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

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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 by 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 fifth year of thesis, I held a PhD research and teaching adjunct contract (PhD 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 studies public health interventions in infectious disease epidemiology, and individual behaviors regarding prevention, from the perspective of mathematical modeling. The approach is interdisciplinary, covering epidemiological studies and the implementation of public health interventions, next to epidemiological models of disease transmission, economics models of 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 a 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 and the development of effective vaccines against COVID-19. All these events highlight the pertinence and urgency to study epidemic control through prevention interventions accounting for the active voluntary 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 this subject. As part of my doctoral research, two scientific articles were produced (Jijón et al., 2017, 2021), which constitute the cores of chapter 2 and chapter 3, 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 starts with a custom introduction, where the epidemiology of the public health issue that motivated our work is presented, as well as some additional material which was not included in the articles. Chapter 4 presents a general discussion and conclusions.

Appendix A includes a note on what our results may offer to the current sanitary situation, along with a short overview of the currently published applications of behavioral epidemiology to the COVID-19 epidemic. This thesis is written in English, and 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 get treated in the case of acquiring infection. Whereas treatment is generally well accepted by infected individuals, the acceptability of prevention may vary among individuals, which can lead to preventive behaviors that differ vastly 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 disease transmission at the population level with decision-making at the individual level. We model disease transmission using a compartmental model defined by a system of ordinary differential equations. For the individual-level decision-making, we propose a game-theoretic approach, which assumes that individuals solve the prevention versus treatment dilemma by choosing the strategy that benefits them the most, in the long term. Individuals adopt a proposed prevention strategy provided that it is perceived as more beneficial than treatment. The decision-making thus 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 infection by the individuals who are most at risk. 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 preven-

tive methods are highly effective and that individuals perceive the relative cost of prevention versus treatment to be low. However, epidemic elimination may only be 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 (IPLESP – UMRS 1136 Sorbonne Université (SU) & Inserm), dans l'équipe Maladies Transmissibles : Surveillance et Modélisation.

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Cette thèse étudie les interventions de santé publique contre les épidémies de maladies infectieuses du point de vue de la modélisation mathématique, en tenant compte des comportements individuels en matière de prévention. Une approche interdisciplinaire est utilisée, couvrant des essais cliniques et la mise en place d'interventions de santé publique, des modèles mathématique de transmission épidémique, des modèles de prise de décision et des données sur les comportements individuels.

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 prevention 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 s'identifiant à haut risque

d'infection. Troisièmement, l'émergence de la pandémie du SARS-CoV-2 et la mise en place des programmes de vaccination contre la COVID-19.

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 contexte où des traitements efficaces existent, ainsi que le cadre conceptuel et les approches de modélisation que nous avons utilisés pour étudier ce sujet. Dans le cadre de la thèse, deux articles scientifiques ont été rédigés (Jijón et al., 2017, 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 commence par une introduction spécifique, où l'épidémiologie du problème de santé publique qui a motivé 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.

L'l'Appendice A inclut une brève note sur ce que nos résultats pourraient offrir à la situation sanitaire actuelle, ainsi qu'un aperçu des publications sur des modèles issus de l'épidémiologie comportementale appliqués à l'épidémie du COVID-19. 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 à être traité en cas d'infection. Alors que le traitement est généralement bien accepté par les individus infectés, l'acceptabilité de la prévention peut varier considérablement 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 qui lui bénéficie le plus, à long terme. La prise de décision dépend de la perception individuelle du risque d'infection ainsi que de la perception du coût relatif de la prévention versus du traitement, qui comprend des aspects monétaires et/ou non monétaires, comme le prix, les politiques de remboursement, l'accessibilité, la stigmatisation, la morbidité de la maladie, les effets secondaires indésirables, etc.

Deux cas de dilemme de prévention versus le traitement sont étudiés. 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 les 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 maintenir l'élimination de l'épidémie à long terme.

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

Scientific production during the PhD

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

Jijón, S., Molina J.-M., Costagliola D., Supervie, V., and Breban, R. (2021). Can HIV epidemics among men who have sex with men be eliminated through participation in PrEP rollouts? *AIDS*. Published ahead of print. doi: 10.1097/QAD.0000000000003012

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]. Website: https://pintofscience.fr/event/its-contagious-tackling-the-dangerous-english.

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.

Contents

Acronyms and abbreviations

Acronyms

AIDS	Acquired immunodeficiency syndrome
ANSM	Agence nationale de sécurité du médicament et des produits de santé (National agency for medical drugs and health products safety)
ANRS-MIE	Agence nationale de recherches sur le sida et les hépatites virales – Maladies infectieuses émergentes (French agency for research on HIV and emerging infectious diseases)
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
ÎdF	Île-de-France
MCV	Measles-containing vaccine
MMR	Measles-mumps-rubella vaccine
MMWR	Morbidity and mortality weekly CDC journal
MSM	Men who have sex with men
ODE	Ordinary differential equations

Acronyms (continuation)

PAHO	Pan American health organization
PrEP	Pre-exposure prophylaxis
SM	Supplementary material
STI	Sexually-transmitted infections
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)

Chapter 1

General introduction

1.1 Prevention interventions aiming to the elimination of infectious diseases

The prevention of infectious diseases has greatly improved, not only as a result of the development of safe, highly-effective preventive methods, but also thanks to regional and global public health programs aiming at infectious diseases' elimination. Immunization alone can now prevent more than 20 life-threatening diseases (WHO, 2019). Mass immunization programs achieved the eradication of smallpox in 1980[1] (CDC, 2001). The number of cases of poliomyelitis (commonly known as polio) has decreased from an estimated 350 000 cases in 1988, to 33 reported cases in 2018 (WHO, 2019c). 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). 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).

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-

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

preventable diseases (WHO, 2020). As a result, vaccine coverage among children and vaccine development have shown remarkable progress, but many other 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, 2020). 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, 2020). As a result, the currently ongoing Immunization Agenda 2030, the successor of the GVAP 2011–2020, places 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, at 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).

1.1.1 Epidemic elimination

Unlike infectious disease *eradication*, which is defined as the complete termination of the infectious disease transmission or the total elimination of the infectious agent (Porta, 2013), there is no consensus for the definition of disease and epidemic *elimination*. Global (respectively, regional) epidemic elimination often 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). Global and regional programs aiming at disease elimination set specific targets to be met in a certain amount of time and thus, declaring disease elimination may depend on the specific infectious disease and its context. See table 1.1 for some disease-specific targets currently included in WHO programs aiming at regional and/or global elimination.

The classical approach of the WHO to declare the end of an epidemic is to observe no new cases after a significant period of time after the last reported case (Nishiura, 2016); for

instance, twice as long as the empirical maximum of the incubation period. Other, rather heuristic ways to determine the end of an epidemic have also been used: the end of a Middle East respiratory syndrome (MERS) outbreak in South Korea was declared after the removal of movement restriction for the last quarantined case, which was almost a week before the date that would have be determined by the WHO criteria (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). Mathematical models can help overcome some of these difficulties. For instance, modeling studies have found that asymptomatic cases of poliomyelitis infection may still occur with a probability lower than 1%, 5 years after having no symptomatic cases within a population of 200 000 (Eichner and Dietz, 1996). In addition, mathematical modeling may provide estimates for unobserved disease 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.
AIDS	• 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	• Absence of cases for at least 3 years • High regional coverage of vaccination	2020[a,b]	(WHO, 2018a)
Poliomyelitis	• Absence of cases for at least 3 years • No circulation of wild strains		(Eichner and Dietz, 1996)
Rubella	• 95% reduction in the regional number of cases • Absence of cases for at least 3 years • High regional coverage of vaccination	2020[b]	(WHO, 2018a)
Yellow fever	• Reduction of the number of outbreaks to none	2026	(WHO, 2019)

Table 1.1 – Targets of some recent, global WHO programs aiming to end infectious diseases 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' 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 depending, for instance, on age and health state (Luyten et al., 2015) or the perception of the urgency of adopting a preventive intervention (Meertens et al., 2013). Individuals' attitudes towards prevention may thus 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 may engage in a *prevention versus treatment dilemma*, and make the decision between adopting or not prevention, while having the option for treatment in the case of infection.

Here, *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 authorities' — in contrast to mandatory prevention (i.e., required by law or community rules). The voluntary adoption of prevention mainly depends on the individuals' perception of its benefits and inconveniences versus those of treatment, as well as their perception on their own risk of infection, and of the consequences of being infected. Public health authorities and healthcare providers may play an essential role shaping these perceptions: 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 facilitating access.

To evaluate the impact of voluntary prevention on the epidemic dynamics, in the context where efficient treatment exists, it is thus essential to account for individuals' resolution of the prevention versus treatment dilemma. Here, we focus on the role of decision-making by individuals facing epidemic threat in a context where efficient preventive and therapeutic methods are available, from the epidemiological and mathematical modeling perspective.

1.3 Mathematical and behavioral epidemiology

Mathematical modeling of infectious diseases was used to assist public health decision-making for the first time in 1760[2], when Daniel Bernoulli (1700–1782) studied the smallpox epidemic and recommended universal variolation to alleviate smallpox-related mortality: "...it has been noticed that, on the 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" (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 analyzing surveillance data on 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 (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 mathematical models have been developed to describe epidemic dynamics (Brauer, 2017). Models can be useful to understand the transmission mechanisms behind surveillance data, to estimate the values of disease parameters that cannot be directly 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 arising from the need to include, explicitly, the behavioral changes of individuals facing epidemics. Epidemic dynamics are coupled to behavioral dynamics, which are determined, for instance, by the individuals' attitudes towards preventive and therapeutic tools and/or compliance to public health policies. Behavioral epidemiology thus studies the interplay between human behavior and the course of an epidemic, by considering human behavior as a key component of both epidemic

[2]The paper was first presented at the Royal Academy of Sciences in Paris in 1760 and then published in 1766 (Bernoulli, 1766).

spread and the implementation of public health policies (Bauch et al., 2013).

The early scientific production in the field may be found in a systematic review by Funk et al. (2010) and an overview of the growth of behavioral epidemiology by Bauch et al. (2013). Later work can be found in an article review on behavioral change models during the period 2010–2015 by Verelst et al. (2016). In addition, a review by Wang et al. (2016) focusing on mathematical epidemiology of vaccination includes a large section on behavioral models, and a review by Wang et al. (2015) presents models of epidemic spread through contact networks accounting for changes in the individual behaviors.

From the modeling perspective, the issue of voluntary prevention and its impact on epidemics 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 models[3] and individual-based models (which allow to consider stochasticity and high heterogeneity between individuals). 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 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 information about the epidemic and the change in behavior has been modeled, for instance, as a threshold that triggers the prevention adoption, as a dynamic parameter which affects and is affected by prevention adoption or as a transfer between compartments explicitly representing the awareness level of the individual (Verelst et al., 2016). Other models based in networked

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

populations have used multiple layers to couple the epidemic-spreading network to a 'virtual' information-spreading network (Wang et al., 2016). Some models have used the risk of infection perceived by individuals to explicitly address the prevention versus treatment dilemma (see section 1.3.3). Only a few hybrid models have been calibrated using available data (Verelst et al., 2016).

1.3.1 Modeling infectious disease transmission using deterministic compartmental models

Deterministic compartmental models have been widely used to model disease progression and transmission among large populations since 1900 (Brauer, 2017). These models can be expressed as a system of ordinary differential equations (ODE), whose state variables represent the number or proportion of individuals in each compartment, and whose parameters relate to the rates of transition from one compartment to another (Hethcote, 2000); for instance, from susceptible to infected, then to infectious or contagious, to recovered, susceptible again, or dead, and so on. The transition of individuals from being susceptible to being infected, is often modeled by the the rate of infection, also called *force of infection*. The force of infection may be defined by a constant rate or by a function, depending explicitly 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, 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 compartmental model accounting for prevention adoption. Susceptible individuals (S) can get infected (I) and then recover (R), or die at any time. A compartment for the proportion of susceptible individuals who adopt prevention (P) is added to the model; the classical SIR thus becomes an $PSIR$ model. An imperfect preventive method is modeled, for instance, by individuals getting infected despite using prevention and by waining protection (useful for modeling waning immunity in vaccination models) [4].

[4] On the contrary, in the case where perfect prevention is considered, individuals using prevention are immune to the disease and thus directly removed from the population — to the R compartment.

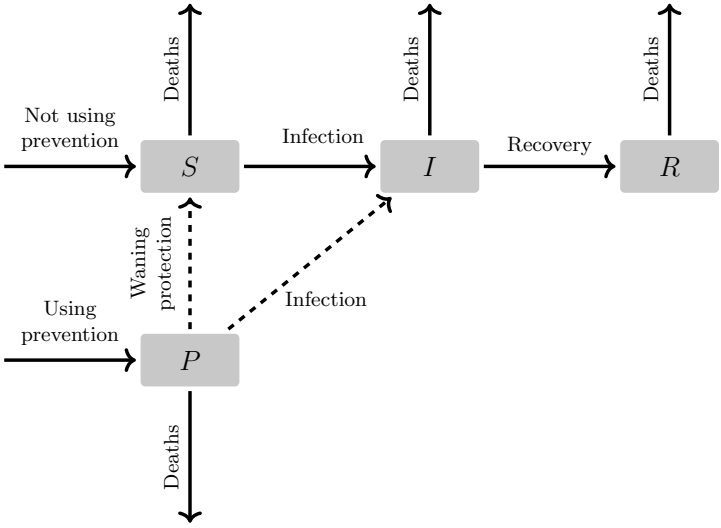

Figure 1.1 – Conceptual compartmental model including a prevention intervention

Flow diagram of a classical *SIR*-type compartmental model accounting for prevention adoption. The model describes the transmission of an infectious agent and disease progression, within a population by modeling individuals' transitions through different states, during their lifetime. Individuals may use prevention (P) against the infectious disease or not. Susceptible (S) individuals get infected (I) and then recover (R). An imperfect preventive method is modeled, for instance, by individuals getting infected despite using prevention, and/or by waning the protection offered by the preventive method with time (dashed arrows).

More complex compartmental models can include population stratification by disease progression (e.g., acute infection, chronic or asymptomatic period), 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.; see 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).

The basic and the effective reproduction numbers reflect epidemic severity, and thus are useful to study the impact of preventive methods on epidemic dynamics: a large basic reproduction number may be interpreted as a fast epidemic spread among the susceptible population exposed to the infectious disease; a decrease in the effective reproduction number reflects epidemic mitigation.

The basic and the effective reproduction numbers can be estimated from mathematical models (Ridenhour et al., 2018). In particular, they can be computed from deterministic compartmental models, and thus be expressed as functions of the ODE system parameters (Heffernan et al., 2005). 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, 2008). ODE systems defining classical deterministic compartmental models for disease transmission, similar to the model depicted in fig. 1.1, often 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). The reproduction number is a threshold parameter for the ODE system equilibria: there is a transcritical bifurcation (that is, an exchange in the stability between the equilibria) for the ODE system when the reproduction number equals to 1. When the reproduction number is lower 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)[5]. See fig. 1.2 for a conceptual visualization of the transcritical bifurcation.

Using the reproduction numbers to determine the herd immunity threshold

Prevention-induced *herd* or *community immunity* refers to the situation in which susceptible individuals are indirectly protected against infection, due to a sufficiently large prevention coverage (i.e., the proportion of the population adopting the preventive method against the pathogen) (Porta, 2013). As a result, disease transmission is greatly reduced and the population is said

[5]Other bifurcations may arise, depending on the assumptions made in the compartmental models. For instance, backward bifurcations may be found in SIS models where contact rates are non-constant Van Den Driessche and Watmough (2000), and Hopf bifurcations may be found in SIR models considering time delays for vaccination (Bhattacharyya and Bauch, 2010), delay in the immunity offered by vaccination (Khan and Greenhalgh, 1999), or limited resources for treatment (Wang and Ruan, 2004).

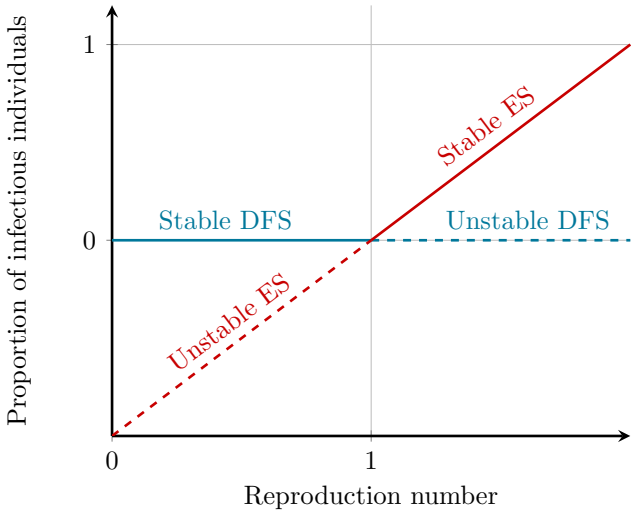

Figure 1.2 – Conceptual diagram of a bifurcation in the ODE system
Classical systems of ordinary differential equations (ODE) describing disease transmission usually have two equilibria: the disease-free state (DFS, depicted in blue), where there are no new infections, and the endemic state (ES, depicted in red), where the epidemic persists. A change in the 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 corresponding to the solutions of the ODE system, have no biological interpretation.

to be immune as a group; the epidemic is expected to be eliminated in the long run (i.e., the DFS is reached); see Fine et al. (2011). From the modeling perspective, the prevention coverage required for the community to reach herd immunity may be obtained by identifying the prevention coverage yielding an effective reproduction number[6] lower than 1. The larger the basic reproduction number, the larger the prevention coverage required to eliminate the epidemic.

Public health authorities usually set the target for prevention interventions depending on the prevention coverage threshold that results in herd immunity. However, as discussed in section 1.2, different public sentiments and strategies towards the prevention versus treatment dilemma may yield a sub-optimal prevention coverage (i.e., lower than the prevention coverage threshold), despite public health recommendations. Hence, to know whether the level of prevention coverage required for herd immunity can be reached voluntarily is key for the implementation of public health interventions.

[6]The effective reproduction number depends (implicitly or explicitly, depending on the modeling choices) on the prevention coverage.

1.3.3 Modeling the decision-making about prevention adoption using a game-theoretical approach

Among the epidemiological models accounting for behavioral change, game-theoretic approaches have been used to address the individual's decision-making through the study of the prevention versus treatment dilemma; see an early example in Bauch et al. (2013), the two previously mentioned reviews about behavioral epidemiology (Verelst et al., 2016; Wang et al., 2016) and a recent review, concerning specifically game-theoretic models by Chang et al. (2020). Game theory is a mathematical framework that allows to model rational decision-making and individual's 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). Game theory postulates that the rational resolution of the prevention versus treatment dilemma can be mathematically modeled by maximizing the individual's expected *utility*.

Utility thus becomes a fundamental tool for modeling decision-making. In the framework of infectious disease prevention, individuals assess their risk of getting infected, and the expected utility for adopting or not prevention. Since the resolution of the dilemma of prevention versus treatment is considered to be rather costly for an uninfected individual, the individuals' expected utility may be established from the perspective of the total *cost*: maximizing the expected utility is equivalent to minimizing the total expected cost. The total expected cost balances the individual's perception of the cost for adopting the strategy of using prevention versus that of adopting the strategy of being treated in the case of infection. A simplified definition of the total expected cost takes the following form:

$$\text{Total cost} = \begin{pmatrix} \text{Probability of} \\ \text{using prevention} \end{pmatrix} \times \begin{pmatrix} \text{Cost of} \\ \text{prevention} \end{pmatrix} + \begin{pmatrix} \text{Probability of} \\ \text{getting infected} \end{pmatrix} \times \begin{pmatrix} \text{Cost of infection} \\ \text{and treatment} \end{pmatrix}.$$

Identifying the probability of using prevention that minimizes the total cost yields the voluntary prevention coverage.

Modeling studies using a game-theoretic approach for the individual decision-making have

typically used deterministic compartmental models to describe the epidemic dynamics at the population level (Bauch et al., 2003; Bauch and Earn, 2004; Breban et al., 2007; D'Onofrio et al., 2007; Vardavas et al., 2007; Galvani et al., 2007; Breban, 2011; Liu et al., 2012). Applications of compartmental models include vaccination facing a biological attack (Bauch et al., 2003), voluntary 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 influenza (Breban et al., 2007; Galvani et al., 2007), among others. 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., 2007; 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, including recurrent decision-making (Breban et al., 2007).

Most of the above-mentioned 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., 2007; Galvani et al., 2007; Breban, 2011), unless incentives are offered (Vardavas et al., 2007; Liu et al., 2012) and thus, prevention programs may fail to achieve disease elimination. However, as discussed in section 1.1, 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 and discussed.

1.4 General objectives of this 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 voluntary prevention could eliminate epidemics.

Two applications were explored. The first part of my doctoral research focuses on voluntary vaccination against treatable childhood infectious diseases; see chapter 2. The project was designed for analytical understanding of the results. We intended to apply our methods and findings to the epidemiology of an infectious disease preventable by vaccination allowing to assess epidemic elimination; we thus discussed our results in the context of the measles epidemiology. The second part of my thesis focuses on the voluntary use of pre-exposure prophylaxis (PrEP) by men who have sex with men (MSM) 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. A more complex model for HIV transmission was built and the model was studied using numerical methods.

1.5 General description of our methods

1.5.1 Conceptual framework

We study the interplay between individual behavior and infectious diseases' epidemic dynamics, in the context where effective treatment and imperfect preventive methods are available. We consider the adoption of prevention to be voluntary (that is, not a product of mandatory health policies), whereas treatment is assumed to be immediately adopted after disease diagnosis. That is, we do not study the individual's decision-making regarding the adoption of treatment.

Three assumptions are key to this research project:

i) **Individuals' decision maximizes their own benefit.** We assume that individuals are rational, in the sense that they do not act randomly, but rather choose a strategy after assessing their personal situation. In particular, we assume that individuals' decision-making is driven by weighing the perceived pros and cons of prevention versus treatment, as well as their perception of the risk of infection, and choose the strategy that benefits them the most from, in the long run.

ii) **The costs perceived by individuals concern monetary and/or non-monetary**

factors. We assume that individuals' decision-making is driven by the weighing of the perceived 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.

iii) **Voluntary prevention coverage may differ from the estimated coverage for epidemic control, recommended by public health authorities.** Since the the risk of infection and the prevention-related barriers perceived by individuals may be biased, the prevention coverage recommended by public health authorities, and allowing herd immunity to be reached, may not be achieved. In addition, these perceptions may be susceptible to external factors; for instance, available information and rumors may shape the individuals' attitudes towards the available preventive and therapeutic tools.

