is currently under review.

The preprint of the main text is included below, along with the supplementary material,
815 where the mathematics of our model is presented in detail. The computations and proofs of the analytical results presented in the article's supplementary material are available in [section 3.4](#) of this chapter. A few additional figures are also found in [section 3.4](#). The implementation of HIV prevention programs are further discussed in [section 3.5](#), as well as the limitations and perspectives of our modeling choices.

820 3.3.1 Description of the article

We propose a mathematical model describing the interplay between the HIV epidemic among MSM and the individual-level decision-making on whether or not to adopt PrEP as a prevention method against HIV infection, in the current therapeutic context, where universal effective ART is in place. In particular, we addressed this issue for one of the most at risk populations in
825 mainland France: MSM in ÎdF (the Paris region).

3.3.2 Results statement

We obtained a mathematical characterization of the probability for a typical individual to adopt PrEP on his own, which would yield the voluntary PrEP coverage at the population level. We thus obtained the PrEP coverage reached voluntarily by high-risk MSM, as a function of the
830 risk of HIV infection, the PrEP parameters and the HIV epidemic's intrinsic parameters, unlike previous studies, in which values are predetermined for the prevention coverage ([Gomez et al., 2012](#); [Punyacharoensin et al., 2016](#); [Robineau et al., 2017](#); [Rozhnova et al., 2018](#)) or full PrEP coverage is assumed ([Kim et al., 2014](#)). In particular, we study the PrEP coverage in terms of the PrEP effectiveness and the relative cost of PrEP versus ART perceived by individuals.

835 We evaluated the impact of PrEP on the HIV epidemic among MSM, when PrEP is taken voluntarily by those who find themselves most at risk. Moreover, we identified the conditions for which epidemic control (i.e., reduction in HIV incidence) or elimination (i.e., reduction of HIV incidence to zero) are possible owing to voluntary adoption of PrEP by MSM at high risk of HIV infection in a typical urban setting of a high-income country (e.g., the Paris region).

840 According to our findings, risk compensation (the reduction in condom use with PrEP adop-

tion) may not play an essential role against epidemic elimination because PrEP is highly effective. However, several conditions regarding the relative cost of PrEP versus ART and risk perception need to be fulfilled to reach elimination. Specifically, the relative cost must be perceived by eligible MSM as sufficiently low, and the perception of the risk of acquiring HIV infection should
845 be fair; if risk is underestimated, an even lower cost of PrEP is required for elimination. In addition, we found that lower testing rates among PrEP users require PrEP effectiveness to be high, in order to ensure epidemic elimination. Importantly, and similarly to our previous work on voluntary vaccination (Jijón et al., 2017), we found that epidemic elimination is temporary unless active maintenance of the PrEP rollout is in place.

850 We conclude that current PrEP rollout protocols, including that of the Paris region, may not reduce enough the cost of PrEP to achieve epidemic elimination. Active efforts are thus needed to increase PrEP demand by easing PrEP access, identifying MSM at high risk of infection, and communicating HIV risk information to the target population. If these efforts lead to HIV elimination, the next challenge will be to maintain, in a context of less epidemic adversity, a low
855 perception of the cost of PrEP and a fair perception of the HIV risk.

3.4 Additional material

Here, we present the computations and proofs of the results shown in the article’s supplementary material (cf. section 3.4.1). Namely, the explicit computations of some epidemiological indicators, using the ODE system (see sections 3.4.1–3.4.1), the thresholds for the PrEP effectiveness and
860 the perceived relative cost yielding epidemic control and elimination (see sections 3.4.1–3.4.1 and 3.4.1), and a description of the numerical approximation of the voluntary PrEP coverage (see section 3.4.1).

This section also contains some additional figures that were not included in the paper submission, but may help visualizing the system behavior from other perspectives (cf. section 3.4.2).
865 For instance, we present the values of the reproduction number before PrEP introduction for the calibrated model (see fig. 3.5 in section 3.4.2) and the number of HIV infections among on-PrEP MSM—despite PrEP adoption—for the baseline scenario (that is, assuming that individuals have a fair perception of HIV risk, a PrEP-induced condom drop from 30% to 20% and a 3-monthly HIV testing rate among on-PrEP MSM; see fig. 3.6 in section 3.4.2). Some additional

⁸⁷⁰ figures and results for the scenario where on-PrEP MSM do not follow the recommendations on frequently testing for HIV are presented as well (see figs. 3.7–3.11 in section 3.4.2).

3.4.1 Computations and proofs of our analytical results

The effectiveness of PrEP

PrEP effectiveness has been estimated at 86% (95% CI: 40%–98%) in two clinical trials conducted ⁸⁷⁵ among MSM (Molina and Earn, 2015; McCormack et al., 2016) and at 85%–96% in simulation studies (Dimitrov et al., 2019), using the PrEP-induced relative reduction of the HIV incidence,

$$1 - \frac{\text{HIV incidence with PrEP}}{\text{HIV incidence without PrEP}}.$$

Here, we analyze a simplified version of our HIV transmission model (cf. eqs. (S6)) that mimics the IPERGAY trial (Molina et al., 2018), in order to estimate the parameter representing the effectiveness of PrEP, ε .

We consider the population at high risk of infection, exclusively. We use Q to denote the individuals in the control group and P to denote the individuals using PrEP. We suppose the control group and the study group are matched and use Λ to denote their force of infection. Then, the following ODE system models the HIV infections dynamics that occur during the study:

$$\frac{dQ}{dt} = -\Lambda Q, \tag{3.1}$$

$$\frac{dP}{dt} = -(1 - \varepsilon)\Lambda P. \tag{3.2}$$

⁸⁸⁰ We use τ to denote the duration of the study follow-up. Dividing eq. (3.1) by eq. (3.2), and integrating on the interval $[0, \tau]$, we obtain

$$\int_0^\tau \frac{dQ}{Q} = \int_0^\tau \frac{dP}{(1 - \varepsilon)P}. \tag{3.3}$$

We solve [eq. \(3.3\)](#) for the PrEP effectiveness, ε :

$$\varepsilon = 1 - \frac{\ln P(\tau) - \ln P(0)}{\ln Q(\tau) - \ln Q(0)}. \quad (3.4)$$

Using the number of participants and the number of seroconversions that took place during the ANRS IPERGAY study ([Molina and Earn, 2015](#)),

$$\begin{aligned} P(0) &= 199, & Q(0) &= 201, \\ P(\tau) &= 197, & Q(\tau) &= 187, \end{aligned} \quad (3.5)$$

885 we have $\varepsilon = 0.86$. Hence, we found a value equivalent to the efficacy estimated in from the ANRS IPERGAY trial, corroborating our modeling choices in [section 1.2](#) of the article's appendix.

The disease-free equilibrium

The disease-free state (DFS) of the ODE system [\(S6\)](#) is given by

$$P^{\text{DFS}} = \frac{\pi_h p}{\mu}, \quad S_h^{\text{DFS}} = \frac{\pi_h(1-p)}{\mu}, \quad S_\ell^{\text{DFS}} = \frac{\pi_\ell}{\mu}, \quad (3.6)$$

and

$$I_i^{k,\text{DFS}} = T_i^{\text{DFS}} = 0, \quad \text{for all } i \in \{h, \ell\}, k \in \{a, c\}. \quad (3.7)$$

890 The total population at i risk of infection at the DFS is thus given by $N_i^{\text{DFS}} = \pi_i/\mu$, for $i \in \{h, \ell\}$. Then, the total population at the DFS is given by

$$N^{\text{DFS}} = N_h^{\text{DFS}} + N_\ell^{\text{DFS}} = \frac{\pi_h + \pi_\ell}{\mu}. \quad (3.8)$$

Equations [eq. \(3.6\)](#)–[eq. \(3.8\)](#) are used to compute the effective reproduction number, below.

Computing the effective reproduction number

To compute the effective reproduction number for the ODE system [\(S6\)](#), we follow the methods and notation presented in ([van den Driessche and Watmough, 2002](#)), where $R(p, \varepsilon)$ is defined as the larger eigenvalue of the *next generation matrix* ([van den Driessche and Watmough, 2008](#);

Diekmann et al., 1990).

We start considering the vector

$$X = \begin{pmatrix} I_P^a \\ I_h^a \\ I_\ell^a \\ I_P^c \\ I_h^c \\ I_\ell^c \\ T_h \\ T_\ell \\ P \\ S_h \\ S_\ell \end{pmatrix}, \quad (3.9)$$

where the first 8 compartments correspond to infected individuals. Then, we identify the vectors \mathcal{F} and \mathcal{V} (which represent the new infections and the transfers in and out of the compartments, respectively), satisfying $dX/dt = \mathcal{F} - \mathcal{V}$:

$$\mathcal{F} = \begin{pmatrix} (1 - \varepsilon)\Lambda_P P \\ \Lambda_h S_h \\ \Lambda_\ell S_\ell \\ 0 \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} (\sigma_P + \theta_P + \mu) I_P^a \\ (\sigma + \theta + \mu) I_h^a \\ (\sigma + \theta + \mu) I_\ell^a \\ -\sigma_P I_P^a + (\theta_P + \mu) I_P^c \\ -\sigma I_h^a + (\theta + \mu) I_h^c \\ -\sigma I_\ell^a + (\theta + \mu) I_\ell^c \\ -\theta_P (I_P^a + I_P^c) - \theta (I_h^a + I_h^c) + \mu_T T_h \\ -\theta (I_\ell^a + I_\ell^c) + \mu_T T_\ell \\ -p\pi_h + [(1 - \varepsilon)\Lambda_P + \mu] P \\ -(1 - p)\pi_h + (\Lambda_h + \mu) S_h \\ -\pi_\ell + (\Lambda_\ell + \mu) S_\ell \end{pmatrix}. \quad (3.10)$$

We use the subscript n to denote the n -th entry of a vector and the subscript nm to denote the (n, m) entry of a matrix. The matrix V , with elements $V_{mn} = \partial \mathcal{V}_m / \partial X_n \Big|_{\text{DFS}}$, where $n, m = 1, \dots, 8$, is given by

$$V = \begin{pmatrix} \sigma + \theta_P + \mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma + \theta + \mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma + \theta + \mu & 0 & 0 & 0 & 0 & 0 \\ -\sigma & 0 & 0 & \theta_P + \mu & 0 & 0 & 0 & 0 \\ 0 & -\sigma & 0 & 0 & \theta + \mu & 0 & 0 & 0 \\ 0 & 0 & -\sigma & 0 & 0 & \theta + \mu & 0 & 0 \\ -\theta_P & -\theta & 0 & -\theta_P & -\theta & 0 & \mu_T & 0 \\ 0 & 0 & -\theta & 0 & 0 & -\theta & 0 & \mu_T \end{pmatrix}, \quad (3.11)$$