1.5.2 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 population level and one for the decision-making on whether or not to use prevention, at the individual level. We assume that, when facing an ongoing epidemic, individuals address the dilemma of prevention versus treatment 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 epidemic dynamics, 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; see fig. 1.3 for an illustration of our hybrid model.

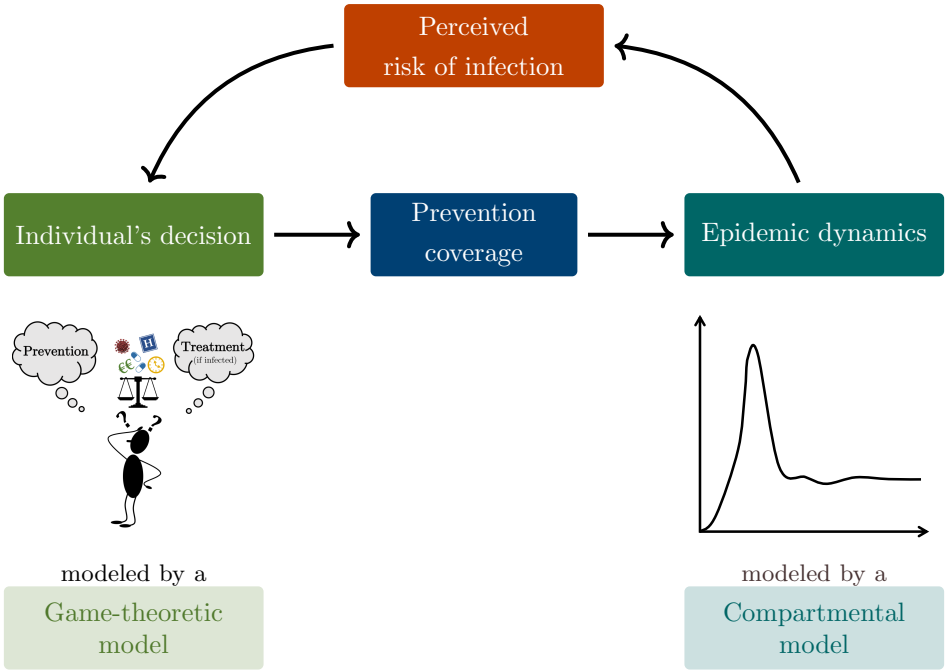

Figure 1.3 – Diagram of our hybrid model
When facing an ongoing epidemic, individuals address the prevention versus treatment dilemma by evaluating the benefits and constraints of both preventive and therapeutic tools, as well as evaluating the risk of getting infected. The risk of infection perceived by individuals depends on the epidemic dynamics, 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. We consider additional compartments representing individuals adopting prevention. As stated above, we do not consider that prevention is 100% effective and thus, individuals adopting prevention can nevertheless get 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 system[7], we observe the behavior of the epidemic in the long run, which is used for the decision-making component of the model (see below).

We compute the effective reproduction number from the ODE system, following the methods developed by van den Driessche and Watmough (2002) and express it as a function of the prevention parameters (namely, the prevention coverage and effectiveness). As mentioned in section 1.3.2, we use the effective reproduction number 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— remains below 1. In the case where the effective reproduction decreases with prevention adoption[8], we say that the epidemic is mitigated or *controlled* by the preventive method, since a reduction in 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 epidemic elimination or epidemic persistence occur, in the long run. 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 and under what conditions this theoretical threshold for epidemic elimination could be reached voluntarily. In addition, we use the effective reproduction number resulting from voluntary prevention coverage to identify a threshold for epidemic control, by finding the conditions under which individuals are motivated to adopt prevention.

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 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,

[7]The 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.

[8]In the case of infectious diseases where no other preventive method is available, epidemic control induced by prevention may be characterized by the effective reproduction number being lower than the basic reproduction number.

these factors define the perceived costs. The relative cost of prevention versus treatment thus remains a rather qualitative parameter that indicates how much more beneficial prevention is perceived over treatment.

We formally define the total expected utility as a function of the endemic risk of infection and the *relative cost of prevention versus treatment*, perceived by individuals. We further assume that individuals may acknowledge their true risk of infection (through official estimations of the epidemiological indicators obtained, for instance, from the transmission model, and could be communicated to the public by health authorities, healthcare providers, scientific journalists, associations, etc.), but may also make their decision based on misperception of their risk of infection (based in personal experience, rumors, peer pressure, etc.).

Model's main outcomes

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. Hence, we obtain the *voluntary prevention coverage*, the prevention coverage reached voluntarily by the individuals who perceive themselves 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 reduction in the effective reproduction number.

Chapter 2

Voluntary vaccination against treatable childhood infectious diseases

2.1 Introduction

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 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 (Hamborsky et al., 2015)[1].

Some of these infectious diseases have reached — or been close to reach — elimination status,

[1]See (Ministère des Solidarités et de la Santé, 2019) for the vaccination schedule recommended in France.

at least regionally, owing 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). Immunization programs reduced the number of polio cases by 99% since 1988, worldwide. Polio was declared eliminated from the Americas in 1994, from the Western Pacific region in 2000 and from the European region in 2002. In 2019, polio remained endemic in only 3 countries (WHO, 2019c). 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 remarkable reduction of disease cases inspired the worldwide priority goal to eliminate rubella and measles by 2020 (Andrus et al., 2011; WHO, 2012), which remains yet to be achieved.

As discussed in chapter 1, epidemic control and elimination require safe, highly-effective vaccines, as well as high levels of vaccine coverage. However, despite the vast evidence of vaccine-induced reduction in the number of infections and the public health authorities' recommendations about vaccination, parents still hesitate to vaccinate their children (Larson et al., 2016). Therefore, in many settings, the coverage of vaccines against childhood infectious diseases remains suboptimal (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 (Hamborsky et al., 2015)	95%[a] (Hamborsky et al., 2015)	80%–85% (Anderson and May, 1990)	85%[d] (2019) (WHO, 2020c)
Measles	8–18 (Anderson and May, 1991)	1963 (Hamborsky et al., 2015)	>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] (Hamborsky et al., 2015)	80%–85% (Anderson and May, 1990)	86%[c] (2019) (WHO, 2020c)
Rubella	6–16 6(Anderson and May, 1991)	1969 (Hamborsky et al., 2015)	∼100% (Plotkin et al., 2012)	85%–87% (Anderson and May, 1990)	71% (2019) (WHO, 2020c)
Smallpox	3–10 (Plotkin et al., 2012)	1796 (WHO, 2016b)	95% (CDC, 2015)	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.

[a] After four spaced doses between 2 and 18 months old.

[b] After two shortly separated doses.

[c] After three doses of inactivated poliovirus vaccine.

[d] Corresponding 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

The WHO (2014) defines vaccine hesitancy as the "delay in acceptance or refusal of vaccines despite availability of vaccine services". In 2019, vaccine hesitancy was listed among the ten threats to global health by the 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).

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). Seven of the ten least confident countries were identified in the European region. Among the 67 countries included in the survey, France was identified as the country having the lowest confidence in vaccine safety: 45.2% of French respondents reported mistrust in vaccine safety (of note, the global average was 13%) (Larson et al., 2016); see fig. 2.1.

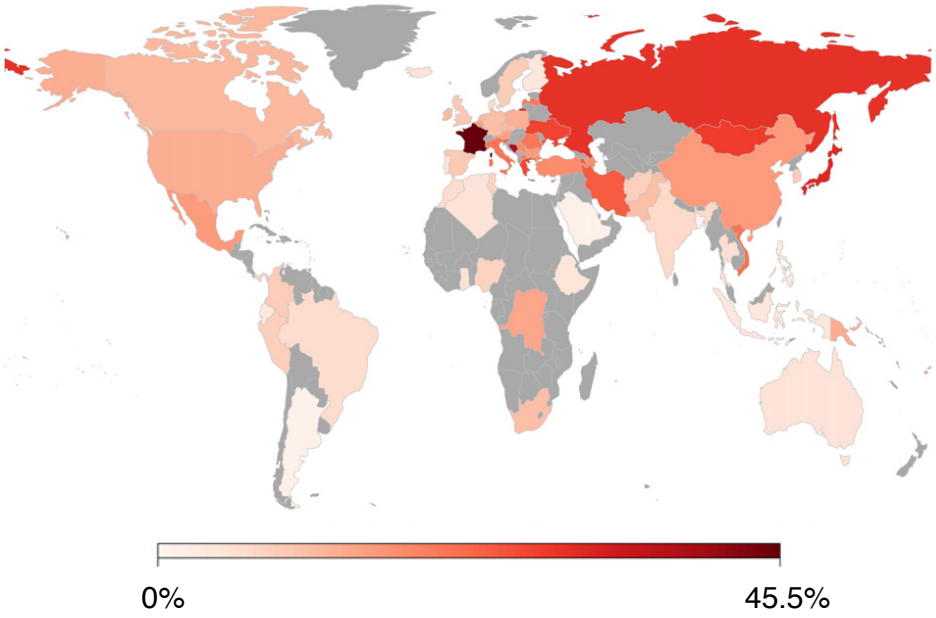

Figure 2.1 – Immunization mistrust, worlwide
World map of the proportion of negative responses ("tend to disagree" or "strongly agree") to the survey the statement "Overall I think vaccines are safe". Figure extracted from (Larson et al., 2016).

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 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 immunization programs for the 2030 SDG (WHO, 2019).

2.1.3 The measles epidemic: its place on the path towards elimination

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 (Gastanaduy et al., 2015; Strebel et al., 2013), 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 and recovery, individuals acquire lifelong immunity. Newborns may by passively immunized through maternal antibodies, which protect them during the first 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).

Treatments for measles do not cure the disease, but may help reduce 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).

The first vaccine against measles[2], 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 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, 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 age of 4 to 6, before entering school. Studies have found that a high proportion of the individuals who did not have 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). Two-dose MMR vaccination has shown to offer long-term protection against severe cases, even in the case of vaccine failure (Bonneton et al., 2020).

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% of the 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).

Measles epidemiology

Before the introduction of the measles vaccines, virtually everybody got infected, mostly before the age of 10 (Strebel et al., 2013). The effective reproduction number for measles has been estimated to be as high as 18 (Anderson, 1992), but estimations may vary by context and estimation method (Guerra et al., 2017). Around 2.6 million deaths were attributed to measles each year, worldwide (WHO, 2019b). The proportion of the population that needs to be vaccinated in order to reach herd immunity has been estimated at 92% to 95% (Strebel et al., 2013).

[2]Called the *Edmonston B* vaccine.

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 to eradicate measles from the Pan American region by 2010 (CDC, 1997). Intensive two-dose vaccination campaigns lead to 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-dose program was reenforced 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 where attributed to virus reintroduction and failure in implementing the recommendations on vaccination strategies (CDC, 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 reemerged in many countries, worldwide, including high-income countries, mostly due to a decrease in MCV 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). 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, 2020b); see fig. 2.2 for a visualization of the measles epidemiology and MMR vaccine coverage in France, during the last decade. The French coverage of MMR vaccination remained below the recommended thresholds, which provoked the reemergence of measles outbreaks in France.

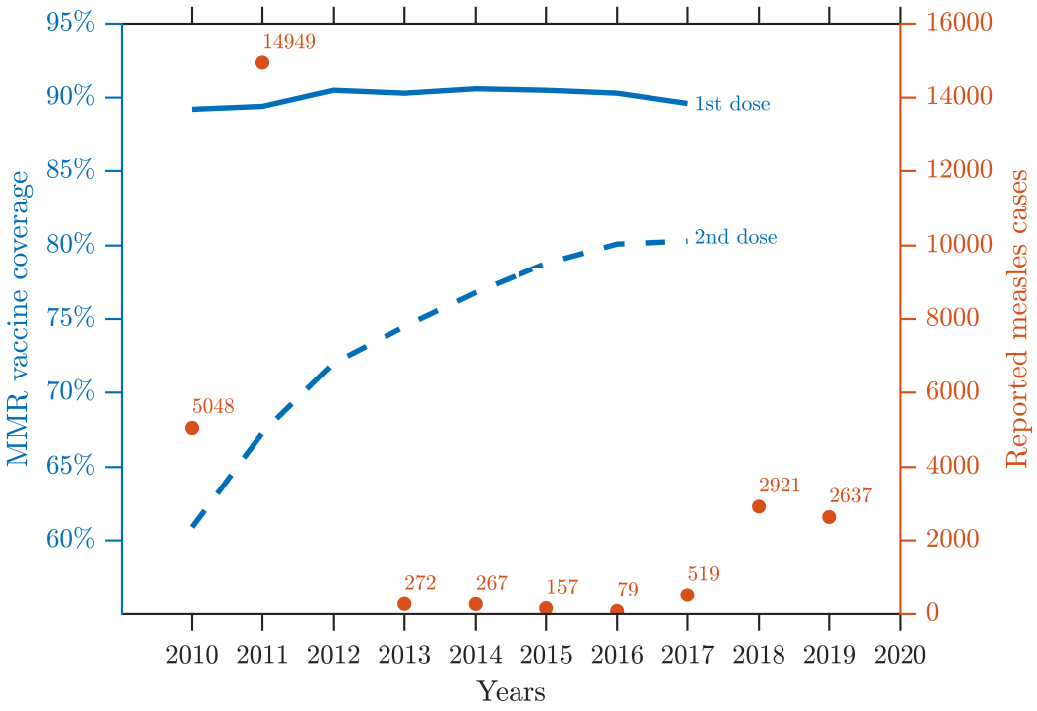

Figure 2.2 – MMR vaccine coverage and measles cases in France
In blue, the coverage for the first (solid line) and the second recommended doses (dashed line) of MMR vaccine, among 2-year-old children, for the period 2010–2017 (Santé Publique France, 2019a). In red, the reported cases of measles in France, for the period 2010–2019 (WHO, 2020b); 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 make epidemic elimination impossible. Indeed, large outbreaks occurred during the period 2010–2011, and again from 2018 onward (WHO, 2020b).

Measles epidemics have thus been shown to be on a path towards epidemic elimination (Graham et al., 2019), at least in some regions and at a given time, but levels of vaccine coverage failing to reach the herd immunity threshold keep yielding measles outbreaks around the world, including high-income settings.

2.1.4 Game-theoretic models for childhood vaccination

Game-theoretic models of vaccination with a focus in childhood infectious diseases such as measles have yielded that epidemics may not be averted through voluntary prevention (Bauch et al., 2003; Bauch and Earn, 2004; Manfredi et al., 2009; Shim et al., 2012b). Game-theoretic approaches have also been used to study the dynamics of voluntary vaccination uptake in the context of vaccine hesitancy (Bauch and Bhattacharyya, 2012). In addition, hybrid models considering imperfect vaccines have shown that the proportion of the effectively vaccinated population increases with vaccine effectiveness (Wu et al., 2011).

The objective of the first part of my PhD was to reassess the issue of epidemic elimination of a treatable childhood infectious disease epidemics, such as measles, through the voluntary adoption of imperfect vaccination.

2.2 Publication

A scientific article titled "Prevention of treatable infectious diseases: a game-theoretic approach" (Jijón et al., 2017) was published in the journal *Vaccine*.

2.2.1 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 bringing game theory to 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. 2.5 of section 2.3. We present in detail the methods used to compute the voluntary vaccination coverage and 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.

2.2.2 Results statements

Combining the decision-making model with the classical disease-transmission model leads to 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 becomes the parameter to be tuned to increase the vaccination coverage.

We found the necessary and sufficient conditions (namely, in terms of vaccine efficacy and the perceived relative cost of vaccination versus treatment) for the voluntary vaccination coverage to reach the herd immunity threshold. Unlike previous studies[3], our findings suggest that voluntary-vaccination programs can successfully avert epidemics, even for imperfect vaccines, provided that vaccines are highly efficient[4], the vaccine-induced immunity is long-lasting (see below) and they are delivered at low perceived cost. However, epidemic elimination may only be temporary (cf. fig. 2.6 in section 2.3) and active efforts from public health authorities are needed to maintain the perceived cost of vaccination low.

In addition, and for the first time to our knowledge, 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 treatment, in the context where epidemics are 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.

Application to measles

We applied our methods to the epidemiology of measles. Our findings are in consistent agreement with regional measles elimination, which 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, the elimination status is unstable and vaccination may be perceived as more costly by individuals in the current context, given that measles disease and its sequelae have been witnessed less. Indeed, a decrease in vaccine coverage has been recently observed in several high-

[3] See Bauch et al. (2003); Bauch and Earn (2004); Manfredi et al. (2009); Shim et al. (2012b).

[4] Our results are in agreement with those of Wu et al. (2011), in that the proportion of effective vaccinated population increases with vaccine efficacy.

income countries and measles outbreaks have occurred as a result. Further reducing the perceived cost of vaccination perceived by individuals may help fighting vaccine hesitancy and thus 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.

2.2.3 Article

The article in its published form is attached from the next page.

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Prevention of treatable infectious diseases: A game-theoretic approach

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ABSTRACT

We model outcomes of voluntary prevention using an imperfect vaccine, which confers protection only to a fraction of vaccinees for a limited duration. Our mathematical model combines a single-player game for the individual-level decision to get vaccinated, and a compartmental model for the epidemic dynamics. Mathematical analysis yields a characterization for the effective vaccination coverage, as a function of the relative cost of prevention versus treatment; note that cost may involve monetary as well as non-monetary aspects. Three behaviors are possible. First, the relative cost may be too high, so individuals do not get vaccinated. Second, the relative cost may be moderate, such that some individuals get vaccinated and voluntary vaccination alleviates the epidemic. In this case, the vaccination coverage grows steadily with decreasing relative cost of vaccination versus treatment. Unlike previous studies, we find a third case where relative cost is sufficiently low so epidemics may be averted through the use of prevention, even for an imperfect vaccine. However, we also found that disease elimination is only temporary—as no equilibrium exists for the individual strategy in this third case—and, with increasing perceived cost of vaccination versus treatment, the situation may be reversed toward the epidemic edge, where the effective reproductive number is 1. Thus, maintaining relative cost sufficiently low will be the main challenge to maintain disease elimination. Furthermore, our model offers insight on vaccine parameters, which are otherwise difficult to estimate. We apply our findings to the epidemiology of measles.

1. Introduction

The 20th century has witnessed tremendous achievements in infectious disease prevention, especially with the development of effective preventive vaccines [1], often far less costly than treatment [2]. Still, the preference between prevention and treatment remains a dilemma. Some studies found no preference [3–5], others a preference for prevention [6,7], or a preference for treatment [8,9], or that preference for prevention versus treatment depends on the circumstances [10,11].

The prevention of treatable infectious diseases still poses challenges for public health authorities [12]. Faced with infection risk, individuals may decide to use prevention, or else get treated if they acquired infection. Whereas treatment is generally well accepted by infected individuals, prevention may have a wide range of acceptability profiles for the susceptible. Individual-level perceptions of risk, as well as weighing pros and cons of prevention versus treatment, may differ from the recommendations of the public health authority [13], for a variety of reasons [14,15].

The decision to use voluntary vaccination and its impact on disease transmission has been theoretically studied using mathematical models with two components: one describing the population-level epidemiology and another describing the strategy by which an individual makes his choice of whether or not to get vaccinated [16–39]. Both compartmental models [16–18,28,33–39] and social networks [19–22] have been used as the population-level model component. For the individual-level component, imitation dynamics [22,23,39], "wait and see" strategies [38], social distancing strategies [24,25], maximization of the utility of prevention [16,26–31] and inductive reasoning [33–36] have been studied. The role of altruism for the individual-level strategy has also been considered [32]. Several modeling studies discuss the impact of public misperceptions about vaccination programs on vaccination uptake [16,23,27,28,22].

The main research direction of the modeling work has been individual and group behavior in the dilemma of whether or not to get vaccinated [16–20,22–32,37–39]. Another direction has been vaccination subsidies and incentives [21,33–36]. A review of recent literature can be found in Ref. [40].

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The purpose of the current work is to assess the performance of a voluntary prevention program, utilizing an imperfect vaccine, which confers protection only to a fraction of vaccinees for a limited duration. We show that voluntary vaccination with an imperfect vaccine may temporarily eliminate epidemics. We apply our findings to the measles epidemiology.

2. Model

We propose a mathematical model describing the interplay between voluntary vaccination and treatment during the course of an epidemic. In particular, our model addresses the setup where vaccination is available as a prevention method against childhood infectious diseases. However, we assume that the vaccine is imperfect [41,42]. We consider two aspects of vaccine failure and introduce appropriate parameters. First, the vaccine may not take for all vaccinees; the fraction of vaccinees for which the vaccine yields an immune response is called *vaccine efficacy*. This has been largely used to model voluntary vaccination [27–29,32,38,39]. In this case, the key epidemiological concept is the *effective vaccination coverage* [43,44], the fraction of the population that acquires immunity due to vaccination. Second, even if the vaccinee acquires an immune response, this may not result in lifelong immunity. That is, the vaccinee acquires a limited *duration of immunity*, a feature much less studied in the modeling of voluntary vaccination [20].

We describe epidemic dynamics using an *SEIR*-type system of ordinary differential equations. Recovery may be reached naturally or through treatment, which may be either symptomatic or therapeutic. Furthermore, we involve an individual-level model of decision-making about whether or not to get vaccinated. We assume that individuals make their decisions by judging pros and cons for vaccination versus treatment, and have a sense of the imminence of getting infected and then treated. According to game theory, such a decision-making process may be modeled as a *non-cooperative game*, where individuals act in their own interest to maximize the utility of vaccination versus treatment. However, an individual's decision is indirectly influenced by those of others: the sum of all individuals' decisions determines the proportion of the population that gets vaccinated, which, in turn, affects the epidemic progression and the probability of acquiring infection. The game model is intertwined with the model of epidemic dynamics. Model analyses assume that the resolution of the dilemma of vaccination versus treatment yields stable disease epidemiology.