Similarly, the elements of the matrix F are defined as $F_{mn} = \partial \mathcal{F}_m / \partial X_n \Big|_{\text{DFS}}$. Therefore,

we calculate the values for $\partial\Lambda_i/\partial I_j^k$. Recalling the definition (S5), we have

$$\Lambda_h = \frac{\lambda_{hh}^a (I_P^a + I_h^a) + \lambda_{hh}^c (I_P^c + I_h^c)}{N_h} + \frac{\lambda_{\ell h}^a I_\ell^a + \lambda_{\ell h}^c I_\ell^c}{N_\ell}, \quad (3.12)$$

and

$$\Lambda_\ell = \frac{\lambda_{h\ell}^a (I_P^a + I_h^a) + \lambda_{h\ell}^c (I_P^c + I_h^c)}{N_h} + \frac{\lambda_{\ell\ell}^a I_\ell^a + \lambda_{\ell\ell}^c I_\ell^c}{N_\ell}, \quad (3.13)$$

where

$$\lambda_{ji}^k = c_i \rho_{ij} \beta_j^k,$$

for $i, j \in \{h, \ell\}$ and $k \in \{a, c\}$. Then,

$$\frac{\partial \Lambda_i}{\partial I_j^k} = \frac{\lambda_{ji}^k}{N_j} - \sum_m \left(\frac{\lambda_{hi}^m I_P^m + \lambda_{hi}^m I_h^m}{N_h^2} + \frac{\lambda_{\ell i}^m I_\ell^m}{N_\ell^2} \right), \quad (3.14)$$

where the sum is considered for all the values of $m \in \{a, c\}$. Evaluating eq. (3.14) at the DFS defined in eqs. eq. (3.7) and eq. (3.8), we get $\partial\Lambda_i/\partial I_j^k|_{\text{DFS}} = \lambda_{ji}^k \mu/\pi_j$. Therefore,

$$\frac{\partial}{\partial I_j^k} \left(\Lambda_h S_h + (1 - \varepsilon) \Lambda_P P \right) \Bigg|_{\text{DFS}} = (1 - \varphi(\varepsilon) p) \left(\frac{\lambda_{jh}^k \pi_h}{\pi_j} \right), \quad (3.15)$$

and

$$\frac{\partial}{\partial I_j^k} \Lambda_\ell S_\ell \Bigg|_{\text{DFS}} = \frac{\lambda_{j\ell}^k \pi_\ell}{\pi_j}. \quad (3.16)$$

The matrix F is thus given by

$$F = \begin{pmatrix} p(1 - \varepsilon)\phi\lambda_{hh}^a & p(1 - \varepsilon)\phi\lambda_{hh}^a & p(1 - \varepsilon)\phi\lambda_{\ell h}^a \pi_h/\pi_l & p(1 - \varepsilon)\phi\lambda_{hh}^c & p(1 - \varepsilon)\phi\lambda_{\ell h}^c & p(1 - \varepsilon)\phi\lambda_{\ell h}^c \pi_h/\pi_l & 0 & 0 \\ (1 - p)\lambda_{hh}^a & (1 - p)\lambda_{hh}^a & (1 - p)\lambda_{\ell h}^a \pi_h/\pi_l & (1 - p)\lambda_{hh}^c & (1 - p)\lambda_{\ell h}^c & (1 - p)\lambda_{\ell h}^c \pi_h/\pi_l & 0 & 0 \\ \lambda_{h\ell}^a \pi_l/\pi_h & \lambda_{h\ell}^a \pi_l/\pi_h & \lambda_{\ell\ell}^a & \lambda_{h\ell}^c \pi_l/\pi_h & \lambda_{h\ell}^c \pi_l/\pi_h & \lambda_{\ell\ell}^c & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix} \quad (3.17)$$

where

$$\phi = \left(\frac{1 - \xi \eta_P}{1 - \xi \eta_h} \right).$$

The PrEP effectiveness threshold for epidemic control

Epidemic control induced by PrEP uptake is defined by a reduction of the effective reproduction number due to PrEP adoption, i.e., $R(p, \varepsilon) < R(0, \varepsilon)$; see [section 1.2.3](#) of the article's appendix. Here, we study the monotony of the reproduction number $R(p, \varepsilon)$ with respect to the PrEP parameters, PrEP effectiveness, ε , and PrEP coverage, p , in order to find the conditions necessary and sufficient to have $R(p, \varepsilon) < R(0, \varepsilon)$.

[920](#) Regarding PrEP effectiveness

Recall the definition of $R(\varepsilon, p)$; see [eqs. \(S14\)–\(S20\)](#) of the article's appendix. Since $A > 0$, the function $R(p, \varepsilon)$ verifies $\partial R(p, \varepsilon)/\partial \varepsilon \leq 0$ if and only if

$$\left(\frac{\partial}{\partial \varepsilon} H(p, \varepsilon) \right) \left(1 + \frac{(H(p, \varepsilon) - M) + 2BM}{\sqrt{(H(p, \varepsilon) - M)^2 + 4BH(p, \varepsilon)M}} \right) \leq 0. \quad (3.18)$$

Indeed, we have $\partial H(p, \varepsilon)/\partial \varepsilon \leq 0$; and, on the other hand, $A > 0$, $M > 0$ and $B \geq 1$, so

$$H(p, \varepsilon) + M(2B - 1) + \sqrt{(H(p, \varepsilon) - M)^2 + 4BH(p, \varepsilon)M} \geq 0. \quad (3.19)$$

Therefore, $\partial R(p, \varepsilon)/\partial \varepsilon \leq 0$; that is, the higher the level of PrEP effectiveness, the higher [925](#) the reduction of the effective reproduction number.

Regarding PrEP coverage

Similarly, $\partial R(p, \varepsilon)/\partial p \leq 0$ if and only if

$$\left(\frac{\partial}{\partial p} H(p, \varepsilon) \right) \left(1 + \frac{(H(p, \varepsilon) - M) + 2BM}{\sqrt{(H(p, \varepsilon) - M)^2 + 4BH(p, \varepsilon)M}} \right) \leq 0. \quad (3.20)$$

From eq. (3.19), we have $\partial R(p, \varepsilon) / \partial p \leq 0$ if and only if

$$\frac{\partial}{\partial p} H(p, \varepsilon) = -H_h + (1 - \varepsilon) \left(\frac{1 - \xi \eta_P}{1 - \xi \eta_h} \right) H_P \leq 0; \quad (3.21)$$

⁹³⁰ Hence, $\partial R(p, \varepsilon) / \partial p \leq 0$ if and only if $\varepsilon \geq \varepsilon_C$, where

$$\varepsilon_C = 1 - \left(\frac{1 - \xi \eta_h}{1 - \xi \eta_P} \right) \left(\frac{H_h}{H_P} \right). \quad (3.22)$$

The PrEP effectiveness threshold for epidemic elimination

Epidemic elimination is defined by $R(p, \varepsilon) \leq 1$; see section 1.2.3 of the article. That is,

$$A \left[H(p, \varepsilon) + M + \sqrt{(H(p, \varepsilon) - M)^2 + 4BH(p, \varepsilon)M} \right] \leq 1. \quad (3.23)$$

Therefore, $R(p, \varepsilon) \leq 1$, is achieved if and only if $p \varphi(\varepsilon) \leq K$, where

$$\varphi(\varepsilon) \equiv H_h - (1 - \varepsilon) \left(\frac{1 - \xi \eta_h}{1 - \xi \eta_P} \right) H_P, \quad (3.24)$$

is a function of PrEP and condom effectiveness, and

$$K \equiv H_h - \left(L - \frac{1}{2A} \right) \left(\frac{1}{1 - 2AL(B - 1)} \right) \quad (3.25)$$

⁹³⁵ is a constant independent of the PrEP parameters.

In addition, assuming $p = 1$, $R(1, \varepsilon) \leq 1$ if and only if $\varphi(\varepsilon) \leq K$, which is equivalent to $\varepsilon > \varepsilon_E$, where

$$\varepsilon_E \equiv 1 - \left(1 - \frac{K}{H_h} \right) (1 - \varepsilon_C). \quad (3.26)$$

In other words, ε_E is the minimum value of PrEP effectiveness for which epidemic elimination is possible, provided that PrEP coverage verifies $p \varphi(\varepsilon_E) \leq K$. Hence, we say that ε_E is the ⁹⁴⁰ threshold for the PrEP effectiveness above which epidemic elimination is possible.

Note that eq. (3.22) can also be obtained from setting $\varphi(\varepsilon) \geq 0$. Therefore, $\varphi(\varepsilon)$ can be interpreted as the effectiveness of PrEP and condom altogether. This can be straightforwardly identified in the scenario where individuals do not change testing behavior, i.e., where $\theta = \theta_P$; see fig. 3.7 below.

945 **The rescaled perceived costs for the PrEP-adoption strategies**

We expanded analytically the costs defined by integrals in [eqs. \(S26\)–\(S27\)](#) of the article's appendix

$$C_{\text{No-PrEP}}(p; \varepsilon) = \begin{cases} L e^{-\Lambda_h^{\text{ES}}(p; \varepsilon)L} + L_T \left(1 - e^{-\Lambda_h^{\text{ES}}(p; \varepsilon)L} \right) - \frac{1 - e^{-\Lambda_h^{\text{ES}}(p; \varepsilon)L}}{\Lambda_h^{\text{ES}}(p; \varepsilon)}, & \text{if } R > 1 \\ 0, & \text{if } R \leq 1, \end{cases} \quad (3.27)$$

and

$$C_{\text{PrEP}}(p; \varepsilon, r) = \begin{cases} r \left(\frac{1 - e^{-(1-\varepsilon)\Lambda_P^{\text{ES}}(p; \varepsilon)L}}{(1-\varepsilon)\Lambda_P^{\text{ES}}(p; \varepsilon)} \right) + L e^{-((1-\varepsilon)\Lambda_P^{\text{ES}}(p; \varepsilon)+\theta)L} \\ \quad + L_T \left(1 - e^{-(1-\varepsilon)\Lambda_P^{\text{ES}}(p; \varepsilon)L} \right) - \frac{1 - e^{-(1-\varepsilon)\Lambda_P^{\text{ES}}(p; \varepsilon)L}}{(1-\varepsilon)\Lambda_P^{\text{ES}}(p; \varepsilon)}, & \text{if } R > 1 \\ rL, & \text{if } R \leq 1. \end{cases} \quad (3.28)$$

The equations above were used to compute the expected utility directly and efficiently, and not

950 in its integral form; cf. [pseudo-algorithm 3.1](#).

Numerical approximation of the voluntary PrEP coverage

The voluntary PrEP coverage was obtained numerically, as detailed in the [pseudo-algorithm 3.1](#) below.

Algorithm 3.1 Numerical approximation of the voluntary PrEP coverage

Require: Set of parameters for HIV transmission, small $\delta < 0$.

Ensure: The voluntary PrEP coverage, $\hat{p}(\varepsilon, r)$

```

1: procedure ENDEMIC FORCE OF INFECTION,  $\Lambda_i^{\text{ES}}(p, \varepsilon)$  for  $i \in \{h, P\}$      $\triangleright$  We used parallel
   computation.

2:   for  $0 \leq p \leq 1$  do
3:     for  $0 \leq \varepsilon \leq 1$  do
4:       Compute  $R(p, \varepsilon)$ ; cf. eqs. (S14)–(S20)
5:       if  $R(p, \varepsilon) > 1$  then
6:         Set  $T$ 
7:         while  $\log(|(N(t) - N(t-1)) / N(t-1)|) > \delta$  do
8:           Increase  $T$ 
9:           Solve ODE system (S6) until  $t = T$ 
10:          end while
11:          Endemic state (ES)  $\leftarrow$  ODE system at  $t = T$ 
12:          Compute  $\Lambda_h^{\text{ES}}(p, \varepsilon)$ ; see eq. (S9)
13:        else
14:           $\Lambda_h^{\text{ES}}(p, \varepsilon) = 0$ 
15:        end if
16:      end for
17:    end for
18:    Compute  $\Lambda_P^{\text{ES}}(p, \varepsilon)$ ; see eq. (S13)
19: end procedure

20: procedure UTILITY MAXIMIZATION,  $\max_p U(p; \varepsilon, r)$ 
21:   Compute  $U(p; \varepsilon, r)$ ; cf. eq. (S25) and eqs. (3.27)–(3.28)
22:   for  $0 \leq r \leq 1$  do
23:     for  $0 \leq \varepsilon \leq 1$  do
24:        $\hat{p} \leftarrow$  The value of  $p$  for which  $U(p, \varepsilon, r)$  attains its maximum
25:     end for
26:   end for
27: end procedure
28: Return  $\hat{p}(\varepsilon, r)$ 

```

955 Identifying the thresholds in relative cost for epidemic control and elimination

The relative cost thresholds for epidemic control and elimination, $r_C(\varepsilon)$ and $r_E(\varepsilon)$ (cf. [section 3.2.1](#) of the article's appendix), were numerically extracted from $\hat{p}(\varepsilon, r)$, by identifying the boundaries between the regions; see [fig. 3.4](#).