2.1. The compartmental model

We make further assumptions for our deterministic *SEIR*-type model. The vaccination program is constantly in place, regardless of whether or not there is an epidemic. Treatment is available in unlimited supply, and no decision-making is involved about when to start treatment. Complete recovery is possible, with the benefit of lifelong immunity. These assumptions lead to the following ordinary differential equations of *SEIR* type:

$$\begin{aligned}
\tfrac{dV}{dt} &= \epsilon p\,\pi - (\rho+\mu)V,\\
\tfrac{dS}{dt} &= (1-\epsilon p)\,\pi + \rho V - \tfrac{\beta I}{N} S - \mu S,\\
\tfrac{dE}{dt} &= \tfrac{\beta I}{N} S - (\nu+\mu)E,\\
\tfrac{dI}{dt} &= \nu E - (\sigma+\gamma+\mu)I,\\
\tfrac{dR}{dt} &= (1-\xi)\,\sigma I + \gamma I - \mu R,\\
\tfrac{dT}{dt} &= \xi\,\sigma I - \mu T.
\end{aligned} \tag{1}$$

Newborns can remain susceptible (S) or acquire vaccine-induced immunity (V), in which case they may become susceptible thereafter, as vaccine-induced immunity wanes. Recently infected individuals (E) pass through a latent stage of infection. Then, they become infectious (I) and can recover either naturally (R) or through treatment (T). The total population size is given by $N = V + S + E + I + R + T$.

The probability of getting vaccinated is denoted by p and the vaccine parameters are ϵ, the vaccine efficacy, and ρ, the rate of waning of vaccine-induced immunity. The parameter π stands for the inflow of newborns, μ is the disease-unrelated death rate, β stands for the disease transmissibility, ν for the progression through the latency stage, σ is the rate at which individuals start treatment, ξ represents the treatment efficacy and γ is the natural recovery rate. All variables and parameters are positively defined.

The model has two equilibria: a disease-free state (DFS) where

$$V_{\mathrm{DFS}} = \frac{\epsilon p \pi}{\rho+\mu}, \quad S_{\mathrm{DFS}} = \frac{\rho \epsilon p \pi}{\mu(\rho+\mu)} + \frac{(1-\epsilon p)\pi}{\mu}, \tag{2}$$

and $E_{\mathrm{DFS}} = I_{\mathrm{DFS}} = R_{\mathrm{DFS}} = T_{\mathrm{DFS}} = 0$, and an endemic state (ES) where all the equilibrium components are non-zero

$$\begin{aligned}
&V_{\mathrm{ES}} = \frac{\epsilon p \pi}{\rho+\mu}, \quad S_{\mathrm{ES}} = \frac{\pi}{\mu R_0}, \quad I_{\mathrm{ES}} = \frac{\pi}{\beta}(R^*-1),\\
&E_{\mathrm{ES}} = \frac{\sigma+\gamma+\mu}{\nu} I_{\mathrm{ES}}, \quad R_{\mathrm{ES}} = \frac{(1-\xi)\sigma+\gamma}{\mu} I_{\mathrm{ES}}, \quad T_{\mathrm{ES}} = \frac{\xi\sigma}{\mu} I_{\mathrm{ES}},
\end{aligned} \tag{3}$$

where

$$R^* = \left(1 - \frac{\epsilon p \mu}{\rho+\mu}\right) R_0, \tag{4}$$

and

$$R_0 = \frac{\beta \nu}{(\nu+\mu)(\sigma+\gamma+\mu)}. \tag{5}$$

R^* is called the *effective reproduction number*, representing the expected number of secondary cases produced by a single infectious individual within a disease-naive population. It is important to note that, in a population undergoing disease prevention, R^* depends on the level of disease susceptibility. In our case, R^* is a function of p, the probability of getting vaccinated. The *SEIR*-type model (1) undergoes a transcritical bifurcation [45] at $R^* = 1$. If $R^* > 1$, then ES will be reached; otherwise, $R^* \leqslant 1$ and DFS will be reached. R_0 is the *basic reproduction number* [46,47,45], obtained from the model in the absence of prevention (i.e., $p = 0$). To quantify the impact of vaccination on epidemics, we analyze $R^*(p)$ given that there is an epidemic in absence of vaccination; i.e., $R_0 > 1$.

Using Eqs. (2) and (3), the *endemic prevalence* of the infectious disease can be written as

$$\Pi(p) = \begin{cases} \Pi_{\mathrm{DFS}}(p), & \text{if } R^* \leqslant 1,\\ \Pi_{\mathrm{ES}}(p), & \text{if } R^* > 1; \end{cases} \tag{6}$$

where

$$\Pi_{\mathrm{DFS}}(p) = \frac{I_{\mathrm{DFS}} + E_{\mathrm{DFS}}}{N_{\mathrm{DFS}}} = 0, \tag{7}$$

and

$$\Pi_{\mathrm{ES}}(p) = \frac{I_{\mathrm{ES}} + E_{\mathrm{ES}}}{N_{\mathrm{ES}}} = \frac{\mu}{\beta}\left(1 + \frac{\sigma+\gamma+\mu}{\nu}\right)(R^*(p) - 1). \tag{8}$$

A critical vaccination coverage, p_c, may be defined using $R^*(p_c) = 1$ or, equivalently, $\Pi_{\mathrm{ES}}(p_c) = 0$, and verifies

$$\epsilon p_c = \left(1 + \frac{\rho}{\mu}\right)\left(1 - \frac{1}{R_0}\right). \tag{9}$$

A similar formula is provided in Ref. [41, Eq. (8)]. In the case of a perfect vaccine (i.e., $\rho = 0$ and $\epsilon = 1$), Eq. (9) recovers a well-known result; see Refs. [46, p. 87] and [47, ch. 6].

A diagram of disease prevalence at the equilibria of the *SEIR*-type model (1), as a function of p, is shown in Fig. 1. ES is always

stable (attracting), while DFS is unstable (repelling) for $p < p_c$ and stable for $p > p_c$. It is important to note that, in the general case where the vaccination coverage is a function of time, disease-free dynamics, where $E = I = R = T = 0$, is possible for all values of R_0.

2.2. The single-player game

We assume vaccination to be voluntary. The pros and cons of vaccination versus treatment perceived by a typical individual may be biased and involve monetary and/or non-monetary aspects [15] such as: price, undesired vaccine effects, accessibility of vaccination, vaccination schedule, time spent to get vaccinated, disease morbidity, secondary effects induced by (symptomatic or/and therapeutic) treatment, etc. In game theory, they are generally expressed as *cost*. A *utility function* is employed to make the balance of all the cost with respect to vaccination versus treatment, as described below. Game theory postulates that the individual-level decision of whether or not to get vaccinated maximizes the utility of vaccination. Mathematically, this is expressed by maximizing the utility function. As a result, we obtain the probability that a typical individual gets vaccinated, depending on cost and vaccine and epidemiological parameters. In turn, this yields the voluntary vaccination coverage. Hence, the addition of game theory to the *SEIR*-type model (1) makes explicit that the vaccination coverage is not a parameter of the model that may be easily tuned. Rather, the relative cost of vaccination versus recovery is a more tunable parameter, as we will see below.

We assume that individuals address the matter of vaccination as long as they acknowledge an epidemic threat in the absence of vaccination (i.e., $R_0 > 1$). Otherwise, individuals do not get vaccinated. We also assume that individuals have a sense of the probability of acquiring infection when there is an epidemic threat. We express this probability using the endemic prevalence of the infectious disease, Π, defined by Eqs. (6)–(8).

The balance of cost is as follows. To prevent getting infected under epidemic threat, an individual would pay the cost of vaccination, c_p, with probability p of getting vaccinated, and the cost of recovery, c_r, with probability $(1 - \epsilon p)\Pi(p)$ of getting infected. A similar account of costs may be found in Ref. [23, Eqs. (2.1) and (2.2)]. The utility function of vaccination versus treatment when $R_0 > 1$ becomes:

$$U(p; c_p, c_r) = -p\, c_p - (1 - \epsilon p)\, c_r\, \Pi(p), \tag{10}$$

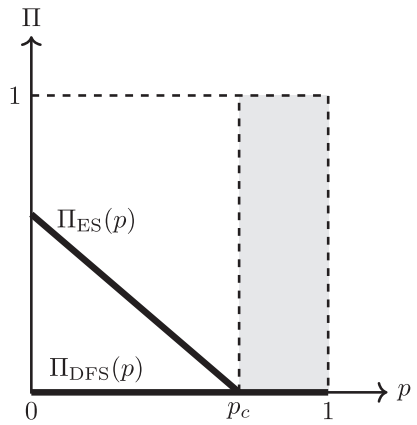

Fig. 1. The endemic prevalence, Π, as a function of the vaccine coverage, p. If $R^* \leqslant 1$ ($p > p_c$), the system reaches the disease-free state (DFS) where $\Pi_{\mathrm{DFS}} = 0$. On the other hand, if $R^* > 1$ ($p < p_c$), the system reaches the endemic state (ES) with endemic prevalence Π_{ES}. We note that DFS still exists for $p < p_c$, but it is unstable.

where c_p and c_r are positive. Introducing the relative cost of vaccination versus recovery $r = c_p/c_r$ and rescaling the utility function $U(p; r)$ by c_r, we obtain

$$U(p; r) = -p\, r - (1 - \epsilon p)\, \Pi(p). \tag{11}$$

3. Results

By maximizing the utility function $U(p; r)$ for the individual player, we obtain an expression of the probability for an individual to get vaccinated as a function of the relative cost of vaccination versus recovery. We denote this probability by $\hat{p}(r)$.

Case 1: $R^* > 1$. The probability $\hat{p}(r)$ is a solution of $\partial U(p; r)/\partial p = 0$ and verifies

$$\epsilon\hat{p}(r) = \begin{cases} \frac{r_b - r}{\tilde{r}}, & \text{if } r_a < r < r_b, \\ 0, & \text{if } r \geqslant r_b, \end{cases} \tag{12}$$

where

$$\tilde{r} = \frac{2\epsilon\mu^2}{(\nu + \mu)(\rho + \mu)}\left(1 + \frac{\nu}{\sigma + \gamma + \mu}\right), \tag{13}$$

and

$$r_b = \tilde{r}\left[1 - \frac{1}{2R_0} + \frac{\rho}{2\mu}\left(1 - \frac{1}{R_0}\right)\right]. \tag{14}$$

The restriction $R^*(\hat{p}) > 1$ yields $r > r_a$, where

$$r_a = \tilde{r}\left[\frac{1}{2R_0} - \frac{\rho}{2\mu}\left(1 - \frac{1}{R_0}\right)\right]. \tag{15}$$

Eqs. (14) and (15) yield $r_a < r_b$ whenever $R_0 > 1$. A threshold for the probability for an individual to be effectively vaccinated is immediately obtained

$$\epsilon\hat{p}(r_a) = \left(1 + \frac{\rho}{\mu}\right)\left(1 - \frac{1}{R_0}\right), \tag{16}$$

retrieving Eq. (9) for p_c.

Case 2: $R^* \leqslant 1$. In this case, $0 \leqslant r \leqslant r_a$ and the endemic prevalence is zero; cf. Eq. (7). Utility reaches the maximum value of zero at $\hat{p}(r) = 0$; cf. Eq. (11). Along with Eq. (4), this implies $R^* = R_0 > 1$ and leads to contradiction. We conclude that the game theoretic assumption of an equilibrium resolution of the vaccination-versus-treatment dilemma is not tenable. There exists no equilibrium coverage for voluntary vaccination once the epidemic has been averted; $\hat{p}(r)$ does not have a stable equilibrium when $R^* \leqslant 1$.

The results on voluntary vaccination coverage are summarized in Fig. 2. Given the vaccine efficacy, ϵ, the domain of the function $\epsilon\hat{p}(r)$, representing the probability of *effective* vaccination, is divided into three regions. Region (c) corresponds to $r \geqslant r_b$, where individuals find the relative cost of vaccination versus treatment too high and do not get vaccinated; i.e., $R^* = R_0 > 1$. Region (b) corresponds to $r_a < r < r_b$, where some individuals adopt prevention and the epidemic is alleviated; i.e., $R_0 > R^* > 1$. Region (a) corresponds to $0 \leqslant r \leqslant r_a$ and $R^* \leqslant 1$. Individuals will get vaccinated in sufficient numbers to avert the epidemic, as long as they have the motivation to do so. However, according to our model, a long-term motivation based on disease prevalence does not exist.

This situation may be reversed if an incentive is used and individuals perceive a net gain from being vaccinated (i.e., r is allowed to take negative values) when $R^* \leqslant 1$. Straightforward calculations show that, in this case, $\hat{p}(r) = 1$ maximizes the utility of vaccination, independently of the perceived gain.

Fig. 1, intended for the SEIR-type model (1), remains illustrative for the two-component model using game theory, as well. Just as before, ES exists for the region $0 \leqslant p < \hat{p}(r_a) = p_c$ (i.e., $R^* > 1$) and

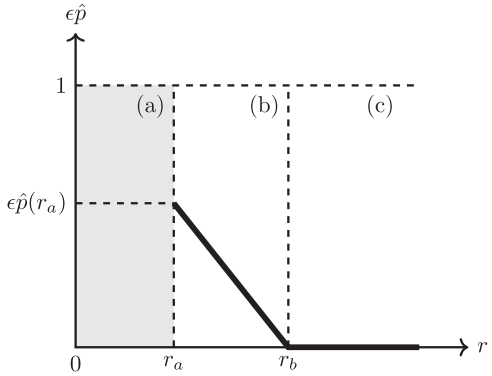

Fig. 2. The probability that individuals get effectively vaccinated, $\epsilon\hat{p}(\epsilon, r)$, as a function of the relative cost of vaccination versus treatment, r. The domain is divided into three regions. In region (c), individuals do not get vaccinated due to the high cost of vaccination versus treatment. Region (b) corresponds to the case where lower cost encourages some individuals to adopt vaccination and, as a result, the epidemic is alleviated. For region (a), the relative cost is significantly reduced. However, the interplay between vaccination and treatment there does not lead to steady disease epidemiology.

is stable. However, DFS exists only for $p = 0$ and is unstable, as we assumed $R_0 > 1$.

The equilibrium structures uncovered in Figs. 1 and 2 invite to a discussion about vaccine parameters. From the point of view of public health, the first and key desideratum is the ability to prevent epidemics; i.e., $p_c \leqslant 1$. This yields (cf. Eq. (9))

$$\frac{\epsilon}{1+\rho/\mu} \geqslant 1 - \frac{1}{R_0}, \tag{17}$$

and guarantees the existence of region (a) in Fig. 2, where epidemics may be temporarily prevented. From Eq. (15), we obtain that $r_a > 0$ if and only if

$$\frac{R_0 - 1}{\mu} < \frac{1}{\rho}. \tag{18}$$

That is, region (a) exists if and only if the duration of vaccine-induced immunity, $1/\rho$, is larger than $(R_0 - 1)$ expected lifetimes, $1/\mu$.

The second desideratum is that region (a) be as large as possible in terms of the relative cost of vaccination versus treatment, to leave room for ample variation in cost. It can be shown that

$$0 \leqslant r_a \leqslant \frac{\mu}{R_0(\mu+\nu)}\left(1 + \frac{\nu}{\sigma+\gamma+\mu}\right). \tag{19}$$

Furthermore, we have $\partial r_a/\partial\epsilon > 0$ and $\partial r_a/\partial\rho^{-1} > 0$; i.e., r_a increases with improving the efficacy and induced duration of immunity of the imperfect vaccine.

3.1. Application to measles

Measles is a very contagious infectious disease, for which only symptomatic treatment and treatment to improve disease outcomes (e.g., vitamin A) are available [48–50]. Recovery from infection is believed to lead to lifelong immunity [50]. However, measles can be prevented through vaccination, which induces long-term protection [51,52]. Before the vaccine was developed, infection with measles virus was nearly universal during childhood [50]. The average number of secondary infections generated by index cases in fully susceptible populations was estimated at $R_0 = 5$–18 [46, p. 70] or 12.5–18 [42].

Mass vaccination campaigns ran in many countries once the vaccine was licensed in the 60's, and were continued by national programs for the vaccination of children. Measles vaccine schedules varied across time and countries [51]. Initially, the recommendation was to administer one dose at 8–9 months of age. Then, the recommended age for vaccination was raised to 12–15 months in some countries, mainly high-income countries, to overcome the inhibitory effect of maternal antibodies on vaccine efficacy [51]. Among children initially vaccinated after 12 months of age, vaccine efficacy is at least 95%, while it can be lower for children vaccinated before 12 months of age [51]. Starting with the 1980s, most countries introduced a routine second dose of measles vaccine to further reduce the number of children left susceptible after primary vaccination and increase vaccine efficacy. Hence, the second dose is not considered as a booster [51]. The age for the second dose varies across countries: the second dose is either administrated few months apart from the first dose (e.g., France, Austria, Germany, Brazil, Australia) or a few years apart (e.g., USA, UK, Italy, Sweden, Finland), around the age of school enrollment [51,53,54]. The implementation of measles vaccination programs has led in many settings to the elimination of endemic transmission of measles, at least temporarily [51,55,56], even before adopting routine two-dose schedules [57].

We apply our modeling results to the epidemiology of measles vaccination. Because we assume that vaccination occurs shortly after birth, our results apply best for countries where the time interval between measles vaccine doses is relatively short. We propose that measles elimination for current vaccination programs is ongoing as described for region (a) in our model; see Fig. 2. Reaching this region was possible because, when vaccination programs were implemented, the relative cost of vaccination versus treatment (i.e., r) for measles was most certainly perceived as low by individuals, for the following main reasons: measles was endemic, parents witnessed measles-related morbidity and mortality, public health authorities would make vaccines freely available or subsidized them, and decline of measles incidence would provide direct evidence of vaccination success. However, our results also show that there is no stable equilibrium in region (a). This implies that measles epidemiology is evolving toward the border between regions (a) and (b). The transition may, however, take a long time because national vaccination programs only induce small changes in vaccination coverage, compared to mass vaccination campaigns. This transition occurs because, as high levels of coverage are achieved, individuals may perceive a larger cost of vaccination versus treatment (i.e., higher r) and lose motivation to vaccinate their children. Indeed, when measles is not endemic, most parents do not witness measles-related morbidity and mortality. Furthermore, vaccine rumors/controversies [13] may lead to vaccine hesitation [15] and lower vaccination coverage. A decrease below the critical coverage, $\hat{p}(r_a)$, may lead to epidemic resurgence [50,58], and thus to a transition from region (a) to region (b), where the disease is endemic and individuals will find, once more, the motivation to vaccinate.

Our theoretical findings offer insight on vaccine parameters when the epidemic was eliminated at least temporarily through voluntary vaccination. We consider countries where measles vaccination programs have led to the elimination of measles using a one-dose routine vaccination schedule (e.g., some countries in the Americas [57]) or two doses administered in a relatively short period of time (e.g., Australia [56]). In this case, according to Eq. (18), measles vaccination provides immunity for at least $(R_0 - 1)$ expected lifetimes. The current value of R_0 is not known, but we may assume that R_0 remains in the range of 5–18, as before the vaccination campaigns. We may thus conclude that measles vaccine provides immunity for a duration much longer than the

expected lifetime (4–17 times the expected lifetime). The duration of immunity of current measles vaccines is difficult to determine directly, as it requires long-term studies. A 15-year observational study in China [59] reported that the negative conversion rate of measles vaccinated individuals was 8.1–20.0% over 14 years, which leads to an estimated 63–166 years for the duration of vaccine-induced measles immunity. This is in qualitative agreement with our modeling results.

4. Discussion

In this paper, we used game theory and ordinary differential equations to address the dilemma of prevention versus treatment. In particular, we focused on a classic *SEIR*-type model for childhood infectious diseases subject to both vaccine prevention and treatment.

We found that voluntary vaccination may lead toward epidemic elimination if two conditions are met. First, the duration of vaccine-induced immunity should be sufficiently long; we derived a mathematical formula for this duration, depending on the basic reproduction number of the epidemic, R_0. Second, the relative cost of prevention versus treatment must be sufficiently low; we found a threshold cost, r_a. Disease elimination may occur when a high-performance vaccine is made available, at low cost, in an endemic setting where individuals witness disease-related morbidity and mortality, as well as the benefits of vaccination, as disease incidence declines. All together, this yields a low relative cost of prevention versus treatment (i.e., lower than r_a), resulting in a vaccination coverage high enough to avert the epidemic. However, our modeling results show that disease epidemic elimination is only temporary; this is captured by the absence of an equilibrium for the effective coverage when $R^* < 1$. Indeed, as vaccination coverage increases, leading to less epidemic adversity, individuals may also lose their initial motivation to vaccinate. Hence, with epidemic elimination, the perception of cost in the dilemma of prevention versus treatment may change and increase up to r_a. In turn, this causes a decrease in vaccination coverage and reverses disease elimination to the situation where $R^* = 1$. Previous results consider this to be the maximum long-term impact of voluntary vaccination [16,18,60]. However, it is very important to note that, once the epidemic is averted (in region (a)), the dynamics toward the situation where $R^* = 1$ may be slowed down significantly, owing to continuous effort from the public health authority to maintain a low cost for vaccination.

These findings have implications for prevention and public health programs. For the condition on vaccine quality to be met, it is essential to develop one-shot highly effective vaccines that provide long-lasting immunity. For the condition on the relative cost of prevention versus treatment, we have to distinguish two epidemiological phases: the initial phase, when the vaccine is made available in presence of endemic disease, and the elimination phase, when vaccination continues after reaching high coverage. The cost for a highly effective vaccine introduced when the disease is endemic may be easily perceived as low. However, once the epidemic is eliminated, maintaining a low perceived cost for vaccination may become a complex issue, which will depend on the setting [15]. Witnessing almost no epidemic adversity, individuals may lose motivation to vaccinate. In addition, with the increased vaccination coverage, they may be particularly aware of adverse effects [61] and susceptible to vaccine rumors/controversies [13]. In this case, maintaining a low relative cost of prevention versus treatment may be a difficult and long-running task, requiring multi-scale actions.

Costs associated with vaccine accessibility and uptake, encountered by both individuals and health professionals, may act as important barriers [15] and should be reduced. They include monetary cost of the vaccines, as well as time spent on accessing vaccination, communicating about the safety profile, and administrative burden. Furthermore, vaccination incentives could be implemented [62–64]. For instance, modest non-monetary incentives [63,65] and conditional cash transfers [62,64] have been used to increase the vaccination coverage. However, this type of incentives proved effective only for low-and-middle-income settings [66,62]. In addition, dialogue-based interventions (e.g., social mobilization, communication through mass and social media, etc.) and reminders (e.g., telephone calls or letters) have been used to encourage vaccination [65].