On the one hand, $r_C(\varepsilon)$ is the boundary between region III and region II: we defined $r_C(\varepsilon)$
 960 as the lowest value of r for which $\hat{p}(\varepsilon, r) = 0$, for any given PrEP effectiveness level ε . On the other hand, $r_E(\varepsilon)$ is the boundary between region II and region I. Therefore, we identified $r_E(\varepsilon)$ as the highest value of r for which the difference between $\hat{p}(\varepsilon, r)$ and the theoretical threshold for PrEP coverage to yield epidemic elimination, $K/\varphi(\varepsilon)$, was lower than the tolerance we set in our algorithm. See [pseudo-algorithm 3.2](#) below for the numerical implementation and [fig. 3.4](#)
 965 for an illustration of $r_C(\varepsilon)$ and $r_E(\varepsilon)$ for the baseline scenario.

Algorithm 3.2 Identifying the relative cost thresholds for epidemic control and epidemic elimination

Require: $\hat{p}(\varepsilon, r)$ and Δp , the discretization step of the interval $[0, 1]$ of p .

Ensure: r_C and r_E

```

1: for  $0 \leq \varepsilon \leq 1$  do
2:    $r_C(\varepsilon) \leftarrow$  The lowest value of  $r$  for which  $\hat{p}(\varepsilon, r) = 0$ 
3:   if  $\varepsilon < \varepsilon_E$  then
4:      $r_E(\varepsilon) \leftarrow$  The highest value of  $r$  for which  $\hat{p}(\varepsilon, r) = 1$ 
5:   else
6:      $r_E(\varepsilon) \leftarrow$  The highest value of  $r$  for which  $|\hat{p}(\varepsilon, r) - K/\varphi(\varepsilon)| \leq \Delta p$ 
7:   end if
8: end for

9: Return  $r_C(\varepsilon)$  and  $r_E(\varepsilon)$ 
  
```

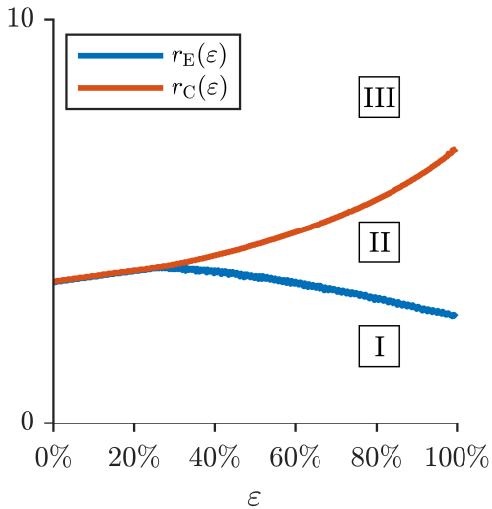


Figure 3.4 – The relative cost thresholds for epidemic control and elimination

The relative cost thresholds for epidemic control and elimination as functions of PrEP effectiveness ($r_C(\varepsilon)$ and $r_E(\varepsilon)$, respectively) assuming fair perception of the risk of HIV infection, for a typical parameter set calibrating our model; see [table S4](#) of the article’s appendix. $r_C(\varepsilon)$ is the boundary between region III and region II, while $r_E(\varepsilon)$ is the boundary between region II and region I.

3.4.2 Additional results and figures

The effective reproduction number in the absence of PrEP

We computed the effective reproduction number in the absence of PrEP, i.e., $R(0,0)$, for the 970 ~ 500 simulations calibrating our model; see [fig. 3.5](#) below. We obtained a mean value of 2.2 (95% CI: 1.7–2.6). The values resulting from our model calibration are broadly in agreement with previous studies where R_0 has been estimated at 2–5 among MSM ([Anderson and May, 1991](#)).

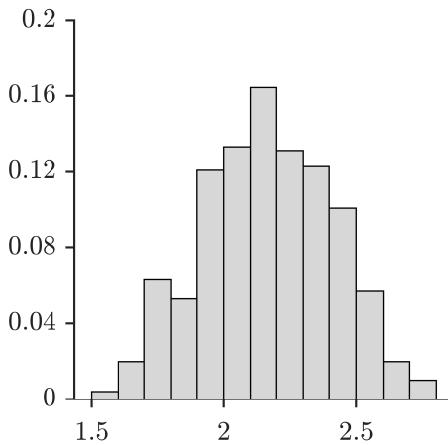


Figure 3.5 – The effective reproduction number in the absence of PrEP

Histogram of the values for the effective reproduction number in the absence of PrEP, $R(0, \varepsilon)$, for any value of PrEP effectiveness, $\varepsilon \in [0, 1]$ and for the calibrated parameters sets; see [table S2](#) of the article's appendix. The mean $R(0, \varepsilon)$ is 2.2 (95% CI: 1.7–2.6).

The number of new HIV infections despite PrEP uptake

- 975 In the baseline scenario, we assumed that on-PrEP MSM incur in risk compensation, decreasing their condom use from 30% to 20%. The impact of risk compensation can be clearly seen in [fig. 3.6](#), which shows the number of new infections among on-PrEP MSM at the endemic state (ES), given by $(1 - \varepsilon)\Lambda_P^{\text{ES}}P^{\text{ES}} = (1 - \varepsilon)(1 - \xi\eta_P)\Lambda_h^{\text{ES}}P^{\text{ES}}/(1 - \xi\eta_h)$, where Λ_P^{ES} and P^{ES} are functions of p and ε ; cf. [eq. \(S13\)](#).

- 980 Given a fixed value of PrEP effectiveness, the number of new infections among on-PrEP MSM behaves as follows. For low levels of PrEP coverage, the increase in the risk of infection induced by risk-compensation outweighs the protection offered by PrEP adoption and thus, the number of infections increases with the number of MSM using PrEP. Then, the trend reverses.

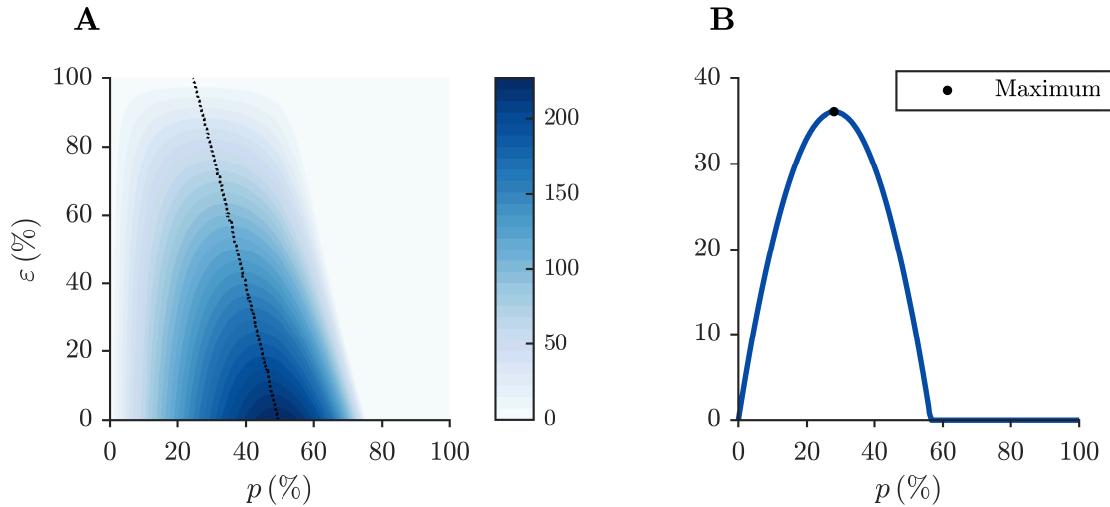


Figure 3.6 – Number of new HIV infections despite PrEP uptake

The number of new infections among on-PrEP MSM for the baseline scenario, at the endemic state, **(A)** as a function of PrEP coverage (p) and PrEP effectiveness (ε), and **(B)** for $\varepsilon = 86\%$. For low levels of PrEP coverage, the PrEP-induced risk compensation (i.e., drop on condom use from 30% to 20% among PrEP users) outweighs the protection offered by PrEP, and the number of new HIV infections among on-PrEP MSM increases with PrEP coverage. The critical values are depicted by black bullets.

The scenario where on-PrEP MSM do not change their HIV testing behavior

985 Current guidelines for PrEP prescription require testing for HIV every 3 months (Molina et al., 2018). However, frequent HIV screening may be perceived as a barrier for some individuals (Calabrese et al., 2016). Therefore, frequent HIV testing may not be guaranteed in the long run. We ran our algorithm considering the scenario where MSM do not follow these recommendations, and keep testing for HIV at the same rate than before adopting PrEP (i.e., every $\theta_P = \theta = 3.1$ 990 years); cf the sensitivity analyses of the article and section 3.3.3 of the article's appendix.

Here, we show the figures analog to those included in the paper and in previous sections, such as the PrEP-induced reduction in HIV incidence (depicted in figure 3.8B), the relative costs thresholds (computed using algorithm pseudo-algorithm 3.2; see fig. 3.9) and the voluntary PrEP coverage resulting from risk misperception (see fig. 3.10), for the scenario where individuals do 995 not change their HIV testing behavior.

We also used ~ 500 sets of parameters calibrating our model, in order to compute the

probability of epidemic elimination (see [figure 3.11A](#)) and to obtain confidence intervals for the PrEP effectiveness thresholds for epidemic control, ε_C , and elimination, ε_E (see [figure 3.11B](#)). [Figure 3.11C](#) depicts the relative cost thresholds for epidemic control and elimination, computed numerically for the ~ 500 parameters sets. Similarly to [section 3.4.1](#), $r_E(\varepsilon)$ is the boundary between region II and regions I–IV together. Therefore, for $\varepsilon < \varepsilon_E$, we identified $r_E(\varepsilon)$ as the highest value of r for which $\hat{p}(\varepsilon, r) = 1$; cf. [figures 3.8](#) and [3.11C](#).

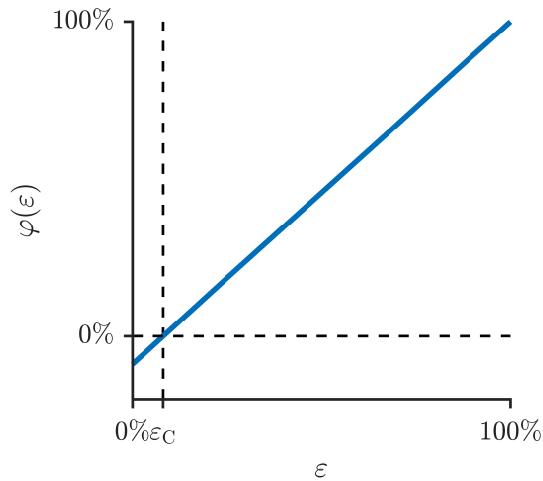


Figure 3.7 – The combined effectiveness of PrEP and condom use, for the scenario where on-PrEP MSM do not change HIV testing behavior

The combined effectiveness of PrEP and condom use among on-PrEP high-risk MSM, relative to the effectiveness of condom use alone among off-PrEP high-risk MSM, $\varphi(\varepsilon)$, when MSM do not change their testing behavior (i.e., $\theta_P = \theta = 3.1$ years), for a condom effectiveness of 70% and a PrEP-induced drop in condom use from 30% to 20%; see [eq. \(S4\)](#) of the article's appendix. As stated in [section 3.4.1](#), epidemic control induced by PrEP and condom use is possible if and only if $\varphi(\varepsilon) > 0$; that is, if $\varepsilon \geq \varepsilon_C$.

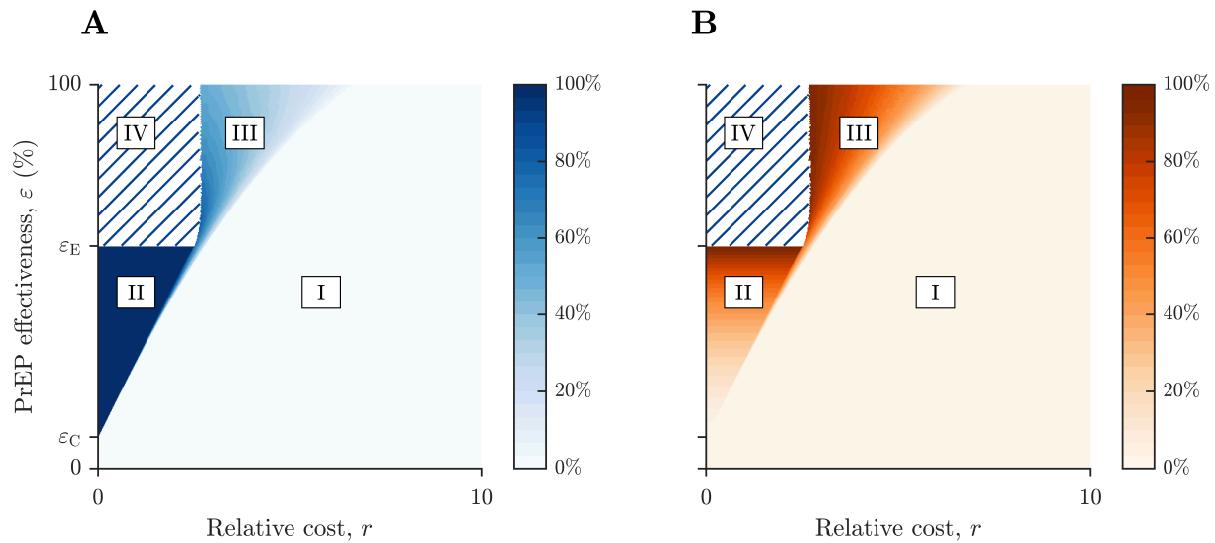


Figure 3.8 – The voluntary PrEP coverage and its impact on HIV incidence, for the scenario where on-PrEP MSM do not change HIV testing behavior, assuming fair risk perception

Color maps of (A) the voluntary PrEP coverage among high-risk MSM (\hat{p}) and (B) the corresponding reduction in the overall endemic HIV incidence rate, as functions of ε and r , assuming that individuals have a fair perception of HIV risk and that individuals do not change their testing behaviors once adopting PrEP (i.e., $\theta_P = \theta = 3.1$ years). The model outputs were obtained for one typical parameter set calibrating our model. PrEP effectiveness thresholds required to reach epidemic control and epidemic elimination are given by $\varepsilon_C = 8\%$ and $\varepsilon_E = 58\%$, respectively. Four regions can be identified, depending on the values of \hat{p} : region IV, where all individuals adopt PrEP ($\hat{p} = 100\%$) and $\varepsilon_C \leq \varepsilon < \varepsilon_E$, so the epidemic is controlled; region III, where no MSM uses PrEP ($\hat{p} = 0\%$) and thus, there is no reduction in HIV incidence; region II, where some, but not enough MSM use PrEP ($0\% < \hat{p} < 100\%$) because r remains high and thus the epidemic is controlled; and region I (marked by blue stripes), where epidemic elimination is possible.

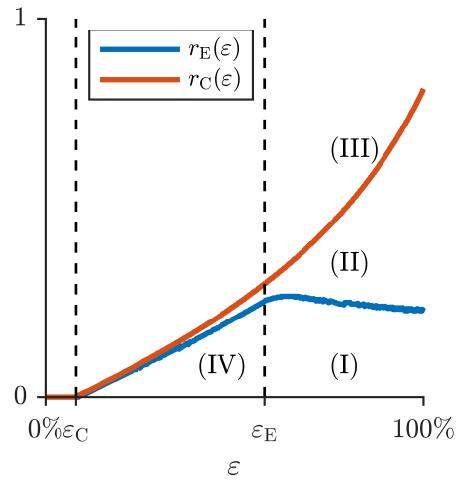


Figure 3.9 – The relative cost thresholds for epidemic control and elimination, for the scenario where on-PrEP MSM do not change HIV testing behavior

The relative costs thresholds for epidemic control and elimination as functions of PrEP effectiveness (noted $r_C(\varepsilon)$ and $r_E(\varepsilon)$, respectively), assuming fair perception of the HIV infection risk, for a typical parameter set calibrating our model; see [table S4](#) of the article's appendix. $r_C(\varepsilon)$ is the boundary between regions II and region III, while $r_E(\varepsilon)$ is the boundary between region II and regions I–VI together. See [section 3.4.1](#) for details on how we identified these thresholds numerically, from the voluntary PrEP coverage.

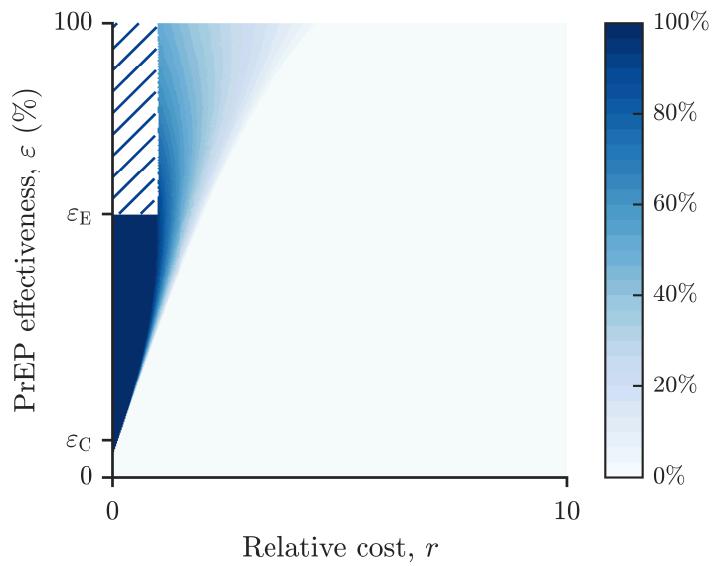


Figure 3.10 – The voluntary PrEP coverage, for the scenario where on-PrEP MSM do not change HIV testing behavior, assuming misperception of the HIV infection risk

Decision-making based on a misperceived risk of acquiring HIV significantly reduces the size of region I, where epidemic elimination is possible (blue stripes). The figure was obtained using the same calibrated parameter set as in [fig. 3.8](#). The PrEP effectiveness thresholds for epidemic control and epidemic elimination are, respectively, $\varepsilon_C = 8\%$ and $\varepsilon_E = 58\%$.

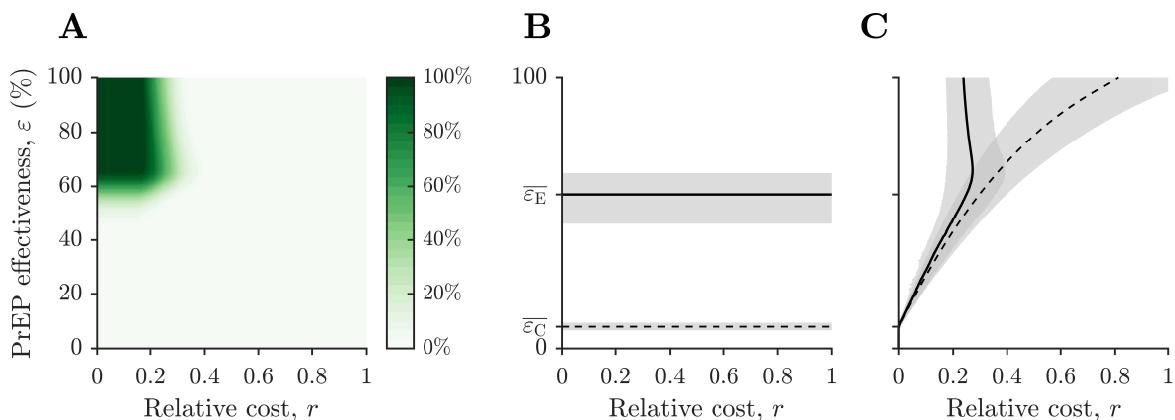


Figure 3.11 – The probability of HIV elimination and boundary uncertainty for the four-regions structure, for the scenario where on-PrEP MSM do not change HIV testing behavior

(A) The probability of HIV epidemic elimination due to voluntary PrEP coverage, obtained from the ~ 500 calibrated parameter sets. (B) The mean values for the epidemic control and epidemic elimination thresholds are given by $\varepsilon_C = 8\%$ (95% CI: 7%–9%) and $\varepsilon_E = 57\%$ (95% CI: 46%–65%), respectively. (C) The boundaries (mean and 95% CI) between region II and regions I and IV (continuous line) and between region II and region III (dashed line).

3.5 Further discussion

3.5.1 Implementing HIV prevention programs aiming at epidemic elimination

Targeted versus universal PrEP

Our approach considers the current recommendations, where PrEP is targeted to populations most at risk of HIV infection (WHO, 2016b). Therefore, in our model, only individuals at high risk of infection may make a decision about PrEP adoption. However, it has been recently discussed to include PrEP into routine prevention healthcare and thus, allowing all sexually active adults to decide whether or not adopt PrEP, in order to improve PrEP adoption by reducing PrEP-related stigma and access inequalities (Calabrese et al., 2017).

Decreasing the perceived cost of PrEP in the French context

Under our modeling assumptions, high-risk MSM adopting PrEP would be required to maintain
1015 high adherence to PrEP for 30 years in average; cf. [Table S2](#). According to our results, increasing PrEP coverage among high-risk MSM in France is essential to eliminate HIV transmission among MSM. Even though PrEP is fully reimbursed by the social security system, not enough MSM have adopted PrEP.

Some difficulties regarding PrEP adoption still need to be addressed. For instance, medical
1020 visits are covered only ~70% by the social security system. In addition, the first PrEP prescription and the yearly renewal must still be done by HIV-specialized doctors working in hospitals or HIV-specialized health centers ([Haute Autorité de Santé; EPI-PHARE, 2020](#)). This may perpetuate social stigma and discourage some individuals. Training general doctors and allowing them to prescribe PrEP may facilitate and, thus, broaden PrEP access.