We propose three additional interventions to maintain a low cost for vaccination. First, vaccination in high-income settings might be encouraged using health insurance policies. For instance, the health insurance provider may offer a progressive reduction of the insurance premium (and/or increase of benefits) along with the completion of the vaccination schedule. Second, the public health authority should acknowledge in the media the participation and success of prevention programs in search for continuous public support. Involving civil society representatives and other relevant stakeholders as full participants in vaccine recommendation and policy, as it was recently done in France [67], may help improving mutual understanding and trust around vaccination. Third, recalling information about disease sequelae, and their statistics, using epidemiological data on childhood diseases from countries where vaccine coverage are low, may help individuals to perceive better the aim of prevention, and maintain a fair perception of prevention cost. This also requires providing clear information about vaccine adverse effects, based, for example, on statistics elaborated from the notification of adverse effects by health professionals and parents.

In addition, using the basic reproduction number, our model provides a lower bound estimate for the duration of vaccine-induced immunity against epidemic diseases controlled through vaccination. This may be a particularly important result, since the duration of vaccine-induced immunity is not precisely known for most vaccines [42]. Measuring long-standing vaccine-induced immunity (years) requires long-term follow-up of large numbers of vaccinated individuals (e.g., [59]). Nonetheless, a precise estimation of the duration of vaccine-induced immunity is key to optimize immunization schedules, guide vaccination policy and enhance public trust in vaccines. Along with traditional epidemiology methods, mathematical modeling may offer valuable insight in estimating this vaccine parameter.

In conclusion, we used a game-theoretic model to discuss the dilemma of prevention versus treatment. We demonstrated the circumstances under which non-cooperative, self-interested individuals arrive to alleviate, and potentially eliminate, an epidemic through the use of an imperfect vaccine. Maintaining a low relative cost of prevention versus treatment will be the main challenge to maintain disease elimination unless incentives are considered.

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Declaration of interest

The authors declare no conflict of interest.

Author contributions

R.B. conceived the model. S.J. and R.B. conducted the calculations. All authors wrote the main manuscript text, analyzed the results and have approved the final version of the article.

References

[1] Roush SW, Murphy TV. Vaccine-preventable disease table working group, historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA 2007;298(18):2155–63. http://dx.doi.org/10.1001/jama.298.18.2155.

[2] Zhou F, Shefer A, Wenger J, Messonnier M, Wang LY, Moore M, et al. Economic evaluation of the routine childhood immunization program in the United States, 2009. Pedriatics 2014;133(4):577–85. http://dx.doi.org/10.1542/peds.2013-0698.

[3] Johannesson M, Johansson PO. A note on prevention versus cure. Health Policy 1997;41(3):181–7. http://dx.doi.org/10.1016/S0168-8510(97)00020-1.

[4] Ubel PA, Spranca MD, Dekay ML, Hershey JC, Asch DA. Public preferences for prevention versus cure: What if an ounce of prevention is worth only an ounce of cure? Med Decis Making 1998;18(2):141–8. http://dx.doi.org/10.1177/0272989X9801800202.

[5] Corso PS. Prevention just in case or treatment just because: measuring societal preferences. Harvard Health Policy Rev 2006;7:32–41.

[6] Bosworth R, Cameron TA, DeShazo JR. Is an ounce of prevention worth a pound of cure? Comparing demand for public prevention and treatment policies. Med Decis Making 2010;30(4):E40–56. http://dx.doi.org/10.1177/0272989X10371681.

[7] Mortimer D, Segal L. Is the value of a life or life-year saved context specific? Further evidence from a discrete choice experiment. Cost Effective Resour Allocat: C/E 2008;6:8. http://dx.doi.org/10.1186/1478-7547-6-8.

[8] Schwappach DLB. The equivalence of numbers: the social value of avoiding health decline: an experimental web-based study. BMC Med Inform Decis Making 2002;2:3. http://dx.doi.org/10.1186/1472-6947-2-3.

[9] Corso PS, Hammitt JK, Graham JD, Dicker RC, Goldie SJ. Assessing preferences for prevention versus treatment using willingness to pay. Med Decis Making 2002;22(Suppl. 5):s92–s101. http://dx.doi.org/10.1177/027298902237713.

[10] Meertens RM, de Gaar VMJ, Spronken M, de Vries NK. Prevention praised, cure preferred: results of between-subjects experimental studies comparing (monetary) appreciation for preventive and curative interventions. BMC Med Inform Decis Making 2013;13:136. http://dx.doi.org/10.1186/1472-6947-13-136.

[11] Luyten J, Kessels R, Goos P, Beutels P. Public preferences for prioritizing preventive and curative health care interventions: a discrete choice experiment. Value Health 2015;18(2):224–33. http://dx.doi.org/10.1016/j.jval.2014.12.007.

[12] Gérvas J, Starfield B, Heath I. Is clinical prevention better than cure? The Lancet 2008;372(9654):1997–9. http://dx.doi.org/10.1016/S0140-6736(08)61843-7.

[13] World Health Organization. Impact of rumors and crises. <http://vaccine-safety-training.org/impact-of-rumours-and-crises.html> [website accessed: March 23, 2017].

[14] Larson HJ, de Figueiredo A, Xiahong Z, Schulz WS, Verger P, Johnston IG, et al. The state of vaccine confidence 2016: global insights through a 67-country survey. EBioMedicine 2016;12:295–301. http://dx.doi.org/10.1016/j.ebiom.2016.08.042.

[15] Larson HJ, Jarrett C, Eckersberger E, Smith DMD, Paterson P. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: a systematic review of published literature, 2007–2012. Vaccine 2014;32(19):2150–9. http://dx.doi.org/10.1016/j.vaccine.2014.01.081.

[16] Bauch CT, Earn DJD. Vaccination and the theory of games. Proc Natl Acad Sci 2004;101(36):13391–4. http://dx.doi.org/10.1073/pnas.0403823101.

[17] Bauch CT, Galvani AP, Earn DJD. Group interest versus self-interest in smallpox vaccination policy. Proc Natl Acad Sci 2003;100(18):10564–7. http://dx.doi.org/10.1073/pnas.1731324100.

[18] Manfredi P, Della Posta P, D'Onofrio A, Salinelli E, Centrone F, Meo C, et al. Optimal vaccination choice, vaccination games, and rational exemption: an appraisal. Vaccine 2009;28(1):98–109. http://dx.doi.org/10.1016/j.vaccine.2009.09.109.

[19] Wang Z, Andrews MA, Wu ZX, Wang L, Bauch CT. Coupled disease-behavior dynamics on complex networks: a review. Phys Life Rev 2015;15:1–29. http://dx.doi.org/10.1016/j.plrev.2015.07.006.

[20] Zhang H, Zhang J, Zhou C, Small M, Wang B. Hub nodes inhibit the outbreak of epidemic under voluntary vaccination. New J Phys 2010;12(2):23015. http://dx.doi.org/10.1088/1367-2630/12/2/023015.

[21] Zhang HF, Wu ZX, Xu XK, Small M, Wang L, Wang BH. Impacts of subsidy policies on vaccination decisions in contact networks. Phys Rev E 2013;88(1):12813. http://dx.doi.org/10.1103/PhysRevE.88.012813.

[22] Fu F, Rosenbloom DI, Wang L, Nowak MA. Imitation dynamics of vaccination behaviour on social networks. Proc Roy Soc London B: Biol Sci 2011;278(1702):42–9. http://dx.doi.org/10.1098/rspb.2010.1107.

[23] Bauch CT. Imitation dynamics predict vaccinating behaviour. Proc Roy Soc B: Biol Sci 2005;272(1573):1669–75. http://dx.doi.org/10.1098/rspb.2005.3153.

[24] Reluga TC. Game theory of social distancing in response to an epidemic. PLOS Comput Biol 2010;6(5):1–9. http://dx.doi.org/10.1371/journal.pcbi.1000793.

[25] Reluga TC, Li J. Games of age-dependent prevention of chronic infections by social distancing. J Math Biol 2013;66(7):1527–53. 0.1007/s00285-012-0543-8.

[26] Reluga TC, Bauch CT, Galvani AP. Evolving public perceptions and stability in vaccine uptake. Math Biosci 2006;204(2):185–98. http://dx.doi.org/10.1016/j.mbs.2006.08.015.

[27] Galvani AP, Reluga TC, Chapman GB. Long-standing influenza vaccination policy is in accord with individual self-interest but not with the utilitarian optimum. Proc Natl Acad Sci 2007;104(13):5692–7. http://dx.doi.org/10.1073/pnas.0606774104.

[28] Reluga TC, Galvani AP. A general approach for population games with application to vaccination. Math Biosci 2011;230(2):67–78. http://dx.doi.org/10.1016/j.mbs.2011.01.003.

[29] Liu J, Kochin BF, Tekle YI, Galvani AP. Epidemiological game-theory dynamics of chickenpox vaccination in the USA and Israel. J Roy Soc Interface 2012;9(66):68–76. http://dx.doi.org/10.1098/rsif.2011.0001.

[30] Sykes D, Rychtář J. A game-theoretic approach to valuating toxoplasmosis vaccination strategies. Theoret Popul Biol 2015;105:33–8. http://dx.doi.org/10.1016/j.tpb.2015.08.003.

[31] Molina C, Earn DJD. Game theory of pre-emptive vaccination before bioterrorism or accidental release of smallpox. J Roy Soc Interface 2015;12:20141387. http://dx.doi.org/10.1098/rsif.2014.1387.

[32] Shim E, Chapman GB, Townsend JP, Galvani AP. The influence of altruism on influenza vaccination decisions. J Roy Soc Interface 2012;9(74):2234–43. http://dx.doi.org/10.1098/rsif.2012.0115.

[33] Vardavas R, Breban R, Blower S. A universal long-term flu vaccine may not prevent severe epidemics. BMC Res Notes 2010;3:92. http://dx.doi.org/10.1186/1756-0500-3-92.

[34] Vardavas R, Breban R, Blower S. Can influenza epidemics be prevented by voluntary vaccination? PLOS Comput Biol 2007;3(5):e85. http://dx.doi.org/10.1371/journal.pcbi.0030085.

[35] Breban R. Health newscasts for increasing influenza vaccination coverage: an inductive reasoning game approach. PLOS One 2011;6(12). http://dx.doi.org/10.1371/journal.pone.0028300. e28300–10.

[36] Breban R, Vardavas R, Blower S. Mean-field analysis of an inductive reasoning game: application to influenza vaccination. Phys Rev E 2007;76(3):31127. http://dx.doi.org/10.1103/PhysRevE.76.031127.

[37] Bhattacharyya S, Bauch CT, Breban R. Role of word-of-mouth for programs of voluntary vaccination: a game-theoretic approach. Math Biosci 2015;269:130–4. http://dx.doi.org/10.1016/j.mbs.2015.08.023.

[38] Bhattacharyya S, Bauch CT. "Wait and see" vaccinating behaviour during a pandemic: a game theoretic analysis. Vaccine 2011;29(33):5519–25.

[39] Wu B, Fu F, Wang L. Imperfect vaccine aggravates the long-standing dilemma of voluntary vaccination. PLoS One 2011;6(6):e20577. http://dx.doi.org/10.1371/journal.pone.0020577.

[40] Verelst F, Willem L, Beutels P. Behavioural change models for infectious disease transmission: a systematic review (2010-2015). J Roy Soc Interface 2016;13(125). http://dx.doi.org/10.1098/rsif.2016.0820.

[41] Mclean AR, Blower SM. Imperfect vaccines and herd immunity to HIV. Proc Roy Soc B: Biol Sci 1993;253(1336):9–13. http://dx.doi.org/10.1098/rspb.1993.0075.

[42] Plotkin SA, Orenstein WA, Offit PA. Vaccines. Sixth ed. Philadelphia (United States): Elsevier, University of Pennsylvania; 2012.

[43] Ng M, Fullman N, Dieleman JL, Flaxman AD, Murray CJL, Lim SS. Effective coverage: a metric for monitoring universal health coverage. PLoS Med 2014;11(9). http://dx.doi.org/10.1371/journal.pmed.1001730.

[44] Colson KE, Zúñiga-Brenes P, Ríos-Zertuche D, Conde-Glez CJ, Gagnier MC, Palmisano E, et al. Comparative estimates of crude and effective coverage of measles immunization in low-resource settings: findings from Salud Mesoamérica 2015. PLoS ONE 2015;10(7):1–21. http://dx.doi.org/10.1371/journal.pone.0130697.

[45] van den Driessche P, Watmough J. Further notes on the basic reproduction number. In: Brauer F, van den Driessche P, Wu J, editors. Mathematical epidemiology, lecture notes in mathematics. Berlin (Heidelberg): Springer Heidelberg Berlin; 2008. p. 159–78. http://dx.doi.org/10.1007/978-3-540-78911-6 [chapter 6].

[46] Anderson RM, May RM. Infectious diseases of humans: dynamics and control. Oxford University Press; 1991.

[47] Diekmann O, Heesterbeek HJAP. Mathematical epidemiology of infectious diseases: model building, analysis and interpretation. In: Wiley series in mathematical and computational biology. Wiley; 2000.

[48] World Health Organization. Measles vaccines: WHO position paper. Weekly Epidemiol Rec 2009;84(35):349–60. http://dx.doi.org/10.1016/j.biologicals.2009.04.005.

[49] Centers for Disease Control Prevention. Measles (Rubeola); 2017. <https://www.cdc.gov/measles/hcp/index.html> [website accessed: July 28, 2017].

[50] Centers for Disease Control Prevention. Epidemiology and prevention of vaccine-preventable diseases: measles; 2017. <https://www.cdc.gov/vaccines/pubs/pinkbook/meas.html> [website accessed: April 27, 2017].

[51] Strebel PM, Papania MJ, Fiebelkorn AP, Halsey NA. Measles vaccine. In: Vaccines. London: Elsevier; 2013. p. 352–87. http://dx.doi.org/10.1016/B978-1-4557-0090-5.00028-8.

[52] Watson JC, Hadler SC, Dykewicz Ca, Reef S, Phillips L. Measles, mumps, and rubella–vaccine use and strategies for elimination of measles, rubella, and congenital rubella syndrome and control of mumps: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. Recommend

Rep: Morbid Mortal Weekly Rep. Recommend Rep/Centers Disease Control 1998;47(RR-8):1–57.
[53] Bundesministerium für Gesundheit und Frauen. Impfplan Österreich, Wien; 2017 [English translation: Austrian vaccination plan, published by the Federal Ministry of Health and Women, Vienna, 2017].
[54] European Centre for Disease Prevention and Control. Vaccine schedule. <http://vaccine-schedule.ecdc.europa.eu/Pages/Scheduler.aspx> [website accessed: August 9, 2017].
[55] Peltola H, Jokinen S, Paunio M, Hovi T, Davidkin I. Measles, mumps, and rubella in Finland: 25 years of a nationwide elimination programme. Lancet Infect Diseas 2008;8(12):796–803. http://dx.doi.org/10.1016/S1473-3099(08)70282-2.
[56] Gidding HF, Martin NV, Stambos V, Tran T, Dey A, Dowse GK, et al. Verification of measles elimination in Australia: application of World Health Organization regional guidelines. J Epidemiol Global Health 2015;6(3):197–209. http://dx.doi.org/10.1016/j.jegh.2015.12.004.
[57] Sever AE, Rainey JJ, Zell ER, Hennessey K, Uzicanin A, Castillo-Solórzano C, et al. Measles elimination in the Americas: a comparison between countries with a one-dose and two-dose routine vaccination schedule. J Infect Diseas 2011;204 (Suppl. 2). http://dx.doi.org/10.1093/infdis/jir445.
[58] Lemos DRQ, Franco AR, de Sá Roriz MLF, Carneiro AKB, de Oliveira Garcia MH, de Souza FL, Duron Andino R, de Góes Cavalcanti LP. Measles epidemic in Brazil in the post-elimination period: coordinated response and containment strategies. Vaccine 2017;35(13):1721–8. http://dx.doi.org/10.1016/j.vaccine.2017.02.023.
[59] Bin D, Chen ZH, Liu QC, Wu T, Guo CY, Wang XZ, et al. Duration of immunity following immunization with live measles vaccine: 15 years of observation in Zhejiang Province, China. Bull World Health Organ 1991;69(4):415–23.
[60] Doutor P, Rodrigues P, do Céu Soares M, Chalub FACC. Optimal vaccination strategies and rational behaviour in seasonal epidemics. J Math Biol 2016;73 (6):1437–65. http://dx.doi.org/10.1007/s00285-016-0997-1.
[61] Serpell L, Green J. Parental decision-making in childhood vaccination. Vaccine 2006;24(19):4041–6. http://dx.doi.org/10.1016/j.vaccine.2006.02.037.
[62] Owusu-Addo E, Cross R. The impact of conditional cash transfers on child health in low- and middle-income countries: a systematic review. Int J Public Health 2014;59(4):609–18. http://dx.doi.org/10.1007/s00038-014-0570-x.
[63] Banerjee AV, Duflo E, Glennerster R, Kothari D. Improving immunisation coverage in rural India: clustered randomised controlled evaluation of immunisation campaigns with and without incentives. BMJ (Clinical research ed.) 2010;340(9655):c2220. http://dx.doi.org/10.1136/bmj.c2220.
[64] Australian Government Department of Health. No jab, no pay – new immunisation requirements for family assistance payments; 2015.
[65] Jarrett C, Wilson R, O'Leary M, Eckersberger E, Larson HJ, the SAGE Working Group on Vaccine Hesitancy. Strategies for addressing vaccine hesitancy – a systematic review. Vaccine 2015;33(34):4180–90. http://dx.doi.org/10.1016/j.vaccine.2015.04.040.
[66] Adams J, McNaughton RJ, Wigham S, Flynn D, Ternent L, Shucksmith J. Acceptability of parental financial incentives and quasi-mandatory interventions for preschool vaccinations: triangulation of findings from three linked studies. PLoS ONE 2016;11(6):1–14. http://dx.doi.org/10.1371/journal.pone.0156843.
[67] Rapport de la Concertation Citoyenne sur la Vaccination; 2016. <http://concertation-vaccination.fr/la-restitution/> [website accessed: April 10, 2017].

2.3 Additional figures

Flow diagram of disease transmission

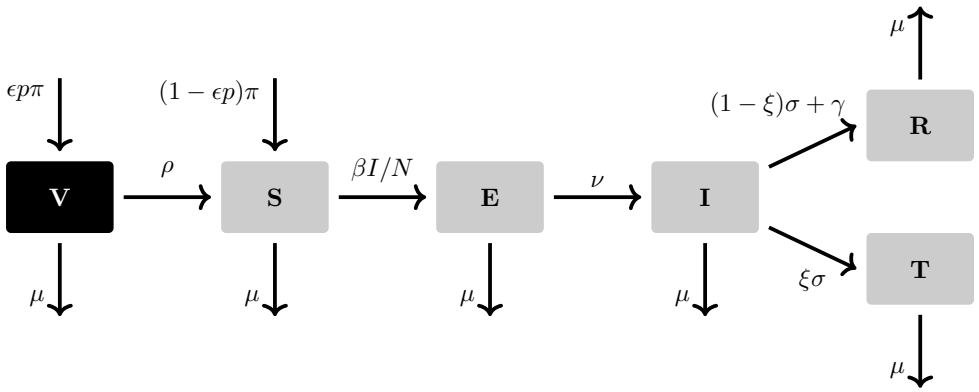

Figure 2.5 – Flow diagram for the compartmental model of vaccination against childhood infectious diseases

The flowchart corresponds to the ODE system (1) of section 2.2. 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 denoted by ξ.

Bifurcation diagram

Fig. 2.6 builds on a variation of fig. 1 of section 2.2, allowing 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.

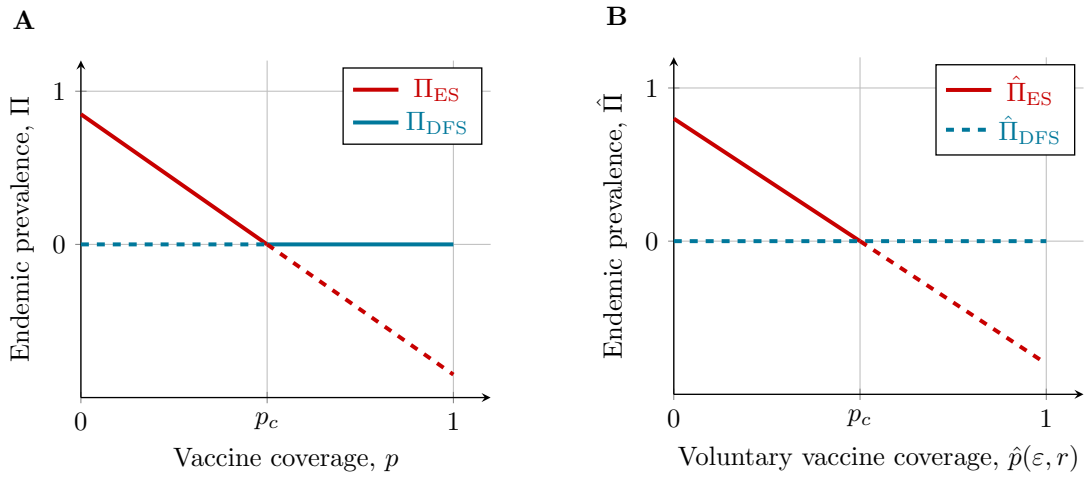

Figure 2.6 – Bifurcation diagram for the endemic prevalence
The disease-free state (DFS) and the endemic state (ES) are depicted in blue and red, respectively. A change in the stability of the system's equilibria occurs when the vaccine coverage (p) reaches the critical value p_c (i.e., when the effective reproduction number equals to 1), which is depicted by the transition from a solid to a dashed line. **(A)** The bifurcation diagram for prevalence, Π, for the model without the individual-level decision-making component. **(B)** The bifurcation diagram for 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 compartimental model: there exists no equilibrium coverage for voluntary vaccination once the epidemic has been averted. Individuals may no longer get vaccinated if the disease is eliminated.

2.4 Further discussion

2.4.1 A note on mandatory vaccination

Some countries have witnessed infectious diseases reemergence and have established mandatory vaccination as a result. As of 2018, vaccination against measles was mandatory in 9 European countries. In 2019, France added 8 mandatory vaccines to a list of 3, and Italy established 10

mandatory vaccines (Bechini et al., 2019). The most common strategies to 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 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 vaccination hesitancy and 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 highlight the importance of addressing the individuals' voluntary participation on vaccination and the pertinence of our results.

Chapter 3

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

3.1 Introduction

3.1.1 The HIV epidemic

HIV infection, diagnosis and treatment

The 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 immune 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, 2020).

The natural stages of the HIV infection (i.e., when left untreated) go as follows. 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 for

a few weeks. Then, for several years, the chronic[1], 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 called 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 for a few years (CDC, 2020). Fig. 3.1 depicts the natural dynamics of CD4 cells count and viral load, during the HIV stages.