1025 In addition, the healthcare providers' attitudes towards PrEP should be considered. PrEP is currently a medication requiring medical prescription. Hence, an increase in PrEP adoption requires an increase in PrEP prescription. Unfortunately, some healthcare providers may remain reluctant to agree with PrEP use, due to concerns about risk compensation and potential increase in STI transmission ([Caumes, 2018](#)). As of the end of 2017, STI diagnoses among MSM
1030 have significantly increased at the national level ([Santé Publique France, 2018](#)), which could be due to low condom use among the MSM population (and not only among PrEP users). Promoting condom use among MSM may help not only preventing STIs, but also increasing PrEP acceptability.

3.5.2 Modeling limitations and perspectives

1035 Assuming perfect PrEP adherence

Our model takes into account perfect PrEP adherence. That is, we assume that individuals who adopt PrEP, take PrEP pills correctly, continuously and for life. This assumption may not represent current reality in the Paris region, where only about 85% of PrEP users got a
1040 prescription renewal the following year, since PrEP rollout ([EPI-PHARE, 2019, 2020](#)). Still, our model may be useful for future presentations of prevention against HIV, such as long-lasting

PrEP () and vaccination (). Modeling recurrent decision-making () or the drop of PrEP while being sexually active may be interesting to study.

Obtaining data on sexual behavior

Including heterogeneity in sexual behavior in modeling studies allows to account for essential behavioral data (for instance, the number of sexual contacts and the proportion of condomless interactions), to which the epidemiology might be very sensitive. However, data on sexual behavior may depend heavily on self-reporting⁷, resulting in high variation of results among some papers (Hess et al., 2017). For instance, there may be some difficulties in obtaining data about the size of the MSM population and the individuals' sexual practices (which gives the population stratification by risk of infection) (Marcus et al., 2013; Baral et al., 2018). Also, data on the number of sexual partners (Hess et al., 2017) and most risky contacts might be hard to trace (van Aar et al., 2015).

Data about stable and occasional relationships (Velter et al., 2015) could also be included in the model in order to account for different probabilities of transmission, as well as different probabilities of condom use during the corresponding sexual encounters. This would allow to define the high-risk group not only in terms of the number of sexual contacts but also in terms of the nature of the sexual encounters.

These difficulties point to the importance of better data collection, but also to the importance of fighting stigma around sexual behaviors and preventive methods, so self-declaration becomes more common and reliable. Online tools may help obtaining more and accurate data on sexual behavior (Velter et al., 2015; Baral et al., 2018), but population samples may be more biased than those of traditional surveys.

Targeting other subpopulations

Considering risk compensation among non-PrEP users (Phanuphak and Phanuphak, 2018) and explicitly modeling condom use among individuals at low risk of infection might strengthen HIV and other sexually transmitted diseases prevention programs. In addition, considering an

⁷It was indeed the case of the data on sexual behavior that we used in our study, collected through the Presse Gays et Lesbiennes survey (Velter et al., 2015)

age-structured model might help better targeting of high-risk subpopulations, such as young MSM ([Siguier and Molina, 2018](#); [WHO, 2016b](#)).

Considering the heterogeneity in the risk and cost perception

- 1070 In our model, we assumed a homogeneous perception of both the risk of infection and the relative cost of PrEP versus ART, among high-risk MSM. However, in reality, individuals who are eligible to PrEP may perceive their risk of infection and/or the cost of PrEP very differently ([Blumenthal et al., 2019](#)). It would be useful to study how the results of our current project change considering heterogeneity in the decision-making and the implications for PrEP rollouts.

1075 Chapter 4

General discussion

4.1 Summary

4.1.1 Reaching epidemic elimination through the voluntary adoption of prevention

1080 We modeled the individual response to an epidemic threat through the resolution of a prevention-versus-treatment dilemma, and studied its impact on epidemic spreading. The individual willingness (respectively, refusal) to adopt preventive methods relies on the perception that the strategy of preventing the infection is more (respectively, less) beneficial than facing the risk of being infected, which could lead to acquiring the disease, and consequently being treated. To model the 1085 individual-level risk assessment, we assumed that individuals acknowledge some epidemiological data (e.g., the disease prevalence ([Jijón et al., 2017](#)) and the incidence rate (?)) provided by, for instance, public health authorities, through communication campaigns.

We used our approach to address two public health issues. First, we studied voluntary vaccination against treatable childhood infectious diseases in a context where efficient, yet imperfect 1090 vaccines are available (cf. [chapter 2](#) and ([Jijón et al., 2017](#))). The results of the vaccination model were obtained analytically, and provided important insights into the system properties, thus constituting a theoretical guide for the coding choices and the interpretation of the results of the second project that involved numerical implementation. Second, we studied the voluntary use

of PrEP to avoid HIV infection, among the population of MSM (cf. [chapter 3](#) and [\(?\)](#)). We accounted for population heterogeneity regarding the risk of infection (namely, due to heterogeneity in sexual behaviors). We considered that the high-risk population drives the epidemic, and thus becomes the target population of PrEP implementation policies (unlike childhood vaccination, which is recommended for the vast majority of newborns and young children).

Our model's main outcome is the prevention coverage reached voluntarily by individuals, expressed as a function of the dynamical system's parameters. In particular, we obtained the voluntary prevention coverage as a function of prevention effectiveness and the relative cost of prevention versus treatment perceived by individuals. From a general point of view, our results suggest that epidemic elimination through the voluntary adoption of prevention is possible, even for imperfect preventive methods, provided that they are highly effective and that individuals perceive the cost of prevention relative to that of treatment being low.

However, epidemic elimination may be only temporary : we found that the game-theoretic assumption of an equilibrium resolution of the prevention versus treatment dilemma is not ensured. In other words, there is no long-term individual motivation to adopt prevention once the epidemic is eliminated. Indeed, an important decrease in the number of infections may induce individuals to witness less disease burden (such as disease morbidity, difficulties regarding treatment adoption, disease mortality, etc.) and thus, to perceive less benefits from prevention. Therefore, epidemic elimination may induce a higher cost of prevention perceived by individuals, provoking the system dynamics to return to its endemic status.

Another key outcome of our model is the effective reproduction number, which we obtained analytically (and not only numerically). This allowed us to study it as a function of the system parameters and thus find the conditions to be met in order to ensure epidemic control (i.e., a decrease in the reproduction number) and/or elimination (i.e., reproduction number below 1).

In the case of vaccination against childhood infectious diseases, we found that epidemic elimination required the vaccine-induced immunity to be long-lasting, in addition to high vaccine effectiveness. In the case of PrEP uptake against HIV infection, we found that the HIV epidemic may be eliminated by targeting the prevention interventions to those who identify themselves most at risk of infection. We found an expression for the PrEP effectiveness threshold yielding epidemic elimination in terms of the level of risk compensation. In addition, we considered an alternative scenario where individuals misperceive their risk of infection, by acknowledging only

1125 the proportion of infected —and diagnosed— individuals among their peers.

In both projects, we found that risk perception plays a major role in achieving epidemic elimination: the higher the risk perceived, the wider the area where epidemic elimination can be reached — concerning the perceived cost dimension. That is, if the perceived risk decreases, the cost that individuals are willing to pay to adopt prevention decreases as well, regardless of
1130 the level of prevention effectiveness. In other words, if individuals do not perceive themselves as being at a high enough risk of infection, they are less willing to adopt preventive methods.

4.1.2 Establishing public health policies aiming at the end of communicable diseases

Our results give insights into the issue of voluntary prevention and epidemic behavior in the long
1135 run. This allows to place our research within the discussion about sustainability of health behaviors and may thus be helpful for public health policies aiming at epidemic elimination ([WHO, 2020a](#)).

Reaching and maintaining epidemic elimination in the long run requires active efforts to keep the cost of prevention perceived as low, as well as ensuring that individuals have access
1140 to accurate, updated epidemiological data allowing them to evaluate their risk of infection. Indeed, global immunization programs aiming to end vaccine-preventable infectious diseases have already pointed to the need of sustaining “trust in vaccines and immunization services in communities, to increase health literacy with a focus on vaccination at all levels, and to build resilience against misinformation” ([WHO, 2019](#)); while PrEP programs have identified the need
1145 to fight uptake-related difficulties perceived by individuals ([Desai et al., 2018; Sidebottom et al., 2018](#)), misinformation regarding PrEP effectiveness ([Young et al., 2014; Underhill et al., 2016](#)) and social stigma and discrimination ([Young et al., 2014; Pérez-Figueroa et al., 2015; Arnold and Steward, 2016](#)), to increase PrEP adoption and adherence.

Roughly speaking, our results suggest that two main phases should be established by public
1150 health policies aiming at disease elimination: i) During an ongoing epidemic, increasing prevention coverage by decreasing the barriers regarding acceptability and accessibility, as well as offering information about the risk of infection and the disease and treatment burden; ii) In the case of epidemic elimination, maintaining high levels of prevention coverage by ensuring acces-

sibility, but also by sharing information about the achievements of preventive programs and the
1155 epidemic severity previous to their implementation.

In addition, our results may add new perspectives in the discussion about voluntary versus mandatory prevention, by supporting individual informed decision-making, which may actually accompany public efforts towards epidemic elimination, under the proper circumstances.

4.2 Limitations

1160 4.2.1 The complexity of modeling human behavior

As with all modeling studies, ours encounters its limits at representing reality in detail. Simple models are useful to understand epidemic dynamics by interpreting their results, while keeping some flexibility for application to other contexts. However, they may leave aside essential factors reflecting the complexity of human behavior.

1165 Notably, we use a system of ordinary differential equations to model disease transmission, which may fail to take into account individual heterogeneity. We try to overcome this limitation in the application concerning PrEP and HIV by accounting for two subpopulations, represented by additional compartments. However, we assign fixed parameters for each subpopulation to transit from one compartment to another; that is, all individual behaviors are summarized into an
1170 average behavior that is assumed to be the same for all individuals within a given compartment. In addition, we model decision-making as a maximisation of utility, which was mainly based in individuals' perception of the relative cost and the risk of infection. However, individuals may perceive these factors differently and the utility function may also be defined differently.

[EXPAND](#)

1175 **4.2.2 Determining and interpreting the relative cost of prevention versus treatment**

Since the decision-making relies not only on monetary, quantitative factors, but also on subjective factors like prevention acceptability and accessibility, as well as self-awareness regarding risk of infection, the resulting values for the total expected utility and the relative cost were read from 1180 a qualitative point of view. Therefore, it is not possible to place a specific situation in a specific point of the *cost-axis*: in our framework, one cannot read that a real-life strategy is “perceived as being x times more beneficial” than another strategy.

Nevertheless, the qualitative interpretation of our results might still offer insight about the dynamical system’s behavior: from an intuitive point of view, a very low cost perceived 1185 by individuals and/or cost reduction may be easier to interpret and to aim to. In addition, our interpretation of the (in)stability of the disease-free equilibria may offer insight on how the dynamical system may respond to interventions.

4.3 Perspectives

4.3.1 Fighting infectious diseases in other socio-economical settings

1190 Our results point to cost reduction being a key public health’s objective to yield epidemic elimination. Our work focuses in fighting epidemic spread within high-income settings, where the notion of cost denotes mostly non-monetary aspects, specially involving the individuals’ acceptability of the preventive methods. However, in low-income settings, the consequences of infections may be 1195 far more severe, and cost-reducing policies may require to target prevention accessibility rather than prevention acceptability.