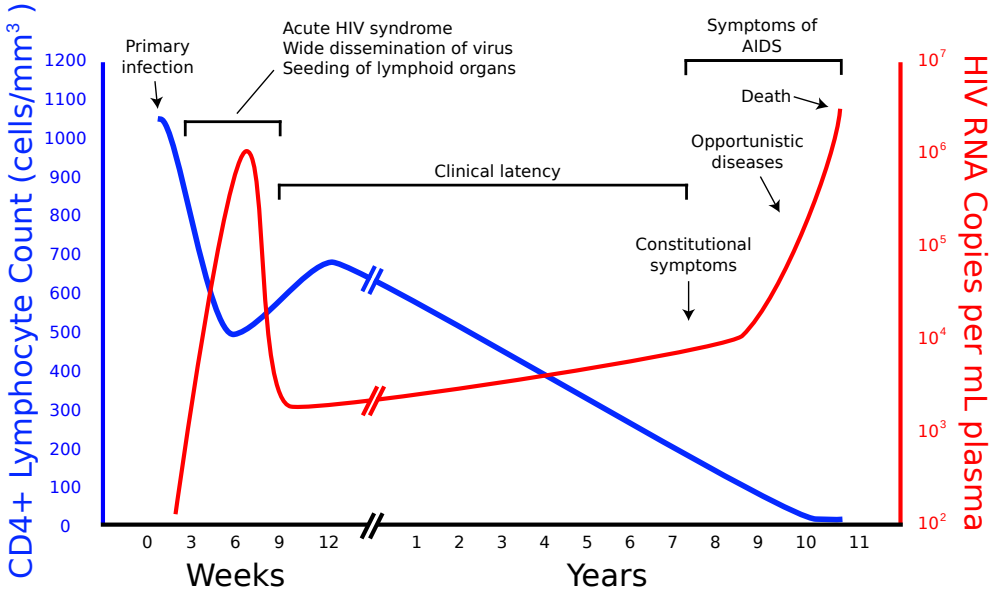

Figure 3.1 – The HIV infection natural progression
Average CD4+ T cell count (blue) and HIV viral load (red) during the course of an untreated HIV infection. Image source: (Sigve, 2011).

HIV infection may be diagnosed 10 to 90 days after exposure to HIV, depending on the testing method used (CDC, 2020). 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 different stages of the HIV life cycle, are currently available. This has allowed to combine two or three different HIV 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 (2016a) currently recommends HIV infected individuals to start ART immediately

[1] Also referred to as the *latent* phase.

after diagnosis, and take ART for life. An infected individual successfully undergoing ART experiences a decrease in the viral load until the viral load is 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 (Rodger 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). Thanks to effective ART, the number of infections, AIDS-related diseases and deaths has been greatly reduced globally (WHO, 2016a).

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).

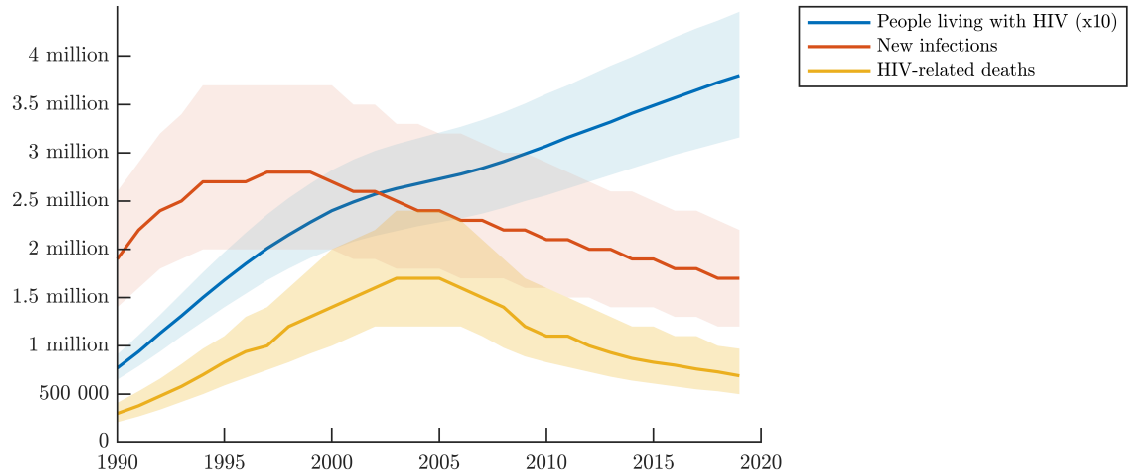

Figure 3.2 – HIV/AIDS epidemiological indicators, worldwide
Total number of people living with HIV (the data was divided by 10 to fit the same figure with the other mesures; i.e., in 2019, there were $\sim$ 38 million people living with HIV), number of new HIV infections and number of HIV-related deaths, from 1990 to 2019, worldwide. Source: UNAIDS HIV estimates (UNAIDS, 2020b).

In most high-income settings, the population of men who have sex with men (MSM) is one of

the most affected by the HIV epidemic (UNAIDS, 2018; WHO, 2016b; Beyrer 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 risky behavioral factors, such as unprotected sexual intercourses, large number of casual partners and the use of recreational drugs (Beyrer et al., 2012).

The prevention of HIV infection

The prevention methods against HIV include, among others: abstinence, condom use (Chen et al., 2017), seroadaptation[2] (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 to prevent infection, in the form of pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP) and treatment as prevention (TasP), where the treatment of infected individuals prevents, indirectly, HIV infection among their sexual contacts (WHO, 2016a). 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). However, HIV incidence among MSM remains high: 64% of the new HIV infections in Western and Central Europe and North America occurring among MSM (UNAIDS, 2020a).

3.1.2 PrEP uptake among MSM

PrEP consists of the use of ART molecules 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 daily or *on demand* (i.e., taken right before and after possible exposure to HIV) (Desai et al., 2018; Siguier and Molina, 2018).

As of June 2018, only 35 countries had at least one public policy implemented regarding PrEP rollout; many of them (15 countries) in the European region (Hodges-Mameletzis et al.,

[2]The 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.

2018). Global efforts thus remain far from the WHO (2016b) recommendations to scale up PrEP programs among high-risk populations.

Efficacy of PrEP

The first randomized, double blind, clinical trial studying the efficacy of PrEP among MSM was the *iPrex* 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 estimating efficacy: the risk reduction increased to 92% when considering only the subgroup of individuals with detectable concentrations of TDF-FTC in the blood (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, which found a PrEP efficacy of 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 in 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 immediate and 1-year deferred 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 (2015, 2016a,b) currently recommends PrEP as a prevention method for MSM at high risk of HIV of infection. Individual-level PrEP eligibility criteria for MSM include, for instance, having unprotected anal intercourse 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; Drabo et al., 2016; Ouellet et al., 2015; Desai et al., 2008), but may remain costly 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 the price of PrEP, which remains a key barrier to provide PrEP broadly through public health programs (ECDC, 2016).

HIV-risk awareness and PrEP acceptability among MSM

The MSM community has shown to be highly aware about HIV risk of infection, which has resulted in the community 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 no longer be adopted (Young et al., 2014).

In addition, MSM have 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).

PrEP 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 interactions and 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 among the MSM population 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). 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). The number of new HIV infections has remained rather stable since 2011 (Siguier and Molina, 2018; Santé Publique France, 2019b).

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 (∼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).

The 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; EPI-PHARE, 2020; Siguier and Molina, 2018; Haute Autorité de Santé, 2019). 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; iii) To have had at least one post-exposure treatment for HIV in the last 12 months; iv) Drug use during sexual intercourse.

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 (EPI-PHARE, 2020). 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 cases of MSM recently diagnosed with HIV that would have been eligible for PrEP prescription (Lions et al., 2019). Also, a 30-month dropout rate of $\sim 32\%$ (Costagliola et al., 2019) from PrEP program was observed, which reveals the need of understanding and addressing PrEP persistence. Among on-PrEP MSM in the Paris region, some evidence of drop in condom use has been observed (Molina et al., 2018).

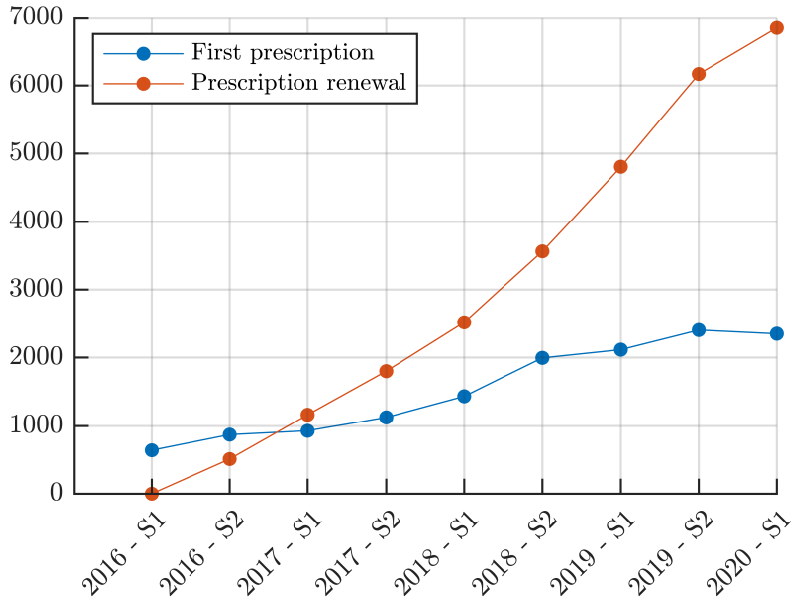

Figure 3.3 – PrEP users in Île-de-France, by semester and year
Number of first PrEP prescriptions (i.e., people starting PrEP; in blue) and PrEP prescription renewals (in red) in the Paris region, by semester (S1 and S2) from January 1st, 2016 to June 30th, 2020. The data suggests that the great majority of PrEP users in the region were MSM. The total number of first prescriptions since PrEP rollout in the region was $\sim$ 13 900. On average, 85% of PrEP users got a prescription renewal the following year. Only $\sim$ 6 850 prescription renewals were established the first semester of 2020. Source: EPI-PHARE (2019, 2020)[3].

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

Specific strategies and objectives to end AIDS globally have been set by the UNAIDS (2011, 2014) during the past decade. Nowadays, the initiative to end AIDS as a public health threat by 2030 is part of the WHO Sustainable Development Goals. One essential direction adopted towards ending 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

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

individuals to reach viral suppression, by 2020 (UNAIDS, 2017). In 2014, 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). As of 2019, a 88%–92%–82% progress was achieved among men of 15 years and older in the region of Western and Central Europe and North America (UNAIDS, 2020a).

A complementary strategy to end AIDS has been to implement HIV prevention interventions, through the combination of behavioral and biomedical approaches (UNAIDS, 2011, 2014). In particular, the WHO has published recommendations targeting the populations most at risk of HIV infection[4], which include MSM (WHO, 2016b). Hopes are that the use of PrEP may curb the HIV epidemic among MSM, down to epidemic elimination. 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 epidemiological settings on the path towards HIV epidemic elimination (Palk et al., 2018; Grulich et al., 2018; Brown et al., 2018).

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; Sood 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-uniformly random (Jacquez et al., 1988, 1989; Gupta et al., 1989; Sattenspiel et al., 1990). The risk categories have been defined

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

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.

There are two main kinds of structured mixing that have been used to model 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 hypotheses made regarding heterogeneity may impact the results: the higher the heterogeneity, the lower the prevalence at the endemic state and, in the case that extremely risky behaviors are considered, two peaks may be observed in the epidemic dynamics (Punyacharoensin et al., 2011), taking longer to reach the equilibrium.

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 below 1 yearly case per 1000 individuals, a 2009 study found that testing the whole population yearly and treating immediately all seropositive 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).

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; Punyacharoensin et al., 2016; Jenness et al., 2016; Robineau et al., 2017; Rozhnova et al., 2018; Palk et al., 2018; Rozhnova et al., 2019; Singleton et al., 2020). Moreover, mathematical models have been recently used to study PrEP interventions among MSM in the context of the WHO 95–95–95 initiative and its 90% incidence reduction target (Scott et al., 2018; Singleton et al., 2020) as well as HIV epidemic elimination through PrEP rollouts among MSM

[5] Sexual 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).

[6] Also referred to as *assortative mixing*.

(Rozhnova et al., 2018; Scott et al., 2018; Hansson et al., 2020). In these models, different levels of PrEP coverage are considered (Gomez et al., 2012; Punyacharoensin et al., 2016; Robineau et al., 2017; Rozhnova et al., 2018; Singleton et al., 2020), including full coverage (Kim et al., 2014). However, high levels of PrEP coverage, which are required to substantially impact or eliminate HIV epidemics, may not be granted in the real world. It remains to know whether and how PrEP coverage levels can be reached and maintained, in the long term.

To the best of our knowledge, no modeling study has addressed the individual-level decision-making on whether or not to adopt PrEP to avoid HIV infection[7]and thus evaluated the impact of voluntary adoption of PrEP on the HIV epidemic. This is the main objective of the second part of my PhD work.

3.2 Publication

A scientific article presenting our findings, titled "Can HIV epidemics among men who have sex with men be eliminated through participation in PrEP rollouts" (Jijón et al., 2021), was accepted for publication in the journal *AIDS* in July, 2021.

The computations and proofs of the analytical results presented in the article's supplementary material are detailed in section 3.3 of this chapter. Additional figures are also found in section 3.3. The implementation of HIV prevention programs are further discussed in section 3.4, as well as the limitations and perspectives of our modeling choices.

3.2.1 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 ART is in place. In particular, we address this issue for one of the most at risk populations in mainland France: MSM in ÎdF (the Paris region).

[7]Game-theoretic approaches have been used to study HIV epidemics and the impact of other prevention methods, such as condom use (Tully et al., 2013, 2016), social distancing (Auld, 2003; Reluga and Li, 2013) and vaccination (Tully et al., 2015).

3.2.2 Results statements

We obtained a mathematical characterization of the probability that a typical individual adopts 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 risk of HIV infection, the PrEP parameters and the HIV epidemic's intrinsic parameters. In particular, we study the PrEP coverage in terms of the PrEP effectiveness and the relative cost of PrEP versus ART perceived by individuals.

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).

According to our findings, the reduction in condom use with PrEP adoption (risk compensation) 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 be fair; if risk is underestimated, an even lower cost of PrEP is required for 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 remains in place.

We conclude that current PrEP rollout protocols, including that of the Paris region, may not reduce the cost of PrEP enough 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 fair perception for the HIV risk and the cost of PrEP perceived as low.

3.2.3 Article

The preprint of the main text is included below, followed by its supplementary material, which presents in detail the mathematics of our model.

Can HIV epidemics among men who have sex with men be eliminated through participation in PrEP rollouts?

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Main text: 3498/3500

Abstract

Objectives: To study the conditions under which PrEP coverage can eliminate HIV among men who have sex with men (MSM) in the Paris region.

Design: Mathematical modeling.

Methods: We propose an innovative approach, combining a transmission model with a game-theoretic model, for decision-making about PrEP use. Individuals at high risk of HIV infection decide to use PrEP, depending on their perceived risk of infection and the relative cost of using PrEP versus antiretroviral treatment (ART), which includes monetary and/or non-monetary aspects, such as price and access model of PrEP, consequences of being infected and lifelong ART.

Results: If individuals assessed correctly their infection risk, and the cost of using PrEP were sufficiently low, then the PrEP rollout could lead to elimination. Specifically, assuming 86% PrEP effectiveness, as observed in two clinical trials, a minimum PrEP coverage of 55% (95% CI:43%–64%) among high-risk MSM would achieve elimination in the Paris region. A complete condom drop by MSM using PrEP slightly increases the minimum PrEP coverage required for elimination, by ~1%, while underestimation of their own HIV infection risk would require PrEP programs reduce the cost of using PrEP by a factor ~2 to achieve elimination.

Conclusions: Elimination conditions are not yet met in the Paris region, where at most 47% of high-risk MSM were using PrEP as of mid-2019. Further lowering the cost of PrEP and promoting a fair perception of HIV risk are required and should be maintained in the long run, to maintain elimination status.

Keywords: Pre-exposure prophylaxis; HIV; men who have sex with men; behavioral epidemiology; game theory; prevention coverage.

Introduction

In many settings, men who have sex with men (MSM) are most affected by HIV [1]. Pre-exposure prophylaxis (PrEP) is a highly effective prevention method recommended by the WHO for individuals at high risk of infection with HIV [2]. Both IPERGAY and PROUD clinical trials showed that PrEP can reduce HIV incidence among MSM by 86% [3,4]. Modeling studies, elaborating on these results, suggested that PrEP has the potential to curtail, and even eliminate HIV epidemics, notably among MSM [5–8]. For instance, in the Netherlands, elimination would require 82% PrEP coverage in the highest-risk group [6].

The question of whether it is possible to achieve a certain PrEP coverage in a population has not been addressed; modeling studies only assume that the coverage reaches certain values, which may not be granted in public health practice. It is therefore unclear whether, and under what conditions, target PrEP coverage levels, required to eliminate HIV epidemics, can be reached voluntarily and maintained in the long run. Currently, PrEP remains underutilized in many settings [9]. For instance, in the United States, 220,000–225,000 individuals were on PrEP as of April 2020 [10], still short of the CDC estimate that 1.2 million persons have indications for considering PrEP use [11]. Furthermore, a recent study shows that only two in five individuals keep using PrEP for >2 years [12].

Mathematical tools for modeling individual-level decision-making are offered by game theory [13–15]. We propose an innovative approach, combining an epidemic model at the population level, and a game-theoretic model for decision-making about PrEP at the individual level. We model PrEP adoption in a population at high risk of HIV infection, to determine whether and under what conditions certain PrEP coverage levels can be reached voluntarily. Particularly, we study the potential impact of PrEP among MSM in the Paris region of France, where universal antiretroviral treatment (ART) is in place, and PrEP is available for eligible individuals.

Methods

We built an HIV epidemic model (Figures S1 and S2) to describe the epidemiological context of an MSM community where eligible individuals make informed decisions about adopting PrEP. The decision making is modeled as a non-cooperative game, where individuals act to maximize the utility of adopting PrEP, or, in other words, minimize the cost of using PrEP to avoid acquiring HIV and taking lifelong ART. Individual's decision is, however, indirectly influenced by that of others. The sum of all individuals' decisions determines the PrEP coverage, which, consequently, affects epidemic progression and the risk of acquiring HIV. The decision-making game model is thus intertwined with the epidemic model. Below, we describe the main features of our two-component model; see the Supplementary Material (SM) for further details.

The epidemic model

The epidemic model stratifies the MSM population into two risk groups: (low and high), to account for heterogeneity in the infection risk. The majority of partnerships occur within the same risk group (i.e., assortative mixing) and individuals at high risk of infection drive the epidemic. The model also stratifies over HIV status, disease progression, diagnosis and the use of PrEP or ART. Once diagnosed, individuals immediately begin ART [16], no longer transmitting HIV. We varied PrEP effectiveness, denoted ε, from 0 to 100% to study sub-optimal PrEP use. The PrEP coverage, p, was not fixed; rather, it was obtained through the decision-making game model (see below).

We computed the effective reproduction number for the epidemic model, R, defined as the expected number of secondary cases caused by one infected individual, during his entire infectious period, in an uninfected population subject to control interventions [17,18]. PrEP use may change individuals' preference for other prevention tools, turning R into a function of PrEP parameters. $R(p, \varepsilon) > 1$ indicates epidemic persistence, meaning that an endemic state will be reached. Elimination requires $R(p, \varepsilon) < 1$, such that the disease-free state will be reached. Elimination implies that incidence is reduced to zero in the studied population, but HIV can re-emerge in absence of control interventions, as it does not imply eradication. We say the epidemic is controlled using PrEP if $R(p, \varepsilon)$ decreases with the PrEP parameters, although the decrease is not below 1. Our model shows that epidemic control and elimination can occur through PrEP, provided that two thresholds in PrEP effectiveness are exceeded; $\varepsilon \geq \varepsilon_C$ is required for epidemic control and $\varepsilon \geq \varepsilon_E$

for epidemic elimination (see SM section 1.2.3). These thresholds are called the epidemic control and the epidemic elimination thresholds, respectively.

The decision-making game model

During an epidemic, individuals may adopt PrEP according to their perceived HIV risk [19], their perceived advantages and disadvantages of PrEP uptake, which includes quality of sex life, price [20] and access model of PrEP [21], adverse effects [22], social stigma [23], perceived consequences of being infected, which includes potential HIV-related stigma, regular clinical visits, lifelong ART, and other pros and cons. These factors, summarizing monetary and/or non-monetary aspects, are expressed in our decision-making model as costs perceived by the individual.

We assume that all high-risk MSM choose between two mutually-exclusive strategies. If an MSM decides not to use PrEP, then in the case of acquiring HIV he will start ART upon positive HIV diagnosis, and pay the cost of being infected and taking ART, called the cost of ART for simplicity, for the rest of his life; we use the notation $C_{\text{No-PrEP}}$ for the lifetime cost of this strategy. Otherwise, the MSM decides to adopt PrEP prevention, including regular testing for HIV. Thus, he takes and pays the cost of PrEP and, in the case of acquiring HIV despite PrEP uptake, being diagnosed and starting ART, pays the cost of ART for the rest of his life. We use the notation C_{PrEP} for the lifetime cost of the second strategy. The total cost depends explicitly on the yearly costs perceived for ART and PrEP, the PrEP parameters, and, implicitly, the yearly risk of acquiring HIV.

We introduce r, the cost perceived for the strategy of adopting PrEP versus the cost perceived for the strategy of not adopting PrEP, which we call, for simplicity, the relative cost of PrEP versus ART. Hence, the balance of cost, when the probability to adopt PrEP is p, is

$$C(p,\varepsilon,r) = pC_{\text{PrEP}}(p,\varepsilon,r) + (1-p)C_{\text{No-PrEP}}(p,\varepsilon),$$

where all functions and parameters, other than p, are given in our mathematical modeling. The value of p that minimizes $C(p,\varepsilon,r)$, denoted $\hat{p}(\varepsilon,r)$, estimates the probability that a typical high-risk individual adopts PrEP, and also represents the voluntary PrEP coverage among high-risk MSM. The solution of the game represents an endemic state where

individuals make decisions to adopt PrEP in stationary epidemiological context. We thus assumed that, in the long run, individuals stand by their decisions about adopting PrEP and we used our model only for long-term predictions.

Application to the HIV epidemic among MSM in the Paris region

We calibrated the epidemic model to represent the epidemiological context before the introduction of PrEP [24,25], and obtained many HIV parameter sets, to reveal uncertainty in the model output (SM section 2 and Tables S1–S4). In our baseline scenario, we assumed that MSM on PrEP get tested for HIV quarterly, according to the French recommendations [26]. The testing frequency on PrEP was thus much higher than that observed off PrEP, as data shows ~3 years for the mean time from HIV infection to diagnosis among MSM before the introduction of PrEP (personal communication with VS). We further assumed that individuals have a fair perception of their infection risk when making decisions about PrEP use; the infection risk was determined by the force of HIV infection of the epidemic model. Furthermore, MSM were assumed to drop condom use from 30% to 20% when adopting PrEP [3], and the condom effectiveness was 58%–80% [27]. Sensitivity scenarios were explored assuming that i) MSM misperceived their risk of acquiring HIV, or ii) MSM adopting PrEP completely dropped condom use [28], (SM Section 3).

Results

About 500 parameter sets calibrated our epidemic model to the HIV epidemiology among MSM in the Paris region, before the introduction of PrEP: total yearly mean incidence was 1.3%, prevalence was 17%, and 17% of the MSM living with HIV were undiagnosed (Table S3). The mean number of MSM was ~111,000, of which 13% (i.e., ~14,200) were at high risk of infection and eligible for PrEP. Yearly incidence for high-risk MSM was 7%. The model parameters implied that the PrEP rollout had two effects: first, it offered the prevention benefits of the regimen, and, second, it behaved as a test-and-treat strategy [29,30], imposing a major change in HIV testing practice (SM Section 3.1 and Figure S3).

The voluntary PrEP coverage if individuals perceived correctly HIV infection risk

We first investigated a typical parameter set calibrating our model; Table S2. The PrEP coverage starts at zero, before introducing PrEP, and then, in the long term, reaches an equilibrium value where the expected cost of adopting PrEP is minimum. The final value reached depends on HIV parameters of the epidemic before the introduction of PrEP, the PrEP effectiveness, ε, and the perceived relative cost of PrEP versus ART, r. Figure 1A shows the voluntary PrEP coverage reached among high-risk MSM, $\hat{p}(\varepsilon, r)$. Figure 1B shows the corresponding relative reduction in HIV incidence in the MSM community. Each of these two figures shows three regions:

- Region III, where no high-risk MSM adopts PrEP, because the perceived relative cost of PrEP versus ART is too high. Therefore, HIV remains endemic, unaffected by the introduction of PrEP (i.e., no reduction in incidence);
- Region II, where some, but not enough, high-risk MSM adopt PrEP, since the relative cost remains high. The epidemic is controlled and incidence decreases, but not enough for elimination ($\text{i.e.}, R(\hat{p}, \varepsilon) > 1$);
- Region I, where PrEP is offered at low relative cost. This allows reaching high levels of PrEP coverage (~54–75%) and the epidemic can be eliminated; for Region I, $R(\hat{p}, \varepsilon) < 1$. HIV elimination for low PrEP effectiveness (bottom part of Figure 1A) occurs as a consequence of the test-and-treat effect of the PrEP rollout; consequently, $\varepsilon_C = \varepsilon_E = 0\%$. In this case, MSM taking PrEP are poorly protected against HIV. However, they are diagnosed and treated very early in the course of infection, because they get tested for HIV every three months. Early diagnosis and treatment prevent further HIV transmission. In contrast, when PrEP effectiveness

is high, most on-PrEP MSM do not acquire HIV, so the test-and-treat benefit of the PrEP rollout is marginal. It is PrEP, particularly its high effectiveness, that contributes decisively to epidemic elimination. If $\varepsilon = 86\%$, as observed in the IPERGAY and PROUD trials, a minimum PrEP coverage of 56% should be reached among high-risk MSM, to eliminate HIV; Figure S4.

It is important to note that elimination is temporary, as the disease-free state is unstable. Indeed, once the epidemic is eliminated, individuals perceive HIV risk as being low and may reevaluate the pros and cons of PrEP. In turn, this may severely increase the relative cost of PrEP versus ART, since the epidemic is considered to be eliminated and prevention is perceived as no longer needed. As fewer individuals consider PrEP use, the PrEP coverage decreases and the HIV epidemic dynamics in Region I can enter Region II, where the epidemic reemerges and becomes again of public health concern.

We generated the outputs in Figure 1 using each of the ~500 parameter sets obtained through calibration, to estimate uncertainty intervals for our results (SM Section 2). Figure 2A shows the probability that HIV is eliminated, as a function of ε and r. The probability is high on the left, where Region I is found, and declines severely toward Region II. In Figure 2B, we illustrate the boundaries between Regions I and II (continuous line), and between Regions II and III (dashed line); the three-region structure appears robust to parameter uncertainties. Additionally, when $\varepsilon = 86\%$, we found that the 95% confidence interval (CI) of the minimum PrEP coverage needed for elimination (i.e., 55%) is 43%–64%.

Sensitivity scenarios

We assumed that individuals could misperceive their HIV risk when deciding to adopt PrEP, and repeated our analyses. Specifically, rather than having a fair sense of HIV risk, based on the force of infection, high-risk MSM could get a sense of HIV risk from, for instance, the proportion of their high-risk MSM peers being diagnosed each year with HIV (SM Section 3.3.1), assuming full disclosure from HIV-diagnosed MSM. The voluntary PrEP coverage computed for this scenario is illustrated in Figure 3 and reveals a qualitatively similar structure to that in Figure 1. However, when high-risk MSM misinterpret and underestimate their HIV risk, Region I is smaller, implying that the relative cost of

PrEP versus ART must be lower to achieve epidemic elimination. In particular, when $\varepsilon = 86\%$, the relative cost needed for epidemic elimination decreases by a factor of ~2, making Region I harder to reach in practice of public health.

We performed another sensitivity analysis, where we analyzed PrEP-driven condom drop. In our baseline scenario, MSM dropped condom use from 30% to 20% when adopting PrEP. Similar results were obtained assuming that PrEP users stopped using condoms completely (SM Section 3.3.2 and Figure S5). We thus concluded that condom drop is not a major factor against HIV elimination when PrEP effectiveness is high. Specifically, epidemic elimination where $\varepsilon = 86\%$ requires a coverage of >57%, rather than >56% in the baseline scenario.

Perspectives on the PrEP rollout in the Paris region

In 2016, a PrEP rollout started in the Paris region, offering fully subsidized PrEP to eligible individuals. As mentioned before, under the baseline scenario, for 86% PrEP effectiveness, we found that at least 55% (95%CI: 43%–64%) of the high-risk MSM would need to take PrEP for the HIV epidemic be eliminated. Since, according to our calibration, the estimated number of PrEP-eligible MSM in the Paris region is 14,200 (95%CI: 9,200–23,000), this means that 7,700 (95%CI: 5,800–10,100) high-risk MSM should remain on PrEP for the long term. This is an objective to be reached. As of mid-2019, ~6,700 men were on PrEP in the Paris region [31], with a marked growing trend. However, the 30-month dropout rate was ~32% [32]. The PrEP coverage among high-risk MSM was then estimated to be at most 47% (95%CI: 30%–73%), assuming that all men on PrEP were indeed high-risk MSM, which is probably an overestimation. If all these MSM remained on PrEP for the long term, our model predicted epidemic control (i.e., Region II), with a reduction of 90% (95%CI: 81%–100%) in HIV incidence at the new endemic state.

Discussion

We addressed the role of individual-level decision-making in the potential impact of PrEP on the HIV epidemic, identified the conditions for epidemic control or elimination, and estimated PrEP coverage levels which may be reached voluntarily. We obtained four major findings for PrEP rollouts. First, HIV epidemics can be eliminated provided that the relative cost of using PrEP versus ART is sufficiently low. Second, frequent HIV testing while taking PrEP can compensate for poor PrEP adherence and act as a test-and-treat intervention. Third, HIV risk perception may play a major role for elimination, while drop in condom use among PrEP users may not. Fourth, epidemic elimination may be only temporary.

We applied our model to the Paris region. Assuming a PrEP effectiveness of 86%, as reported in two major clinical trials, we found that at least 55% (95%CI: 43%–64%) of the high-risk MSM would need to be on PrEP to achieve HIV elimination. As of mid-2019, at most 47% high-risk MSM were on PrEP in the Paris region, meaning that the PrEP-rollout protocol did not reduce enough the cost of PrEP for epidemic elimination, so far. Still, a recent update on new HIV diagnoses in Paris [33] shows that the numbers among French-born MSM decreased by 28%, between 2015 and 2018, with no significant decrease for other MSM. This decrease could be partly due to the PrEP rollout starting in 2016, and, according to our modeling, should continue in the near future. In two other settings, a moderate-high PrEP coverage has been quickly reached. The region of New South Wales witnessed a rapid PrEP rollout (~9,000 MSM on PrEP within 2 years) during an implementation study providing PrEP for free at several sites, including public HIV and sexual health services, and private general practices with expertise in ART prescription [34]. About 41% of the high-risk MSM in Australia were on PrEP in 2017 [35]. Since April 2018, PrEP is subsidized by the Australian government and can be prescribed by any practitioner [36]. In San Francisco, a citywide-coordinated PrEP rollout, within the Getting to Zero program, strongly promoted PrEP and offered PrEP for free or at low monetary cost, through insurance benefits or patient assistance programs. Close to 50% of the eligible MSM were on PrEP in 2017 in San Francisco [37]. Although these levels of PrEP coverage contributed to decreasing HIV transmission [34,37,38], HIV elimination has not been reported.

Moving toward epidemic elimination will require further decreasing the cost perceived for PrEP uptake, which involve reducing monetary and non-monetary barriers to PrEP uptake, such as difficulties in accessing PrEP, pill burden, tolerability of the molecules, social stigma and discrimination, and the acquisition of other sexually transmitted infections in case of dropping condom use [21–23]. Online tools [39], home-based programs [40], long-lasting injectable versions of PrEP [41], rather than daily or on-demand pills, allowing trained general practitioners to prescribe PrEP and interventions that increase awareness, motivations and behavioral skills about risk reduction [42] may also help reduce the perceived cost of PrEP and decrease the drop-out rate. If feasible, estimating the cost of PrEP relative to that of ART would make it possible to predict the resulting PrEP coverage, depending on the PrEP rollout. However, in practice, it may be very complex to estimate this cost, as it depends on many factors. Nevertheless, it is very important to note that estimating the cost is not strictly needed. Indeed, interventions which intuitively increase the accessibility and affordability of PrEP, may be proposed and thus contribute to reducing the cost, placing the PrEP rollout in the right direction. Then, the reduction in cost can be indirectly appreciated by monitoring the increase in PrEP coverage and the decrease in HIV incidence, which can serve as indicators for how far the PrEP rollout is from achieving elimination.

Moving toward epidemic elimination will also require reaching MSM who may not perceive themselves at high risk, and thus require a lower cost for adopting PrEP, in order to join the prevention effort. Recent studies found that high-risk individuals can underestimate their HIV risk [43] and there are many missed opportunities for PrEP uptake [44]. Specifically, in France, >90% of the recently infected individuals were eligible for PrEP [44]. Therefore, assessing and communicating individual-level risk for acquiring HIV remains a key objective for achieving elimination. Promoting a fair perception of HIV risk can be achieved through, not only advertising and marketing PrEP [45], but also through using electronic health records to identify high-risk MSM [46].

Importantly, if HIV is eliminated, interventions will be needed so individuals keep perceiving a low cost for PrEP and fair perception of HIV risk, to maintain a high PrEP coverage. Otherwise, HIV can reemerge and reach again an endemic state of concern for public health. The situation is similar to that of vaccination prevention, which requires continuous vaccine coverage even though the disease is declared to be eliminated [47].

Our study has some notable limitations. First, some of our modeling assumptions may be applicable only to the Parisian setting and other urban high-income settings. Second, we assumed that individuals act out of self-interest and do not cooperate to avoid getting infected by HIV. Modeling PrEP adoption through other theories of health behavior, considering for instance interactions between individuals [15], remains a subject to be studied in further work. Third, assuming full disclosure of HIV status in our sensitivity scenario may be unlikely. Also, we assumed that MSM are homogeneous regarding risk perception, while in reality, fair perception certainly co-exists with misperception. Fourth, we did not account for migration or travel [48], nor social or sex networks, due to lack of specific data, nor for condom drop among non-PrEP users [49], which could influence elimination efforts. Fifth, our estimates of the number of high-risk individuals, who should be on PrEP for HIV elimination, depend on the size of the MSM community, which is a metric difficult to estimate. Also, the number of high-risk MSM on PrEP currently reported, and hence the PrEP coverage, may represent an overestimate because establishing PrEP eligibility relies on self-reported behavior, which is difficult to appraise by practitioners.

Conclusion

Perception of the cost of PrEP and of HIV risk are two important levers to increase voluntary use of PrEP, reach coverage levels necessary to eliminate HIV, and maintain elimination in the context of less epidemic adversity. Current PrEP rollouts should aim at lowering the perceived cost of using PrEP and promoting a fair perception of the risk of acquiring HIV, to realize the full potential of PrEP prevention.

Authors' contributions

SJ, VS an RB conceived the model. SJ conducted the numerical simulations. All authors participated to the writing of the manuscript, analysis and interpretation of the results. All authors read and approved the final manuscript.

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List of abbreviations

ART: Antiretroviral treatment; MSM: Men who have sex with men; PrEP: Pre-exposure prophylaxis; CI: confidence interval.

References

1 Beyrer C, Baral SD, Collins C, Richardson ET, Sullivan PS, Sanchez J, *et al.* **The global response to HIV in men who have sex with men**. *Lancet (London, England)* 2016; **388**:198–206.

2 World Health Organization. Policy brief: WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP). World Heal. Organ. 2015. Available at: https://apps.who.int/iris/handle/10665/197906. [Website accessed on April 20, 2021]

3 Molina J-M, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, *et al.* **On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection.** *N Engl J Med* 2015; **373**:2237–2246.

4 McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, *et al.* **Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): Effectiveness results from the pilot phase of a pragmatic open-label randomised trial**. *Lancet* 2016; **387**:53–60.

5 Jenness SM, Goodreau SM, Rosenberg E, Beylerian EN, Hoover KW, Smith DK, *et al.* **Impact of the Centers for Disease Control's HIV Preexposure Prophylaxis Guidelines for Men Who Have Sex With Men in the United States.** *J Infect Dis* 2016; **214** :1800–1807.

6 Rozhnova G, Heijne J, Bezemer D, van Sighem A, Presanis A, De Angelis D, *et al.* **Elimination prospects of the Dutch HIV epidemic among men who have sex with men in the era of preexposure prophylaxis**. *Aids* 2018; **32**:2615–2623.

7 Scott N, Stoové M, Kelly SL, Wilson DP, Hellard ME. **Achieving 90-90-90 Human Immunodeficiency Virus (HIV) Targets Will Not Be Enough to Achieve the HIV Incidence Reduction Target in Australia**. *Clin Infect Dis* 2018; **66**:1019–1023.

8 Hansson D, Stromdahl S, Leung KY, Britton T. **Introducing pre-exposure prophylaxis to prevent HIV acquisition among men who have sex with men in Sweden: insights from a mathematical pair formation model**. *BMJ Open* 2020; **10**:e033852.

9 Cohen J. **Concern as HIV prevention strategy languishes**. *Science* 2018; **359**:1205.

10 PrEP Watch. Global PrEP Tracker. 2010. Available at: https://www.prepwatch.org/resource/global-prep-tracker/. [Website accessed on April 20, 2021].

11 Smith DK, Van Handel M, Wolitski RJ, Stryker JE, Hall HI, Prejean J, *et al.* **Vital signs: Estimated percentages and numbers of adults with indications for preexposure prophylaxis to prevent HIV acquisition - United States, 2015**. *Morb Mortal Wkly Rep* 2015; **64**:1291–1295.

12 Coy KC, Hazen RJ, Kirkham HS, Delpino A, Siegler AJ. **Persistence on HIV preexposure prophylaxis medication over a 2-year period among a national sample of 7148 PrEP users, United States, 2015 to 2017**. *J Int AIDS Soc* 2019; **22**:e25252.

13 Verelst F, Willem L, Beutels P. **Behavioural change models for infectious disease transmission: a systematic review (2010–2015)**. *J R Soc Interface* 2016; **13**:20160820.

14 Manfredi P, D'Onofrio A, editors. *Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases*. New York, NY: Springer New York; 2013.

15 Chang SL, Piraveenan M, Pattison P, Prokopenko M. **Game theoretic modelling of infectious disease dynamics and intervention methods: a review**. *J Biol Dyn* 2020; **14**:57–89.

16 Dabis F. Achieving 90-90-90 – Implications for HIV epidemic control. 10th IAS Conference on HIV Science. Mexico city, Mexico : July 2019. Avaiable at: http://programme.ias2019.org/Programme/Session/4 [Website accessed on April 20, 2021].

17 Jacquez JA, Simon CP, Koopman J, Sattenspiel L, Perry T. **Modeling and analyzing HIV transmission: the effect of contact patterns**. *Math Biosci* 1988; **92**:119–199.

18 van den Driessche P, Watmough J. **Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission**. *Math Biosci* 2002; **180**:29–48.

19 Bull L, Dimitrijevic P, Beverley S, Scarborough A, Mandalia S, Dosekun O, *et al.* **Perceived need of, and interest in, HIV pre-exposure prophylaxis amongst men who have sex with men attending three sexual health clinics in London, UK**. *Int J STD AIDS* 2018; **29**:435–442.

20 van Dijk M, de Wit JBF, Guadamuz TE, Martinez JE, Jonas KJ. **Slow uptake of PrEP: Behavioral predictors and the influence of price on PrEP uptake among MSM with a high interest in PrEP**. *AIDS Behav* 2021.

21 Gilson RI, Clutterbuck DJ, Chen ZE. **Demand for pre-exposure prophylaxis for HIV and the impact on clinical services: Scottish men who have sex with men perspectives**. *Int J STD AIDS* 2018; **29**:273–277.

22 Thomann M, Grosso A, Zapata R, Chiasson MA. **'WTF is PrEP?': attitudes towards pre-exposure prophylaxis among men who have sex with men and transgender women in New York City**. *Cult Health Sex* 2017; **20**:772–786.

23 Brooks RA, Nieto O, Landrian A, Donohoe TJ. **Persistent stigmatizing and negative perceptions of pre-exposure prophylaxis (PrEP) users: implications for PrEP adoption among Latino men who have sex with men**. *AIDS Care* 2019; **31**:427–435.

24 Marty L, Cazein F, Panjo H, Pillonel J, Costagliola D, Supervie V. **Revealing geographical and population heterogeneity in HIV incidence, undiagnosed HIV prevalence and time to diagnosis to improve prevention and care: estimates for France**. *J Int AIDS Soc* 2018; **21**:e25100.

25 Santé Publique France. Surveillance de l'infection à VIH (dépistage et déclaration obligatoire), 2010-2017. Availabe at: https://www.santepubliquefrance.fr/maladies-et-traumatismes/infections-sexuellement-transmissibles/vih-sida/documents/bulletin-national/bulletin-de-sante-publique-infection-a-vih.-mars-2019 [Website accessed on April 20, 2021].

26 CNS, ANRS. Prise en charge médicale des personnes vivant avec le VIH. 2018. Available at: https://cns.sante.fr/actualites/prise-en-charge-du-vih-recommandations-du-groupe-dexperts/ [Website accessed on April 20, 2021]

27 Smith DK, Herbst JH, Zhang X, Rose CE. **Condom Effectiveness for HIV Prevention by Consistency of Use Among Men Who Have Sex With Men in the United States**. *JAIDS J Acquir Immune Defic Syndr* 2015; **68**:337–344.

28 Holt M, Lea T, Mao L, Kolstee J, Zablotska I, Duck T, *et al.* **Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney, Australia: results of repeated behavioural surveillance in 2013-17**. *Lancet HIV* 2018; **3018**:1–9.

29 Kretzschmar ME, van der Loeff MF, Birrell PJ, De Angelis D, Coutinho RA. **Prospects of elimination of HIV with test-and-treat strategy**. *Proc Natl Acad Sci U S A* 2013; **110**:15538–15543.

30 WHO. Prevent HIV, test and treat all. 2016. Available at: https://www.who.int/hiv/pub/progressreports/2016-progress-report/en/ [Website accessed on April 20, 2021].

31 EPI-PHARE. Suivi de l'utilisation de Truvada® ou génériques pour une prophylaxie pré-exposition (PrEP) au

VIH à partir des données du Système National des Données de Santé (SNDS). 2019. Available at: https://www.epi-phare.fr/rapports-detudes-et-publications/suivi-de-lutilisation-de-truvada-ou-generiques-pour-une-prophylaxie-pre%E2%80%90exposition-prep-au-vih/ [Website accessed on April 20, 2021]

32 Costagliola D, Ghosn J, Spire B *et al.* **PrEP persistence and associated factors: an analysis from the ANRS Prevenir study**. *17th European AIDS Conference,* November 6–9, 2019, Basel. Abstract PS11/1.

33 Santé Publique France. Dépistage du VIH et découvertes de séropositivité VIH à Paris, données 2018. Available at: https://www.santepubliquefrance.fr/les-actualites/2019/depistage-du-vih-et-decouvertes-de-seropositivite-vih-a-paris-donnees-2018 [Website accessed on April 20, 2021]

34 Grulich AE, Guy R, Amin J, Jin F, Selvey C, Holden J, *et al.* **Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study**. *Lancet HIV* 2018; **3018**:1–9.

35 Kirby Institute. HIV diagnoses in Australia drop to lowest number in 18 years. Available at: https://kirby.unsw.edu.au/news/hiv-diagnoses-australia-drop-lowest-number-18-years [Website accessed on April 20, 2021]

36 Australasian Society for HIV VH and SHM (ASHM). HIV PrEP available on PBS in Australia from 1 April. 2018. Available at https://www.ashm.org.au/news/hiv-PrEP-available-announced-on-pbs/ [Website accessed on April 20, 2021].

37 San Francisco Department of Public Health. HIV Epidemiology Annual Report 2017. Available at: https://www.sfdph.org/dph/comupg/oprograms/HIVepiSec/HIVepiSecReports.asp [Website accessed on June 20, 2020].

38 Smith DK, Sullivan PS, Cadwell B, Waller LA, Siddiqi A, Mera-Giler R, *et al.* **Evidence of an Association of Increases in Pre-exposure Prophylaxis Coverage With Decreases in Human Immunodeficiency Virus Diagnosis Rates in the United States, 2012–2016**. *Clin Infect Dis* 2020; **71**: 3144-3151.