For instance, in the case of the measles epidemiology, the mortality rates can be as high as 2% to 15% among children in low-income settings, and mild symptoms like diarrhea and rash can become serious complications, due to malnutrition and hemorrhages ([Sever et al., 2011](#)). 1200 Hence, the MMR vaccine is often well accepted ([Larson et al., 2016](#)), while a common barrier

for vaccination concerns availability issues: as of August 2019, 23 countries had yet to introduce the second dose of MMR vaccine ([WHO, August 2019](#)).

Similarly, in the case of the HIV epidemiology, accessing HIV care in low- and middle-income settings and, in particular, the availability of PrEP might still be challenging ([UNAIDS, 2019a](#)).
1205 Hence, context-specific strategies to facilitate access to PrEP should be implemented ([Rebe et al., 2019](#)).

4.3.2 Including the heterogeneity in the perception of infection risk and cost

Impact of social networks, misinformation, etc

1210 We believe that including heterogeneity in the risk and/or cost perception in the model may help better understanding dynamics in terms of population heterogeneity and developing targeted implementations of prevention programs.

4.3.3 Considering other behavioral models

Also, it could be interesting to account for individuals' acknowledgment of herd immunity to
1215 model *free riders*, individuals who decide not to adopt prevention hoping to benefit from others' preventive behaviors. In the case of vaccination, previous studies have found that high vaccination rate decreased the individual's acceptance of vaccination ([Ibuka et al., 2014](#)). In the case of the use of PrEP, the free-rider phenomenon could be studied by considering, for instance, the probability of undergoing condomless sex with on-PrEP individuals. On the other hand,
1220 considering altruism into the model may also allow to study if voluntary prevention coverage may reach levels that optimize the payoff at the collective level ([Shim et al., 2012](#)).

4.3.4 Applying behavioral epidemiology to other epidemics

Our results may offer some particularly helpful insight for the global efforts to end polio, tuberculosis, malaria and other communicable diseases before 2030 ([WHO, 2020a](#)), as well as the

1225 global immunisation plan ([WHO, 2018a](#)). On the other hand, considering the prevention versus treatment dilemma and thus including individuals' decision-making into mathematical models may also yield new insights into the impact of voluntary prevention on the epidemic in the context of other infectious diseases that are in the path towards elimination, such as hepatitis B, human papillomavirus ([Basu et al., 2008](#)), hepatitis C and syphilis.

1230 Applications to the COVID-19 pandemic

From early January 2020 to mid-February 2021, around 109 million cases of SARS-CoV-2¹ infections resulting in ~ 2.4 million deaths were reported to WHO, worldwide ([WHO, 2021a](#)). Public health authorities have established a variety of mandatory non-pharmaceutical interventions (NPI) aiming to control de epidemic, including social distancing (i.e., reducing the number 1235 of contacts per individual, for instance, by imposing remote work, lockdown, curfews and closing highly-visited places), mask-wearing in public places and promoting regular hands disinfection. NPI have successfully reduced the number of new infections ([Bo et al., 2021](#)), but strict interventions such as national-level lockdowns and closing schools and stores are not tenable in the long run, so focus was addressed to developing immunization tools. Since mid-December 2020, several 1240 two-doses vaccines were placed on the market ([WHO, 2021b](#)), and vaccination campaigns started around the world. As of mid-February 2021, ~ 180 million vaccination doses² were administered worldwide ([Our World in Data, 2021](#)).

Mathematical models have been used to estimate epidemiological parameters (such as the effective reproduction number and time intervals of disease progression ([Xiang et al., 2021](#))), as 1245 well as to predict the impact of intervention measures ([Xiang et al., 2021](#)) on the still ongoing COVID-19 pandemic. In particular, behavioral epidemiology has been used to study the impact of epidemic control interventions demanding the voluntary participation of individuals, such as stay-at-home (SAH) interventions ([Kabir and Tanimoto, 2020](#)) and vaccination ([Choi and Shim, 2020; Jentsch et al., 2020](#)). All three studies used SEIR-type compartmental model for disease 1250 transmission, including symptomatic and asymptomatic individuals. [Kabir and Tanimoto \(2020\)](#) studied the compliance of SAH interventions. They included quarantine after exposure to the

¹Severe acute respiratory syndrome coronavirus 2, the causative agent of COVID-19, the severe coronavirus disease. See the review by [Salzberger et al. \(2020\)](#) for more details on the epidemiology of SARS-CoV-2.

²These data do not allow to infer the number of vaccinated people, since it is unknown how many of these shots are second doses.

virus into the transmission model, as well as hospitalizations and immunity after recovery. The payoff depended on the relative costs perceived by individuals and the number of infected individuals. The authors found that individuals' compliance for SAH interventions wanes with time.

1255 In addition, they studied the final size of the epidemic and the fraction of hospitalized population in terms of the perceived cost and the transmission rate, concluding that SAH and natural immunity complement each other in controlling the epidemic and thus, hospital occupation, as long as cost is perceived low. [Choi and Shim \(2020\)](#) accounted for imperfect vaccination and social distancing (reduction of the number of contacts, by a constant factor) in their transmission model. They analyzed the individuals' expected payoffs (which depended on the strategies' adoption rates and relative perceived costs) when individuals may adopt the strategies of social distancing, vaccination, or both, to avoid infection, finding the threshold relative costs (of vaccination and social distancing) that determined the selection over one strategy over the other.

1260 [Jentsch et al. \(2020\)](#) studied vaccination prioritizing, considering three strategies: i) targeting older first, ii) targeting younger first, iii) vaccinating the whole population uniformly, and iv) a contact-based strategy. The authors used an age-structured compartmental model accounting for imperfect vaccination and contacts by age and location. The decision model concerned the individual adherence to NPI. They calibrated their model using and using mobility data. Their main result in the best strategy (determined by the reduction in the number of deaths),

1265 depending on the reported cases and the proportion of vaccinated individuals.

The subject of ending the COVID-19 epidemic at the regional level has been recently discussed. A petition to end SARS-CoV-2 infections at the European level started in Germany in January 2021 ([ZeroCovid, 2021](#)), suscitating a debate in other European countries, such as France ([Tribune, 2021](#)) and UK ([Nuki, 2021](#)). Our approach may give insights into the subject 1270 of increasing prevention coverage aiming to COVID-19 elimination, by highlighting how essential an accurate perception of the infection risk and a reduction of the perceived cost of preventing SARS-CoV-2 infection are.

Individuals' perception on the risk of SARS-CoV-2 infection may be strongly related to the direct experience with the virus at the familiar and professional level ([Domínguez et al., 2020](#)). In addition, a recent study found that the individuals' knowledge and beliefs about the pandemic were associated with individuals' information sources, which were strongly determined by sociodemographic characteristics ([Ali et al., 2020](#)). Therefore, availability and broad access to accurate information need to be ensured. Official, governmental sources may help ensuring

individuals' trust in the information, which may translate in the successful adoption of preventive behaviors (Lim et al., 2021).

Reducing the perceived cost of prevention in the early stages of an epidemic, specially in a context where therapeutic and immunization tools are not yet available, may be strongly related to disease morbidity and infection scares. However, as times goes by and control measures show their efficacy, individuals' attitudes towards preventive methods may vary more and more. Facilitating the access to both NPI (Sugrue et al., 2020) and immunization programs (Yamey et al., 2020) are needed.

Vaccine attitudes towards vaccination vary widely between countries (?). For instance, a survey on the acceptability of the COVID-19 vaccine found that only 44% of the French respondents where potentially getting vaccinated, versus a 81% of the UK responders (?). Vaccine hesitancy may be addressed, for instance, by increasing communication about vaccines, as well as ensuring broad availability and accessibility (?). In addition, facilitating vaccine adoption may be reached by facilitating the vaccination process itself, for instance, through single-dose vaccines (Sanchez-Felipe et al., 2020).

An additional issue of the COVID-19 epidemic is the high number of asymptomatic infections: an estimated 50% of infections are produced by asymptomatic cases (Johansson et al., 2021). Therefore, testing, tracing and isolating infected individuals has become one of the main strategies to control the epidemic (WHO, 2020b). Reducing the perceived cost of preventing onward SARS-CoV-2 transmission may thus include facilitating testing. For instance, by establishing mass testing programs or by offering tests through salivar samples instead of nasopharyngeal swabs (Yee et al., 2020), as well as at-home alternatives (Valentine-Graves et al., 2020).

4.4 Conclusion

In conclusion, the methods developed in this doctoral research program allowed us to study infectious disease epidemics in terms of individual's attitudes towards the available preventive methods against infection, as well as their perception of the risk of infection. In particular, we focused on studying the conditions under which epidemic elimination could be reached through the voluntary participation of the target population.

We found that public health programs may yield epidemic elimination, provided that i) highly-effective preventive methods are available and perceived as being at low cost; and ii) that so individuals have a fair perception of their risk of infection. However, once the epidemic is 1315 eliminated, active efforts from public health authorities are needed to maintain the individual perception of the prevention cost low, so the willingness to keep using prevention maintains voluntary-prevention coverage at sufficiently high levels.

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Open-source acknowledgements

LaTeX packages

- `algorithmx` (available at: <https://ctan.org/pkg/algorithmicx>)
- 1955 • `pseudocode` (available at: <https://ctan.org/pkg/pseudocode>)
- `multibib` (available at: <https://ctan.org/pkg/multibib>)
- `pdfpages` (available at: <https://ctan.org/pkg/pdfpages>)

Matlab packages

- `ColorBrewer` (available at: <https://www.mathworks.com/matlabcentral/fileexchange/45208-colorbrewer-attractive-and-distinctive-colormaps>)
- 1960 • `hatchfill2` (available at: <https://www.mathworks.com/matlabcentral/fileexchange/53593-hatchfill2>)

Appendices

A Interdisciplinary note

- ¹⁹⁶⁵ During my PhD, I was registered to the RDSP³ (Public health doctoral network), which is organized by the EHESP⁴ (School of high studies in public health). As a part of the RDSP program, I wrote an interdisciplinary note that places my doctoral research within a broader, interdisciplinary context. The corresponding document, titled « *Prevention of infectious diseases : from a game-theoretic approach to a multi-level, interdisciplinary perspective* », is included in
- ¹⁹⁷⁰ the following pages.

Interdisciplinary note

³Réseau doctoral en santé publique.

⁴École des hautes études en santé publique.

INTERDISCIPLINARY NOTE

B Résumé détaillé

« La prévention des maladies infectieuses dans le contexte de traitements efficaces : une approche par la théorie des jeux »

¹⁹⁷⁵ B1. Introduction

Malgré l'existence de méthodes efficaces, la prévention des maladies infectieuses continue de poser des défis aux autorités de santé publique. Face au risque d'infection, les individus décident d'utiliser une méthode de prévention ou bien d'être traités en cas d'acquisition de la maladie ; ceci est appelé *le dilemme de la prévention versus le traitement*. Alors que le traitement est généralement bien accepté par les individus infectés, l'acceptabilité de la prévention peut varier entre individus. La perception individuelle du risque d'infection et l'évaluation des avantages et les inconvénients de la prévention versus le traitement peuvent conduire les individus à adopter des comportements de prévention qui diffèrent des recommandations des autorités de santé publique.