39 Getting to zero San Francisco. PrEP Committee. Available at: http://www.gettingtozerosf.org/prep-committee/ [Website accessed on April 20, 2021]

40 Siegler AJ, Mayer KH, Liu AY, Patel RR, Ahlschlager LM, Kraft CS, *et al.* **Developing and Assessing the Feasibility of a Home-based Preexposure Prophylaxis Monitoring and Support Program**. *Clin Infect Dis*

2019; **68**:501–504.

41 Marshall BDL, Goedel WC, King MRF, Singleton A, Durham DP, Chan PA, *et al.* **Potential effectiveness of long-acting injectable pre-exposure prophylaxis for HIV prevention in men who have sex with men: a modelling study**. *Lancet HIV* 2018; **3018**:1–8.

42 Dubov A, Altice FL, Fraenkel L. **An Information–Motivation–Behavioral Skills Model of PrEP Uptake**. *AIDS Behav* 2018; **22**:3603–3616.

43 Blumenthal J, Jain S, Mulvihill E, Sun S, Hanashiro M, Ellorin E, *et al.* **Perceived Versus Calculated HIV Risk**. *JAIDS J Acquir Immune Defic Syndr* 2019; **80**:e23–e29.

44 Lions C, Cabras O, Cotte L, Huleux T, Gagneux-Brugnon A, Makinson A, *et al.* **Missed opportunities of HIV pre-exposure prophylaxis in France: a retrospective analysis in the French DAT'AIDS cohort**. *BMC Infect Dis* 2019; **19**:278.

45 Amico KR, Bekker L. **Global PrEP roll-out : recommendations for programmatic success**. *Lancet HIV* 2019; **6**:e137–e140.

46 Marcus JL, Hurley LB, Krakower DS, Alexeeff S, Silverberg MJ, Volk JE. **Use of electronic health record data and machine learning to identify candidates for HIV pre-exposure prophylaxis: a modelling study**. *Lancet HIV* 2019; **3018**:1–8.

47 Jijón S, Supervie V, Breban R. **Prevention of treatable infectious diseases: A game-theoretic approach**. *Vaccine* 2017; **35**:5339–5345.

48 Palk L, Gerstoft J, Obel N, Blower S. **A modeling study of the Danish HIV epidemic in men who have sex with men: travel, pre-exposure prophylaxis and elimination**. *Sci Rep* 2018; **8**:16003.

49 Phanuphak N, Phanuphak P. **Time to focus more on condomless anal sex in non-PrEP users**. *Lancet HIV* 2018; **3018**:17–18.

Figures

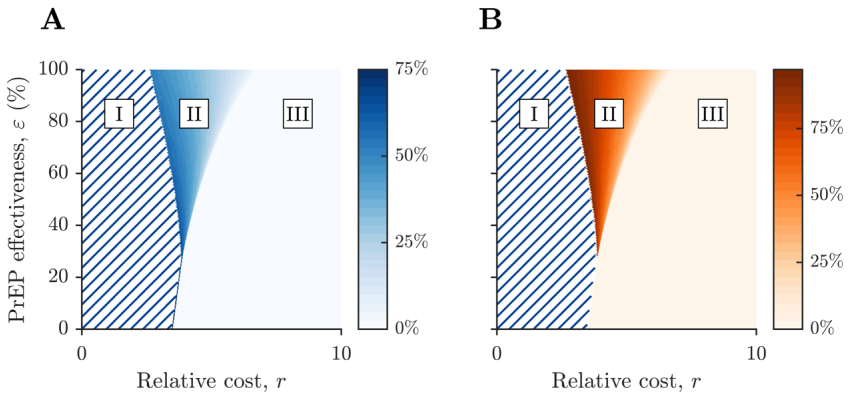

Figure 1. The voluntary PrEP coverage and its impact on HIV incidence, assuming fair risk perception

Color maps of **(A)** the voluntary PrEP coverage among high-risk men who have sex with men (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. The model outputs were obtained for one typical parameter set calibrating our model. Three regions were identified, depending on $\hat{p}$: Region III, where r is high and no MSM uses PrEP ($\hat{p} = 0\%$), so HIV incidence is not reduced; Region II, where some, but not enough MSM use PrEP, since r remains high, and thus the epidemic is controlled; and Region I (marked by blue stripes), where epidemic elimination is possible.

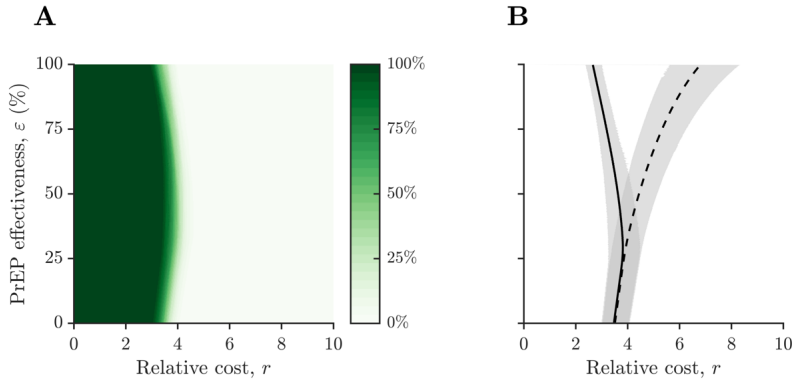

Figure 2. The probability of HIV elimination and boundary uncertainty for the three-region structure

(A) The probability of HIV epidemic elimination due to voluntary PrEP coverage, obtained from the ~500 calibrated parameter sets. **(B)** The boundaries (the mean is represented as a line and the 95% confidence interval as grey area) between Regions I and II (continuous line), and between Regions II and III (dashed line).

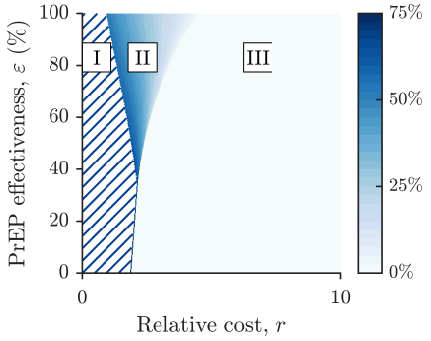

Figure 3. Sensitivity analyses for the baseline scenario

Decision-making based on misperceived risk of acquiring HIV can significantly reduce the size of Region I, where epidemic elimination is possible (blue stripes), despite high levels of PrEP effectiveness. Note that risk misperception also enlarges Region III, where no MSM is willing to adopt PrEP.

Supplementary Material

Can HIV epidemics among men who have sex with men be eliminated through participation in PrEP rollouts?

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Supplementary tables

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S1 Model description

We propose a hybrid mathematical model describing the interplay between the HIV epidemic among men who have sex with men (MSM), and individual-level decision-making on whether or not to adopt pre-exposure prophylaxis (PrEP) against HIV infection, in the current therapeutic context, where efficient antiretroviral treatment (ART) is available. We used a deterministic compartmental model to describe HIV transmission among MSM and a game-theoretical approach to model individual's decision-making about PrEP adoption.

S1.1 Modeling the population-level spread of an HIV epidemic

S1.1.1 Compartmental model without PrEP

We stratified the MSM population into two risk groups (low and high) to account for heterogeneity in sexual behaviors and risk of acquiring HIV;[1] we used the subscript $i \in \{h, \ell\}$ (h stands for high and ℓ stands for low) to denote these two populations. Furthermore, we assumed that individuals at high risk of infection drive the epidemic, and thus there would be no epidemic if all individuals would be at low risk of HIV infection.

The flow diagram of the HIV epidemic model is shown in figure S1. Uninfected MSM join the sexually-mixing population at a rate π_i. Susceptible individuals, S_i, get infected with HIV at a rate Λ_i, which represents the per-capita force of infection; see section S1.1.3 for the definition. Once infected, individuals enter the acute stage of infection and progress to the chronic stage of infection at a rate σ. We used the superscript $k \in \{a, c\}$ (a stands for acute and c stands for chronic) to distinguish between the stages of infection. Infected individuals, I_i^k, are diagnosed at a rate θ, in any stage of infection, and immediately start ART,[2] no longer transmitting HIV.[3] That is, $1/\theta$ is the expected time interval between infection and ART initiation, following HIV diagnosis, and only infected individuals unaware of their status transmit HIV. MSM on ART, T_i, remain stratified by risk group. Susceptible and undiagnosed MSM spend $1/\mu$ years selecting new sexual partners, while MSM on ART leave the sexually-mixing population at a higher rate, $\mu_T > \mu$.

The system of ordinary differential equations (ODE) for the HIV epidemic model is the following

$$\begin{aligned} dS_i/dt &= \pi_i - (\Lambda_i + \mu)\, S_i, \\ dI_i^a/dt &= \Lambda_i S_i - (\sigma + \theta + \mu)\, I_i^a, \\ dI_i^c/dt &= \sigma I_i^a - (\theta + \mu) I_i^c, \\ dT_i/dt &= \theta\, (I_i^a + I_i^c) - \mu_T T_i, \end{aligned} \tag{S1}$$

where $i \in \{h, \ell\}$. All the variables and parameters are positively defined. The total number of individuals in each risk group is $N_i = S_i + I_i^a + I_i^c + T_i$, and the total population is $N = \sum_i N_i$.

S1.1.2 Structured mixing

We consider that individuals do not mix uniformly random (i.e., according to the law of mass action), rather that most partnerships occur within the same risk group (i.e., non-random mixing).[1,4–6] We used ρ_{ij} to denote the probability for an i-risk individual to start a sexual partnership with an j-risk individual. The matrix

$$\rho = \begin{pmatrix} \rho_{hh} & \rho_{h\ell} \\ \rho_{\ell h} & \rho_{\ell\ell} \end{pmatrix} \tag{S2}$$

is called *mixing matrix*, and its elements verify $0 < \rho_{ij} < 1$ and $\sum_j \rho_{ij} = 1$. Since we assumed that individuals mix preferentially within the same risk group, we have $\rho_{ii} > 1/2$.

We further consider that i-risk individuals have c_i new sexual partners per year, and that the number of partners for high-risk individuals was higher than that for low-risk individuals ($c_h > c_\ell$). The total number of partnerships that i-risk individuals have with j-risk individuals per unit of time is given by $\rho_{ij} c_i N_i$. To balance the total number of partnerships,[1] we require $\rho_{ij} c_i N_i = \rho_{ji} c_j N_j$, which yields

$$\rho_{\ell h} = (1 - \rho_{hh}) \frac{c_h N_h}{c_\ell N_\ell}. \tag{S3}$$

Furthermore, $\rho_{ii} > 1/2$ yields

$$c_h < \frac{c_\ell N_\ell}{2(1 - \rho_{hh}) N_h}, \tag{S4}$$

which is an important constraint for the model calibration; see section S2. In simulations, we assumed that the elements of the mixing matrix remain constant, taking the values obtained through calibration.

S1.1.3 The force of infection

We use β_j^k to denote the per-partnership probability of HIV transmission from a j-risk infected individual in stage of infection k. We reasonably assume that individuals in the acute stage of infection are more likely to transmit HIV than individuals in the chronic stage,[7] and therefore set $\beta_j^a = w\beta_j^c$, with $w > 1$.

The rate at which i-risk susceptibles acquire HIV by forming sexual partnerships with infected individuals is called the *force of infection*[4] and is given by

$$\Lambda_i \equiv \sum_{\substack{j \in \{h,\ell\} \\ k \in \{a,c\}}} \frac{c_i \rho_{ij} \beta_j^k I_j^k}{N_j}. \tag{S5}$$

S1.2 Accounting for the uptake of PrEP

S1.2.1 Including PrEP epidemiology into the HIV epidemic model

We adapt the HIV epidemic model (S1) for the context where PrEP is available as an HIV prevention method. We suppose that only susceptible individuals having high risk of acquiring HIV are eligible to adopt PrEP. We

do not consider that individuals go on and off PrEP, rather that they rigorously follow the PrEP regimen for the entire duration of their sexually mixing period. This modeling choice is further discussed in section S1.3, as it matches other modeling choices for the decision-making game model for the adoption of PrEP. We use p and ε to denote, respectively, the PrEP coverage and the PrEP effectiveness. Of note, the PrEP coverage parameter is not imposed, rather, it is obtained by solving the decision-making model; see section S1.3.1. We assume that individuals on PrEP (P) can get infected at a rate $(1-\varepsilon)\Lambda_P$, defined in section S1.2.2, and get tested for HIV and start ART at a rate θ_P. The ODE system of the HIV epidemic model becomes

$$\begin{aligned}
dP/dt &= p\pi_h - \Big((1-\varepsilon)\Lambda_P + \mu\Big)P,\\
dS_h/dt &= (1-p)\pi_h - (\Lambda_h + \mu)\, S_h,\\
dS_\ell/dt &= \pi_\ell - (\Lambda_\ell + \mu)\, S_\ell,\\
dI_P^a/dt &= (1-\varepsilon)\Lambda_P P - (\sigma + \theta_P + \mu)\, I_P^a,\\
dI_h^a/dt &= \Lambda_h S_h - (\sigma + \theta + \mu)\, I_h^a,\\
dI_\ell^a/dt &= \Lambda_\ell S_\ell - (\sigma + \theta + \mu)\, I_\ell^a,\\
dI_P^c/dt &= \sigma I_P^a - (\theta_P + \mu)\, I_P^a,\\
dI_h^c/dt &= \sigma I_h^a - (\theta + \mu) I_h^c,\\
dI_\ell^c/dt &= \sigma I_\ell^a - (\theta + \mu) I_\ell^c,\\
dT_h/dt &= \theta_P\,(I_P^a + I_P^c) + \theta\,(I_h^a + I_h^c) - \mu_T T_h,\\
dT_\ell/dt &= \theta\,(I_\ell^a + I_\ell^c) - \mu_T T_\ell,
\end{aligned} \tag{S6}$$

illustrated by the flow diagram in figure S2. The ODE system (S6) has two equilibria: an endemic state (ES) where all the population compartments are non-empty, and a disease-free state (DFS) with no infected individuals

$$I_i^{k,\mathrm{DFS}} = 0, \quad T_i^{\mathrm{DFS}} = 0, \qquad \text{for all } i \in \{P, h, \ell\},\ k \in \{a, c\}, \tag{S7}$$

only uninfected individuals, whether or not on PrEP

$$P^{\mathrm{DFS}} \neq 0, \quad S_i^{\mathrm{DFS}} \neq 0, \qquad \text{for all } i \in \{h, \ell\}. \tag{S8}$$

We further assume that the per-partnership probability for acquiring HIV from an infected, high-risk MSM is the same, whether or not the MSM is taking PrEP. Hence, the force of infection for the population at i-risk of infection, not taking PrEP, becomes

$$\Lambda_i = c_i \left(\frac{\rho_{ih}\beta_h^a \big(I_P^a + I_h^a\big) + \rho_{ih}\beta_h^c \big(I_P^c + I_h^c\big)}{N_h} + \frac{\rho_{i\ell}\beta_\ell^a I_\ell^a + \rho_{i\ell}\beta_\ell^c I_\ell^c}{N_\ell} \right), \quad \text{for } i \in \{h, \ell\}, \tag{S9}$$

where

$$N_h = P + S_h + I_P^a + I_P^c + I_h^a + I_h^c + T_h, \tag{S10}$$

and

$$N_\ell = S_\ell + I_\ell^a + I_\ell^c + T_\ell. \tag{S11}$$

S1.2.2 PrEP-induced risk compensation

The PREVENIR study reported that MSM using PrEP may use condoms less often;[8] we call this the phenomenon *risk compensation*. We model risk compensation among susceptibles on PrEP explicitly, showing how the force of infection for high-risk susceptibles on PrEP depends on condom effectiveness and condom use among high-risk susceptibles.

We denote by β_{jh}^k the per-partnership probability of HIV transmission from a j-risk individual in k stage of infection toward high-risk susceptibles. This can be written as

$$\beta_{jh}^k \equiv \beta_{j0}^k(1 - \xi\eta_h) = \beta_j^k, \tag{S12}$$

where β_{j0}^k is the baseline (i.e., without condom) per-partnership probability, ξ denotes condom effectiveness and η_h is the probability of using condoms for high-risk susceptibles before the introduction of PrEP.

We assumed that, once PrEP becomes available, high-risk susceptibles, who do not adopt PrEP, continue to use condoms with probability η_h, while high-risk susceptibles who adopt PrEP use condoms with probability $\eta_P < \eta_h$; i.e., they are less likely to use condoms. We thus obtained that the per-partnership probability of HIV transmission to high-risk susceptibles on PrEP is given by $\beta_j^k(1 - \xi\eta_P)/(1 - \xi\eta_h)$. In sum, the force of infection on high-risk susceptibles taking PrEP is given by

$$(1 - \varepsilon)\Lambda_P = (1 - \varepsilon)\left(\frac{1 - \xi\eta_P}{1 - \xi\eta_h}\right)\Lambda_h. \tag{S13}$$

S1.2.3 The effective reproduction number

The *effective reproduction number* is defined as the expected number of secondary cases produced by a single infected individual, during his entire infectious period, in an uninfected population subject to control interventions.[9,10] We computed the effective reproduction number for the ODE system (S6), denoted R, as the largest

eigenvalue of the next generation matrix,[10] $G = FV^{-1}$, where

$$F \equiv \begin{pmatrix} (1-\varepsilon)p\phi\lambda^a_{hh} & (1-\varepsilon)p\phi\lambda^a_{hh} & (1-\varepsilon)p\phi\lambda^a_{\ell h}\pi_h/\pi_l & (1-\varepsilon)p\phi\lambda^c_{hh} & (1-\varepsilon)p\phi\lambda^c_{hh} & (1-\varepsilon)p\phi\lambda^c_{\ell h}\pi_h/\pi_l & 0 & 0 \\ (1-p)\lambda^a_{hh} & (1-p)\lambda^a_{hh} & (1-p)\lambda^a_{\ell h}\pi_h/\pi_l & (1-p)\lambda^c_{hh} & (1-p)\lambda^c_{hh} & (1-p)\lambda^c_{\ell h}\pi_h/\pi_l & 0 & 0 \\ \lambda^a_{h\ell}\pi_l/\pi_h & \lambda^a_{h\ell}\pi_l/\pi_h & \lambda^a_{\ell\ell} & \lambda^c_{h\ell}\pi_l/\pi_h & \lambda^c_{h\ell}\pi_l/\pi_h & \lambda^c_{\ell\ell} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \tag{S14}$$

$$\lambda^k_{ji} \equiv c_i\rho_{ij}\beta^k_j, \qquad \text{for } i,j \in \{h,\ell\}, k \in \{a,c\}, \tag{S15}$$

$$\phi \equiv \left(\frac{1-\xi\eta_P}{1-\xi\eta_h}\right), \tag{S16}$$

and

$$V \equiv \begin{pmatrix} \sigma+\theta_P+\mu & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma+\theta+\mu & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma+\theta+\mu & 0 & 0 & 0 & 0 & 0 \\ -\sigma & 0 & 0 & \theta_P+\mu & 0 & 0 & 0 & 0 \\ 0 & -\sigma & 0 & 0 & \theta+\mu & 0 & 0 & 0 \\ 0 & 0 & -\sigma & 0 & 0 & \theta+\mu & 0 & 0 \\ -\theta_P & -\theta & 0 & -\theta_P & -\theta & 0 & \mu_T & 0 \\ 0 & 0 & -\theta & 0 & 0 & -\theta & 0 & \mu_T \end{pmatrix}. \tag{S17}$$

We expressed R as a function of the PrEP coverage and effectiveness

$$R(p,\varepsilon) = A\left[H(p,\varepsilon) + M + \sqrt{\Big(H(p,\varepsilon) - M\Big)^2 + 4BH(p,\varepsilon)M}\right], \tag{S18}$$

where

$$A^{-1} \equiv 2(\theta+\mu)(\theta_P+\mu)(\sigma+\theta+\mu)(\sigma+\theta_P+\mu), \tag{S19}$$

$$B \equiv \left(\frac{1}{\rho_{hh}} - 1\right)\left(\frac{1}{\rho_{\ell\ell}} - 1\right), \tag{S20}$$

$$M \equiv (\theta_P+\mu)(\sigma+\theta_P+\mu)\Big[(\theta+\mu)c_\ell\rho_{\ell\ell}\beta^a_\ell + \sigma c_\ell\rho_{\ell\ell}\beta^c_\ell\Big], \tag{S21}$$

are independent of the PrEP parameters. In contrast, $H(p,\varepsilon)$ is the following function of p and ε

$$H(p,\varepsilon) \equiv (1-p)H_h + (1-\varepsilon)p\left(\frac{1-\xi\eta_P}{1-\xi\eta_h}\right)H_P, \tag{S22}$$

where

$$H_h \equiv (\theta_P + \mu)(\sigma + \theta_P + \mu)\Big[(\theta + \mu)c_h\rho_{hh}\beta_h^a + \sigma c_h\rho_{hh}\beta_h^c\Big], \tag{S23}$$

and

$$H_P \equiv (\theta + \mu)(\sigma + \theta + \mu)\Big[(\theta_P + \mu)c_h\rho_{hh}\beta_h^a + \sigma c_h\rho_{hh}\beta_h^c\Big], \tag{S24}$$

do not depend on PrEP parameters

We used the effective reproduction number to quantify the impact of PrEP on the HIV epidemic. We refer to the epidemic as being *controlled by PrEP* if the effective reproduction number after the introduction of PrEP is lower than that in the absence of PrEP; i.e., if $R(p,\varepsilon) < R(0,\varepsilon)$. A transcritical bifurcation occurs for the ODE system (S6) when $R(p,\varepsilon) = 1$.[4,10] If $R(p,\varepsilon) > 1$, then the endemic state will be reached; if $R(p,\varepsilon) < 1$ then the disease-free state will be reached. We say the epidemic among MSM is *eliminated by PrEP* if $R(p,\varepsilon) \leq 1$.

It is important to note that the introduction of PrEP does not lead unconditionally to control of the HIV epidemic, especially that the introduction of PrEP can cause less condom use. In the following of this manuscript, we determine the conditions for which PrEP prevention can induce control and elimination of the HIV epidemic.