La prise de décision individuelle peut être biaisée et pourtant, étroitement liée au cours de l'épidémie. En effet, le risque d'infection dépend de la prévalence de la maladie, qui elle-même dépend notamment de l'efficacité et de la couverture tant des outils préventifs que des traitements disponibles. En conséquence, la décision de chaque individu est indirectement influencée par les décisions des autres, puisque la somme des décisions détermine la *couverture volontaire* de la méthode préventive, qui à la fois a un impact sur la progression de l'épidémie.

Ainsi, pour étudier l'impact de la prévention sur une épidémie, il est essentiel de prendre en compte le comportement des individus. Afin d'étudier l'impact de la prévention volontaire, des modèles mathématiques combinant des modèles de transmission de la maladie au niveau populationnel avec des modèles concernant le comportement individuel ont été utilisés ([Verelst et al., 2016](#); [Wang et al., 2016](#)).

L'objectif principal de ma thèse a été de développer un modèle mathématique permettant de déterminer quel peut être l'impact de la prévention adoptée volontairement par les individus sur une épidémie, dans le contexte où il existe des traitements efficaces.

B2. Description générale des méthodes utilisées

Dans cette thèse, nous avons proposé un modèle à deux composants, combinant un modèle pour la transmission d'une maladie infectieuse, avec un modèle pour la prise de décision individuelle d'adopter ou pas une méthode préventive afin de diminuer le risque d'infection. Ce modèle a pour but d'évaluer les conditions pour lesquelles la couverture volontaire de la prévention peut contrôler et, éventuellement, éliminer une épidémie.

B2.1. La modélisation de la transmission d'une maladie infectieuse au niveau populationnel

Nous avons utilisé un modèle compartimental déterministe, décrivant la transition des individus d'un état à l'autre au cours du temps, défini par un système d'équations différentielles ordinaires (EDO). Un modèle classique de transmission de la maladie de ce genre a deux états d'équilibre possibles : un état où l'épidémie reste endémique et un autre où il n'y a plus d'épidémie (ici notés ES et DFS, respectivement, par ses acronymes en anglais) ([Hethcote, 2000](#)).

Le système d'EDO permet de calculer les indicateurs épidémiologiques reflétant la progression de l'épidémie. Nous calculons notamment le *taux de reproduction effectif*, R , défini comme le nombre moyen d'individus infectés par une personne pendant la période où elle est infectieuse. Le taux de reproduction effectif permet de déterminer l'impact de la prévention sur l'épidémie à long terme : si $R > 1$, l'état ES est atteint et l'épidémie persiste ; si $R \leq 1$, l'état DFS est atteint, et on dit que l'épidémie est *éliminée*.

Nous étudions le taux de reproduction effectif en fonction des paramètres concernant la méthode preventive (notamment, la couverture et l'efficacité). En particulier, en fixant la couverture de la prévention à 0, nous obtenons le *taux de reproduction de base*, R_0 : le nombre moyen d'individus infectés par une personne pendant la période où elle est infectieuse, en absence d'interventions de prévention. Autrement dit, le taux de reproduction de base reflète le comportement de l'épidémie à long terme, dans le cas où aucune méthode préventive n'est disponible. Si le taux de reproduction effectif est inférieur au taux de reproduction de base (c'est à dire, $R < R_0$), l'épidémie atteint un nouvel état endémique, moins sévère, et on dit que l'épidémie est *contrôlée* par la méthode préventive. En effet, une réduction du taux de reproduction se traduit par une

réduction du nombre de nouvelles infections.

Nous couplons ce modèle de transmission à un modèle au niveau individuel qui permet de déterminer si une couverture de la prévention permettant d'obtenir $R < 1$ peut être atteints volontairement.

2030 B2.2. La modélisation de la prise de décision concernant l'adoption de la prévention au niveau individuel

Afin de modéliser la résolution du dilemme de la prévention versus le traitement au niveau individuel, nous avons utilisé un jeu individuel non-coopératif (modèle issu de la théorie des jeux). Nous avons supposé que les individus décident d'adopter ou pas une méthode de prévention en évaluant leur probabilité de devenir infectés, la couverture et efficacité de la méthode préventive et le *coût relatif* de la prévention versus le traitement. Ce coût représente les inconvénients associés et à la prévention et au traitement, et concerne des aspects monétaires et/ou non monétaires comme le prix, les effets indésirables, les difficultés d'accès, la morbidité de la maladie, etc.

2040 Une *fonction d'utilité* a été définie en termes de ces éléments. La théorie des jeux postule que la prise de décision des individus maximise l'utilité (ou, de manière équivalente, minimise le coût total affronté par l'individu). La couverture de la méthode préventive qui maximise l'utilité individuelle donne la probabilité d'adopter la prévention pour un individu typique et ainsi, détermine à la fois la *couverture volontaire de la prévention* au niveau populationnel.

2045 Nous avons étudié la couverture volontaire en fonction notamment de l'efficacité de la prévention et du coût relatif de la prévention versus le traitement. En particulier, nous avons étudié les conditions nécessaires et suffisantes pour obtenir l'élimination de l'épidémie (c'est à dire, un taux de reproduction effectif issu de la couverture volontaire de la prévention inférieur à 1).

B3. Travaux de recherche

2050 Nous avons construit des modèles couplés afin d'explorer deux problèmes de santé publique. La première partie de ma thèse concerne un modèle pour la vaccination dans le contexte de maladies

infectieuses infantiles évitables par vaccination, dans un contexte où les traitements permettent la guérison (Jijón et al., 2017). La seconde partie de ma thèse concerne la modélisation de la prise volontaire de la prophylaxie pré-exposition (PrEP) comme méthode de prévention contre l'infection à VIH, au sein de la population des hommes qui ont des rapports sexuels avec les hommes (HSH) en Île-de-France (IdF), et son application numérique (?).

B3.1. La vaccination volontaire dans le cadre des maladies infectieuses infantiles

L'état de confiance vis-à-vis les vaccins est globalement élevé (Larson et al., 2016). Cependant, il existe des régions où l'hésitation face à la vaccination demeure un problème de santé publique. Sept des dix pays qui ont le moins confiance dans la vaccination ont été identifiés dans la région européenne en 2016 (Larson et al., 2016). En 2017, douze pays de l'Union Européenne avaient signalé une diminution de la couverture du vaccin infantile contre la rougeole, les oreillons et la rubéole (ROR) (Larson et al., 2018). Les sentiments des parents vis-à-vis de la vaccination de leur enfants varient considérablement d'un individu à l'autre, les causes sous-jacentes allant de la désinformation sur les effets indésirables, la méfiance à l'égard du système de santé, la pression sociale, les convictions religieuses, entre autres (Brown et al., 2010; Dubé et al., 2013; Larson et al., 2014; Dubé et al., 2018; Quinn et al., 2019).

Des études de modélisation ont conclu que l'élimination d'une épidémie ne serait pas possible via la vaccination volontaire (Bauch and Earn, 2004). Néanmoins, on a témoigné l'éradication globale de la variole (CDC, 2001), et de la déclaration d'élimination de maladies infectieuses dans certaines régions (a.e., la rougeole en Amérique (Sever et al., 2011)), grâce à des programmes de vaccination. Ainsi, l'objectif principal de la première partie de ma thèse était de développer un modèle mathématique permettant de réétudier la vaccination volontaire comme prévention contre une maladie infectieuse de type infantile, afin de déterminer si elle peut contrôler et/ou éliminer une épidémie, et sous quelles conditions.

Modèle

Le modèle de transmission au niveau populationnel a été défini par un modèle compartimental : les individus pouvant rester susceptibles ou être vaccinés (et puis redevenir susceptibles, à cause 2080 de la perte de l'immunité induite par la vaccination), les individus récemment infectés passant par une période de latence de l'infection et puis devenant infectieux, enfin guérissant soit naturellement, soit grâce à une thérapie. Ainsi, deux facteurs rendant le vaccin imparfait ont été considérés : i) l'efficacité du vaccin n'est pas totale (une proportion de la population n'est pas protégée contre la maladie après vaccination) ; et ii) l'immunité induite par le vaccin a une durée 2085 limitée.

En ce qui concerne le modèle de décision, nous avons défini la fonction d'utilité en termes de l'efficacité et la couverture du vaccin, le coût relatif du vaccin versus le la guérison, et le risque d'infection perçu par les individus. Le coût, dans le contexte de la vaccination, comprend des aspects comme le prix, les effets secondaires de la vaccination, l'accessibilité à la vaccination, 2090 la morbidité de la maladie, les effets secondaires du traitement, etc. Le risque d'infection a été défini par la prévalence endémique : la proportion d'individus infectés dans la population quand le système dynamique atteint son état d'équilibre.

Résultats

En maximisant la fonction d'utilité, nous avons obtenu une expression pour la probabilité d'être 2095 effectivement vacciné en fonction notamment du coût relatif. Contrairement aux études précédents ([Bauch and Earn, 2004](#)), nous avons montré que la vaccination volontaire peut éliminer une épidémie, même si le vaccin est imparfait, pourvu que le coût relatif soit suffisamment bas.

Toutefois, cette élimination ne peut être que temporaire et requiert de maintenir un coût relatif de la vaccination versus le traitement suffisamment bas. En effet, il n'y a pas un équilibre 2100 stable pour la stratégie individuelle quand il n'y a pas d'épidémie. Lorsque la couverture vaccinale est élevée, le nombre de cas de la maladie est faible. Ainsi, les individus ne perçoivent plus la morbidité et la mortalité liées à la maladie et des controverses concernant l'innocuité du vaccin peuvent apparaître. Cela peut changer la perception du coût de la prévention versus le traitement et entraîner une diminution de la couverture vaccinale, qui a son tour provoque un retour vers 2105 la situation $R = 1$.

Les conditions nécessaires et suffisantes pour éliminer l'épidémie ont donné lieu à une discussion sur les paramètres concernant le vaccin. Nous avons trouvé que deux conditions sont nécessaires pour atteindre et maintenir l'élimination de l'épidémie : i) Développer des vaccins qui fournissent une immunité de longue durée (nous avons trouvé une borne inférieure pour la 2110 durée de l'immunité induite par le vaccin) ; et ii) Maintenir le coût relatif de la vaccination versus du traitement suffisamment bas (nous avons trouvé un intervalle pour le coût relatif).

Il est important de noter que, une fois le stade d'élimination est atteint, la transition vers $R = 1$ peut être ralentie considérablement grâce aux efforts des autorités de santé pour maintenir le coût de la vaccination faible. Des interventions peuvent être mises en place pour maintenir une 2115 perception du coût bas et donc une motivation pour se faire vacciner. Par exemple, des incentives (monétaires et non monétaires) ont été utilisés. Nous proposons trois possibles interventions additionnelles : a) l'incentive via la diminution des mensualités de l'assurance de santé au fur et à mesure que le calendrier vaccinal est complété ; b) informer sur le succès des programmes de prévention dans les médias ; et c) La promotion d'une perception juste via le rappel en continu des 2120 conséquences des maladies évitables par prévention et ses données épidémiologiques, en parallèle d'une information claire sur les effets indésirables du vaccin et du traitement.

Les résultats de ce premier travail de recherche ont été obtenus de façon entièrement analytique et ont fourni des informations importantes sur les propriétés du système, constituant ainsi un guide théorique pour les choix des algorithmes et l'interprétation des résultats la seconde 2125 partie de la thèse, qui impliquait une implémentation numérique

Application à la rougeole. Nous avons appliqué nos méthodes à l'épidémiologie de la rougeole, qui a été notamment déclaré éliminée dans la région panaméricaine dans les années 90 ([Sever et al., 2011](#); [De Quadros, 2004](#)), et a subi une réemergence récemment ([CDC, August 2019](#)), suite à une baisse de la couverture vaccinale ([WHO, 2018b](#)).

Nos résultats suggèrent que l'élimination de la rougeole pourrait s'expliquer par la longue 2130 durée de l'immunité induite par le vaccin ROR, ainsi que du coût relatif de la vaccination par rapport au traitement qui était certainement perçu comme faible pendant les programmes de vaccination de masse des années 90. Nous concluons que la diminution de la couverture vaccinale observée dans plusieurs pays à revenu élevé peut être due à une augmentation du coût de la 2135 vaccination perçue par les individus dans le contexte actuel, où les individus ne témoignent que

rarement des cas de rougeole et ses séquelles.

Afin d'atteindre l'élimination de l'épidémie par l'adoption volontaire de la vaccination, et de maintenir le statut d'élimination à long terme, le coût perçu par les individus doit être bas, notamment, en tenant la population informée sur l'épidémiologie de la rougeole à l'ère de la pré-vaccination, des séquelles possibles de la maladie et de l'innocuité et la haute performance actuelles du vaccin contre la rougeole.
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B3.2. L'utilisation volontaire de la prophylaxie pré-exposition comme méthode de prévention contre l'infection par le VIH

Malgré les efforts réalisés pour prévenir et traiter l'infection à VIH, l'épidémie continue de progresser (UNAIDS, 2018). Dans la plupart des pays à revenu élevé, c'est parmi la population des HSH que le taux d'incidence est le plus élevé (UNAIDS, 2018; WHO, 2016b; Beyer et al., 2012). La PrEP est une méthode de prévention hautement efficace qui a été récemment développée et qui est recommandée pour les populations à haut risque d'infection par le VIH (Siguier and Molina, 2018).
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Des études de modélisation ont estimé que la PrEP pourrait conduire à une réduction considérable du nombre de nouvelles infections (Punyacharoen et al., 2016; Kim et al., 2014; Robineau et al., 2017; Gomez et al., 2012) et même l'élimination de l'épidémie (Palk et al., 2018; Rozhnova et al., 2018) chez les HSH. Dans ces études, les auteurs font l'hypothèse, et donc imposent, qu'une certaine fraction de la population utiliseront la PrEP. Or la fraction de la population qui acceptera d'utiliser la PrEP reste incertaine. Le succès d'un programme de prévention basé sur la PrEP dépendra de la participation active et continue de la population cible.
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Les individus feront face au dilemme d'adopter ou pas la PrEP, dans le contexte actuel de l'épidémie du VIH, où des traitement par antirétroviraux (TARV) efficaces existent. Les individus prendront leur décision en évaluant leur risque d'infection au VIH, ses conséquences, ainsi que les bénéfices et contraintes associés à la PrEP et aux TARV (par exemple, les effets secondaires, le prix, les politiques de remboursement, l'accessibilité, la stigmatisation sociale, la morbidité de la maladie, la peur de contracter d'autres infections sexuellement transmissibles en raison de la baisse de l'utilisation du préservatif, etc. (Young et al., 2014; Taylor et al., 2014; Pérez-Figueroa
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2165 et al., 2015; Holt et al., 2018; Desai et al., 2018)).

À notre connaissance, aucune étude de modélisation sur l'impact de la PrEP n'a pris en compte et analysé la prise de décision individuelle provoquant la participation volontaire de la population cible. L'objectif principal de ce travail de recherche a été de modéliser la transmission du VIH en prenant en compte le dilemme de la prévention versus le traitement, dans le contexte 2170 actuel. Ainsi, nous avons pris en compte l'utilisation du préservatif comme méthode préventive supplémentaire, une haute efficacité des TARV et un choix d'adopter ou pas la PrEP parmi les individus qui sont à haut risque d'infection.

Nous cherchions à déterminer si l'utilisation volontaire de la PrEP par la sous-population la plus à risque d'infection pourrait contrôler et éventuellement éliminer l'épidémie du VIH 2175 au niveau de la population globale, et sous quelles conditions. En particulier, notre but a été d'étudier cette problématique dans le contexte d'une des communautés les plus touchées par le VIH en France métropolitaine : les HSH en IdF.

Modèle

Le modèle compartimental a été défini par un système d'EDO décrivant la transmission du 2180 VIH au niveau populationnel, en prenant en compte la progression de l'infection et son TARV. L'hétérogénéité en termes du risque d'infection (à savoir, en raison de l'hétérogénéité des comportements sexuels) auquel les individus sont exposés a été prise en compte en stratifiant la population en deux groupes, selon leurs comportements sexuels (Velter et al., 2015) : le groupe des individus à haut risque d'infection et transmission, et le groupe à risque faible. Nous avons 2185 considéré des contacts non-aléatoires entre les individus (Jacquez et al., 1988). De plus, nous avons considéré que la population à haut risque est le moteur de l'épidémie, et devient ainsi la population cible des politiques de mise en œuvre de la PrEP (contrairement à la vaccination des enfants, qui est recommandée pour la grande majorité des nouveau-nés et des jeunes enfants).

La PrEP a été introduite dans le modèle compartimental en supposant que uniquement les 2190 individus à haut risque d'infection peuvent adopter la PrEP comme prévention contre l'infection à VIH. Nous avons considéré que les MSM sous PrEP peuvent utiliser moins le préservatif (diminution de la couverture du préservatif du 30% au 20%) et que la prescription de la PrEP peut être renouvelée tous les 3 mois sous condition de rester séronégatif (Molina and Earn, 2015).

En ce qui concerne le modèle de décision, la fonction d'utilité a été définie en termes de
2195 la perception individuelle du risque d'infection au VIH (donné par le taux d'incidence) chez les HSH en ÎdF, de la couverture et l'efficacité de la PrEP, du coût associé à la PrEP et du coût associé aux TARV.

Analyses de sensibilité

Nous avons réalisé des analyses de sensibilité du modèle en ce qui concerne :

- 2200 i) **La perception du risque d'infection.** Nous avons considéré un scénario où les individus à haut risque d'infection perçoivent leur risque en évaluant la proportion de leur pairs qui sont infectés par le VIH (au lieu de considérer le taux d'incidence).
- ii) **L'utilisation du préservatif par les HSH sous PrEP.** Nous avons considéré que les HSH sous PrEP arrêtent complètement d'utiliser le préservatif lors des rapports sexuels
2205 (au lieu de seulement diminuer leur utilisation).
- iii) **La fréquence à laquelle les HSH à haut risque d'infection se font tester.** Nous avons considéré que les individus sous PrEP ne suivent pas les recommandations des autorités de santé publique en ce qui concerne la fréquence de dépistage du VIH, et maintiennent leur comportement d'avant d'adopter la PrEP, en se faisant tester tous les ~ 3 ans ([Marty et al., 2018](#)), au lieu de tous les 3 mois ([Molina et al., 2018](#)).
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Résultats

Nous avons étudié le rôle de la prise de décision au niveau individuel pour évaluer l'impact de la PrEP sur l'épidémie de VIH, et déterminé comment un certain niveau de couverture PrEP peut être atteint volontairement.

- 2215 Les résultats de ce travail de recherche ont été obtenus de façon numérique. Le modèle compartimental a été calibré afin de reproduire la situation épidémiologique actuelle chez les HSH en ÎdF ([Marty et al., 2018](#)). Nous avons trouvé la couverture volontaire de la PrEP parmi les HSH à haut risque d'infection par le VIH, en fonction de l'efficacité de la PrEP et le coût relatif de la PrEP versus le TARV. Nous avons ensuite identifié les conditions pour lesquelles le
2220 contrôle et/ou l'élimination de l'épidémie au niveau de la population globale sont possibles.

Nous avons obtenu quatre résultats principaux pour les déploiements de la PrEP : i) Les épidémies de VIH peuvent être éliminées par l'utilisation volontaire de la PrEP à condition que le coût relatif de l'utilisation de la PrEP versus le TARV soit perçu suffisamment bas ; ii) Des tests de dépistage du VIH fréquents pendant la prise de PrEP peuvent compenser une mauvaise adhésion à la PrEP et agir comme une intervention ‘test and treat’, où l'on dépiste et soigne tout de suite ; iii) La perception du risque de VIH peut jouer un rôle majeur pour l'élimination, tandis que la baisse de l'utilisation du préservatif chez les MSM sous PrEP non ; et iv) L'élimination de l'épidémie peut n'être que temporaire.

En particulier, en supposant une efficacité de 86% de la PrEP, comme on l'a observé lors de deux essais cliniques ([Siguier and Molina, 2018](#)), et une perception juste du risque d'infection, l'élimination de l'épidémie serait possible si la couverture de la PrEP serait au minimum de 55% parmi les HSH à haut risque. Une chute totale de l'utilisation du préservatif parmi les utilisateurs de la PrEP augmente légèrement ce taux à 57%. Cependant, si les individus sous-estiment leur risque d'infection, il serait nécessaire de réduire le coût de la PrEP d'un facteur de ~ 2, pour que le programme PrEP permette l'élimination de l'épidémie.

Ainsi, nous avons trouvé que les conditions d'élimination ne sont pas encore réunies en région parisienne, où au plus 47% des HSH à haut risque d'infection utilisaient la PrEP mi-2019. Il est nécessaire de réduire davantage le coût perçu de la PrEP et de promouvoir une perception juste du risque de VIH pour parvenir à l'élimination. Ces conditions doivent être maintenues à long terme pour maintenir le statut d'élimination.

B4. Conclusions

Le résultat principal de notre modèle est la couverture de la prévention atteinte volontairement par les individus. En particulier, nous avons étudié la couverture de cette prévention volontaire en fonction de l'efficacité de la prévention et du coût relatif de la prévention par rapport au traitement perçu par les individus. D'un point de vue général, nos résultats suggèrent que l'élimination des épidémies par l'adoption volontaire de la prévention est possible, même en utilisant les méthodes imparfaites et des perceptions des risques individuelles biaisées, à condition que l'efficacité de la prévention soit élevée et que le coût de la prévention perçu par les individus soit faible.

2250 Nous avons constaté que la perception du risque joue un rôle majeur dans la réussite de l'élimination de l'épidémie. Si le risque perçu diminue, le coût auquel les individus sont prêts à faire face pour adopter la prévention diminue également, quel que soit le niveau d'efficacité de la prévention. En d'autres termes, si les individus ne se perçoivent pas comme étant à un risque d'infection suffisamment élevé, ils sont moins disposés à adopter des méthodes préventives.

2255 Nos résultats peuvent être utiles pour les politiques de santé publique visant à éliminer les épidémies, et en particulier dans le cadre des objectifs pour le développement durable de l'Organisation Mondiale de la Santé ([WHO, 2020a](#)). Deux phases peuvent être établies afin d'atteindre et maintenir l'élimination des maladies infectieuses à long terme. Pendant une épidémie en cours, la couverture de la prévention peut augmenter grâce à la diminution des barrières perçues par
2260 les individus, ainsi qu'en offrant des informations sur le risque d'infection et la maladie et la charge de traitement. Puis, en cas d'élimination d'une épidémie, les niveaux élevés de couverture de prévention peuvent être maintenus grâce à l'accessibilité à la prévention, mais aussi grâce à l'accès aux informations sur le succès des programmes de prévention passés, ainsi que sur la gravité de l'épidémie avant leur mise en place.

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