The epidemic control threshold. For the epidemic to be controlled, certain conditions for PrEP uptake, HIV testing and condom use parameters must be satisfied. In particular, we found a threshold value for the PrEP effectiveness, denoted ε_{C}, ensuring $R(p,\varepsilon) < R(0,\varepsilon)$ if and only if $\varepsilon \geq \varepsilon_{\mathrm{C}}$, where

$$\varepsilon_{\mathrm{C}} \equiv 1 - \left(\frac{1-\xi\eta_h}{1-\xi\eta_P}\right)\left(\frac{H_h}{H_P}\right). \tag{S25}$$

The epidemic elimination threshold. In our model, epidemic elimination (i.e., $R(p,\varepsilon) \leq 1$) is possible if and only if the *effective PrEP coverage*, $\varphi(\varepsilon)\,p$, is equal to or larger than K, where

$$\varphi(\varepsilon) \equiv H_h - (1-\varepsilon)\left(\frac{1-\xi\eta_P}{1-\xi\eta_h}\right)H_P, \tag{S26}$$

and K is a constant independent of the PrEP parameters defined by

$$K \equiv H_h - \left(M - \frac{1}{2A}\right)\left(\frac{1}{2AM(1-B)-1}\right). \tag{S27}$$

The lowest value for the PrEP effectiveness allowing for the HIV epidemic elimination is obtained assuming full PrEP coverage: $R(p=1,\varepsilon) \leq 1$ if and only if $\varepsilon \geq \varepsilon_{\mathrm{E}}$, where

$$\varepsilon_{\mathrm{E}} \equiv 1 - \left(1 - \frac{K}{H_h}\right)(1-\varepsilon_{\mathrm{C}}). \tag{S28}$$

Hence, the epidemic elimination condition $R(p,\varepsilon) \leq 1$ is met when $\varphi(\varepsilon)\,p \geq K$, for $\varepsilon \geq \varepsilon_{\mathrm{E}}$ and $0 \leq p \leq 1$.

S1.3 Modeling individual-level decision-making on PrEP adoption

S1.3.1 Decision model

We propose a mathematical model for the individual-level decision-making on whether or not to adopt PrEP for HIV prevention. As mentioned in section S1.2.1, we assume that only uninfected individuals at high risk of infection are eligible to adopt PrEP.

We use a game-theoretical approach, where individuals act alone and in their own interest. We assume that high-risk MSM decide whether or not to adopt PrEP by weighing the pros and cons perceived for using PrEP, versus those of getting infected and consequently undergoing lifelong ART. These pros and cons consist of monetary and/or non-monetary aspects such as: undesired secondary effects, price, reimbursement policies, accessibility, quality of sex life, social stigma and discrimination, disease morbidity and other perceived consequences of being infected, etc.[11–14] These factors are expressed in our decision-making model as *costs* perceived by the individual and they are balanced in a *utility function*. Then, the individual-level decision-making on whether or not to adopt PrEP is modeled by the maximization of the utility, which is equivalent to the minimization of the total expected cost by the individual MSM.

The solution of the game model is an equilibrium situation for the HIV epidemiology, where a fraction of the individuals adopt PrEP in stationary epidemic conditions; i.e. there are no longer changes in prevention behavior. In the very long run, MSM commit to follow one of two simple patterns of PrEP use: either on-PrEP or off-PrEP. No other PrEP use patterns are under discussion. Individual MSM evaluate whether they should adopt PrEP, take and respect their own decisions. We therefore assume that, in the long term, the individuals are pleased with their decision regarding PrEP adoption, which they maintain for the duration of their sexually mixing period. That is, we do not model changes of decision and recurrent decision-making. As the utility of PrEP is maximized, PrEP use patterns would start to strongly resemble the on-PrEP and off-PrEP patterns. In addition, we consider no formal difference between on-PrEP regimens (daily or event-driven PrEP regimen).

S1.3.2 Utility of PrEP for the individual-level decision-making

An individual at high risk of infection can adopt one of the two mutually exclusive strategies: not to use PrEP, at a perceived cost $C_{\text{No-PrEP}} > 0$ or to use PrEP for HIV prevention, at a perceived cost $C_{\text{PrEP}} > 0$. For a probability p to adopt PrEP, the expected utility $U(p)$ for the individual is given by

$$U(p) = -p\,C_{\text{PrEP}} - (1-p)\,C_{\text{No-PrEP}} \equiv -C(p), \tag{S29}$$

where $C(p)$ stands for the total expected cost.

The cost of adopting the strategy of not using PrEP. In the case where an individual decides not to use PrEP, he may get infected, start treatment upon positive HIV diagnosis, and eventually pay the expected cost of being infected with HIV and use ART for the rest of his life. For the sake of simplicity, we say that an

individual who decides not to use PrEP pays, once he becomes HIV infected during his sexually-mixing period, the cost of ART. After leaving the sexually-mixing population, if infected with HIV, the individual continues to pay the cost of ART for the rest of his life. An individual who decides not to use PrEP and does not get infected with HIV pays no cost. Mathematically, the cost of adopting the strategy of not using PrEP can be written as

$$C_{\text{No-PrEP}}(p,\varepsilon) \equiv \int_0^L \left(1 - e^{-\lambda(p,\varepsilon)t}\right) c_T \, dt + \int_L^{L+L_T} \left(1 - e^{-\lambda(p,\varepsilon)L}\right) c_T \, dt, \tag{S30}$$

where c_T is the per-year perceived cost of ART, L is the number of years that an infected individual stays sexually mixing, L_T is the number of life years remaining after leaving the sexually-mixing population for individuals on ART, λ is the rate of getting infected with HIV; see section S1.3.3.

The cost of adopting the strategy of using PrEP to avoid HIV infection. Similarly, in the case where an individual decides to adopt PrEP, he would take and pay the cost of the PrEP regimen (including frequent testing) or, in the case of acquiring HIV despite PrEP uptake, would stop using PrEP and start ART upon HIV diagnosis, paying the cost of treatment for the rest of his life. For the sake of simplicity, we refer to the cost perceived for PrEP interventions as the cost of PrEP. This is summarized mathematically as follows

$$C_{\text{PrEP}}(p,\varepsilon) \equiv \int_0^L e^{-\lambda_P(p,\varepsilon)t} c_P \, dt + \int_0^L \left(1 - e^{-\lambda_P(p,\varepsilon)t}\right) c_T \, dt + \int_L^{L+L_T} \left(1 - e^{-\lambda_P(p,\varepsilon)L}\right) c_T \, dt, \tag{S31}$$

where c_P is the per-year perceived cost of PrEP and λ_P is the rate of getting infected with HIV despite taking PrEP; see section S1.3.3.

We introduce the *relative cost of prevention versus treatment* (i.e., PrEP versus ART), $r = c_P/c_T > 0$. Rescaling equations (S30) and (S31) by c_T and maintaining the notation (namely, keeping the symbols $C_{\text{No-PrEP}}$, C_{PrEP} and U for the rescaled quantities), we rewrite the utility function as follows:

$$U(p;\varepsilon,r) = -p\, C_{\text{PrEP}}(p;\varepsilon,r) - (1-p)\, C_{\text{No-PrEP}}(p;\varepsilon) \equiv -C(p;\varepsilon,r). \tag{S32}$$

The PrEP coverage that maximizes $U(p;\varepsilon,r)$ or, equivalently, minimizes the expected cost $C(p;\varepsilon,r)$ is interpreted as the probability of an MSM at high risk of infection to use PrEP, which yields the *voluntary PrEP coverage*, $\hat{p}(\varepsilon,r)$, as a function of PrEP effectiveness, ε, and the relative cost of PrEP versus ART, r.

S1.3.3 Risk of HIV infection perceived by high-risk individuals

In the baseline scenario, we assumed that individuals have a fair sense of their own risk to acquire HIV. Thus, in the absence of an HIV epidemic, individuals (whether or not on PrEP) acknowledge zero risk; that is,

$$\Lambda_h^{\mathrm{DFS}} = \Lambda_P^{\mathrm{DFS}} = 0. \tag{S33}$$

In the case of adopting the No-PrEP strategy, individuals acknowledge a risk of infection given by the force of infection for high-risk individuals not on PrEP, at the endemic state,

$$\Lambda_h^{\mathrm{ES}}(p,\varepsilon) = c_h \left(\frac{\rho_{ih}\beta_h^a \left(I_P^{a,\mathrm{ES}} + I_h^{a,\mathrm{ES}} \right) + \rho_{ih}\beta_h^c \left(I_P^{c,\mathrm{ES}} + I_h^{c,\mathrm{ES}} \right)}{N_h^{\mathrm{ES}}} + \frac{\rho_{i\ell}\beta_\ell^a I_\ell^{a,\mathrm{ES}} + \rho_{i\ell}\beta_\ell^c I_\ell^{c,\mathrm{ES}}}{N_\ell^{\mathrm{ES}}} \right), \tag{S34}$$

where the population variables $I_j^{k,\mathrm{ES}}$, for $j \in \{P,h,\ell\}$, $k \in \{a,c\}$ and N_j^{ES}, for $i \in \{h,\ell\}$ depend implicitly on p and ε. In the case of adopting PrEP, individuals acknowledge a risk of infection given by the force of infection for high-risk individuals on PrEP at the endemic state

$$(1-\varepsilon)\Lambda_P^{\mathrm{ES}}(p,\varepsilon) = (1-\varepsilon)\left(\frac{1-\xi\eta_P}{1-\xi\eta_h} \right) \Lambda_h^{\mathrm{ES}}(p,\varepsilon). \tag{S35}$$

Specifically, $\lambda(p,\varepsilon)$, the rate of HIV infection for individuals, who decide not to use PrEP, is given by

$$\lambda(p,\varepsilon) = \begin{cases} \Lambda_h^{\mathrm{ES}}(p,\varepsilon), & \text{if } R(p,\varepsilon) > 1, \\ \Lambda_h^{\mathrm{DFS}}, & \text{if } R(p,\varepsilon) \leq 1; \end{cases} \tag{S36}$$

while λ_P, the rate of becoming infected despite taking PrEP for individuals who decide to use PrEP (cf. equation (S31)), is given by

$$\lambda_P(p,\varepsilon) = \begin{cases} (1-\varepsilon)\Lambda_P^{\mathrm{ES}}(p,\varepsilon), & \text{if } R(p,\varepsilon) > 1, \\ \Lambda_P^{\mathrm{DFS}}, & \text{if } R(p,\varepsilon) \leq 1. \end{cases} \tag{S37}$$

The quantities $\lambda(p,\varepsilon)$ and $\lambda_P(p,\varepsilon)$ are used in the definitions of $C_{\mathrm{PrEP}}(p;\varepsilon,r)$ and $C_{\mathrm{No\text{-}PrEP}}(p;\varepsilon)$, the perceived costs for the strategies to adopt PrEP and not to adopt PrEP, respectively; see section S1.3.2.

S2 Model calibration

The hybrid model combining the ODE system and the decision model was built in MATLAB (release 2018). We first calibrated the model (S1) to reproduce the HIV epidemiology among MSM in the Paris region, Île-de-France, assumed to be close to an endemic state in 2016.[15] The initial values used for the HIV transmission parameters in the calibration process are listed in tables S1 and S2, respectively. As calibration criteria, we used estimates for MSM in Île-de-France, listed in table S3, regarding the HIV incidence rate, prevalence of undiagnosed infections,[16] prevalence of HIV,[17] size of the MSM population;[18,19] we used the HIV incidence estimated by the ANRS IPERGAY study in Paris[8] as an upper bound for the incidence among high-risk MSM. The epidemiological indicators were related to model simulations according to the formulae given in table S4.

Using the initial ranges (cf. tables S1 and S2), we generated 500 000 parameter sets through latin hypercube sampling, assuming that each parameter follows a uniform distribution. Out of these 500 000 parameter sets, 111 passed the calibration checks. Then, to refine the calibration, we generated additional 1 400 parameters sets, by sampling nearby the previously obtained parameter sets. In total, 505 parameter sets passed the calibration checks. Summary statistics for each HIV parameter yields a mean and a 95% confidence interval (CI); see table S2. Of note, the parameters sets yielding $R(0,0) > 1$ were constrained so high-risk MSM to drive the epidemic. Note that the model calibration selects $\beta_h^k > \beta_\ell^k$, which, indeed, suggests an intrinsically higher risk of HIV-transmission for individuals with high number of sexual partners.

Using our ~ 500 calibrated parameter sets, we estimated epidemiological indicators for the HIV epidemic in the MSM community of Île-de-France. They provide our modeling perspective on the HIV epidemiology before the introduction of PrEP (cf. table S3): overall yearly mean incidence was 1.3%, mean prevalence 17%, and 17% of MSM living with HIV were unaware of their HIV status. The mean number of MSM was $\sim 111\,000$, of which $\sim 14\,200$ were at high risk of HIV infection and eligible for PrEP. Yearly mean HIV incidence for high-risk MSM was 7%. We note, however, that our estimates for the HIV epidemiological indicators, resulting from the model calibration, do not differ much from the estimates obtained through direct data analyses (cf. table S3), indicative of successful calibration. The ~ 500 calibrated parameter sets were further used for simulations regarding the introduction of PrEP and the decision model.

S3 Supplementary results

S3.1 Impact of PrEP rollouts on HIV epidemics

In France, PrEP prescriptions need to be renewed every three months.[20] Meanwhile, the PrEP-eligible individual must provide proof that they tested negative for HIV infection. Consequently, on-PrEP MSM get tested for HIV every three months, which determines our parameter $1/\theta_P = 3$ months; see table S2. It is very important to note that testing frequency for on-PrEP MSM is thus much higher than that observed among off-PrEP MSM, as data shows ~ 3 years for the mean time from HIV infection to diagnosis (personal communication with VS). Due

to the dramatic change in testing behavior, the PrEP rollout can act as a test-and-treat intervention, where individuals get tested very often for HIV infection, and start treatment upon positive diagnostic, no longer transmitting HIV. In principle, this can be sufficient to eliminate the HIV epidemic, even without PrEP.[21,22]

The deterministic component of our HIV model (S6) can offer insight into the epidemic-level impact of a PrEP rollout, and the action of various parameters. Figure S3A depicts the effective reproduction number R versus ε and p, for one typical parameter set calibrating our model. According to our baseline scenario, we assumed that high-risk MSM, not taking PrEP, use condom with probability 30%, and if they take PrEP, the probability drops at 20%; condom effectiveness was considered to be 70%. The fact that a 70%–80% PrEP coverage is sufficient to eliminate HIV, even when PrEP efficacy is zero, is entirely due to the test-and-treat effect of the PrEP rollout, as explained before. In particular, this implies that the thresholds in PrEP effectiveness, such that epidemic control and elimination are possible, are zero; i.e., $\varepsilon_{\mathrm{E}} = \varepsilon_{\mathrm{C}} = 0$. The test-and-treat action of the PrEP rollout is further evidenced in figure S3B, which represents R as a function of the PrEP coverage p and testing rate θ_P, assuming that the effectiveness of PrEP is zero ($\varepsilon = 0$); that is, there is no PrEP and p is the coverage of frequent testing, with the rate θ_P. Figure S3B reveals that, for HIV elimination in the absence of PrEP (i.e., or using a PrEP regimen with no efficacy), it would suffice that $\sim 80\%$ of the high-risk MSM in the Paris region got tested every three months; see figure S3 for $p = 80\%$ and $\theta_P = 4$ years^{-1}. Still, an intervention based just on the test-and-treat strategy may be difficult to implement. The individual at risk is not directly protected from acquiring HIV, by joining a test-and-treat program. Rather, the benefits are indirect, emerging from the success of the test-and-treat intervention at the population level. It is thus expected that test-and-treat interventions have low acceptability. The French guidelines recommend, since 2009, annual HIV testing for MSM at risk, and 3-month testing since 2017. Yet, as mentioned above, testing rate estimates are estimated significantly lower (~ 3 years).

The distinct advantage of PrEP rollouts is that they offer direct protection to individuals at risk of acquiring HIV, through highly effective PrEP regimens. Hence, the individual recognizes his interest in adopting PrEP, and may join the PrEP rollout voluntarily, ensuring high acceptability for PrEP rollouts. Furthermore, as more and more individuals join the prevention effort, population-level benefits emerge, down to HIV elimination.

S3.2 Adoption of PrEP under the baseline scenario

In the baseline scenario, we assumed that individuals have a fair sense of their risk of infection and condom use drops from 30% to 20% when individuals adopt PrEP.[23] The risk of HIV infection is computed using the HIV transmission model, and corresponds to the force of HIV infection (cf. section S1.3.3). In addition, we considered that on-PrEP MSM follow the recommendations of the regimen, which requires 3-month testing to renew their PrEP prescription.[23] Therefore, MSM on PrEP are advised to test much more frequently than what is the current practice of MSM not taking PrEP; i.e., $\theta_P \ll \theta$ and the PrEP rollout can share the action of a test-and-treat intervention. We found that, in this case, the thresholds in PrEP effectiveness, such that

epidemic control and elimination are possible, are zero; i.e., $\varepsilon_{\mathrm{E}} = \varepsilon_{\mathrm{C}} = 0$.

S3.2.1 Voluntary PrEP coverage

We computed the voluntary PrEP coverage among high-risk MSM, denoted $\hat{p}$, for one typical parameter set calibrating our model; see table S2. The PrEP coverage starts at zero, before the introduction of PrEP, and then reaches an optimal value where the expected cost of adopting PrEP is minimum. The final value reached by $\hat{p}$ depends on HIV epidemic parameters before the introduction of PrEP, that were found by calibration, PrEP effectiveness, ε, and perceived relative cost of PrEP versus ART, r, which were varied over broad ranges.

Our previous work[24] helped identify the conditions for which our model algorithms could be reliably implemented. Indeed, if $R(\hat{p}, \varepsilon) \leq 1$, then there is no stable equilibrium for the individual strategies and numerical methods fail to compute an approximation for the voluntary PrEP coverage, $\hat{p}(\varepsilon, r)$; otherwise, numerical estimation of $\hat{p}(\varepsilon, r)$ is possible. We say that, for $R(\hat{p}, \varepsilon) \leq 1$, the game regarding the adoption of PrEP has no solution.

As a supplement to the colormaps in figure 1 of the main text, figure S4 depicts the PrEP coverage reached voluntarily among high-risk MSM, $\hat{p}(\varepsilon, r)$, and the corresponding endemic force of infection among high-risk MSM when the PrEP effectiveness is $\varepsilon = 86\%$; n.b., $\hat{\Lambda}_h^{\mathrm{ES}}(\varepsilon, r) \equiv \Lambda_h^{\mathrm{ES}}\left(\hat{p}(\varepsilon, r), \varepsilon\right)$. For a given value of the PrEP effectiveness, ε, we used $r_{\mathrm{E}}(\varepsilon)$ and $r_{\mathrm{C}}(\varepsilon)$ to denote, respectively, the elimination and control threshold values for the relative cost; n.b., $0 < r_{\mathrm{E}}(\varepsilon) < r < r_{\mathrm{C}}(\varepsilon)$ implies $0\% < \hat{p}(\varepsilon, r) < 100\%$. The three regions identified in figure 1 of the main text are also present in figure S4, delimited by the thresholds in PrEP effectiveness and relative cost (n.b., $\varepsilon = 86\%$ for figure S4):

- Region III, where $r \geq r_{\mathrm{C}}(\varepsilon)$. The relative cost of prevention versus treatment is perceived as being too high. Therefore, no one adopts the strategy of using PrEP to prevent HIV infection (i.e., $\hat{p}(\varepsilon, r) = 0\%$) and the endemic state of the epidemic stays unaffected (i.e., $\hat{\Lambda}_h^{\mathrm{ES}}(\varepsilon, r) = \Lambda_h^{\mathrm{ES}}(0, 0)$).

- Region II, where $r_{\mathrm{E}}(\varepsilon) < r < r_{\mathrm{C}}(\varepsilon)$. The relative cost is low enough, so a proportion of high-risk MSM adopts the strategy of using PrEP (i.e., $0\% < \hat{p}(\varepsilon, r) < 100\%$). However, not enough MSM adopt PrEP and thus, the *effective, voluntary PrEP coverage*, $\varphi(\varepsilon)\,\hat{p}(\varepsilon, r)$, is below the threshold K. Hence, the HIV epidemic is controlled (i.e., $\hat{\Lambda}_h^{\mathrm{ES}}(\varepsilon, r) < \Lambda_h^{\mathrm{ES}}(0, 0)$), but not eliminated.

- Region I, where $0 \leq r \leq r_{\mathrm{E}}(\varepsilon)$. The relative cost is low, and the PrEP effectiveness is above the elimination threshold, thus the effective, voluntary PrEP coverage, $\varphi(\varepsilon)\,\hat{p}(\varepsilon, r)$, may reach or exceed the threshold K, so the epidemic may be averted. Hence, in Region I, the reproduction number is below 1 (i.e., $R\left(\hat{p}(\varepsilon, r), \varepsilon\right) \leq 1$).

S3.2.2 Relative reduction in HIV incidence rate

The endemic HIV incidence rate reached after the introduction of PrEP (cf. model (S6)) is given by

$$\mathcal{I}^{\mathrm{ES}}(p,\varepsilon) \equiv \frac{(1-\varepsilon)\left(\frac{1-\xi\eta_P}{1-\xi\eta_h}\right)\Lambda_h^{\mathrm{ES}}P^{\mathrm{ES}} + \Lambda_h^{\mathrm{ES}}S_h^{\mathrm{ES}} + \Lambda_\ell^{\mathrm{ES}}S_\ell^{\mathrm{ES}}}{P^{\mathrm{ES}} + S_h^{\mathrm{ES}} + S_\ell^{\mathrm{ES}}}. \tag{S38}$$

The endemic incidence rate in the absence of PrEP is $\mathcal{I}^{\mathrm{ES}}(0,0) = 1.3\%$. Figure 1B of the main text depicts the relative reduction in the endemic HIV incidence rate due to voluntary PrEP coverage, $1-\left[\mathcal{I}^{\mathrm{ES}}(\hat{p}(\varepsilon,r),r)/\mathcal{I}^{\mathrm{ES}}(0,0)\right]$.

Note that increasing PrEP effectiveness and reducing PrEP cost results in greater reduction of the endemic incidence rate, provided that the condition for epidemic control regarding PrEP effectiveness is met; i.e., $\varepsilon > \varepsilon_{\mathrm{C}}$.

S3.3 Sensitivity analyses

S3.3.1 Risk misperception

In the baseline scenario, we assumed that high-risk MSM have a fair sense of their risk of infection when deciding whether or not to adopt PrEP; this risk of infection was computed using the HIV transmission model, and corresponds to the force of HIV infection; see section S1.3.3. However, individuals could misperceive their risk of acquiring infection.[25] In a sensitivity scenario, we assumed that individuals underestimate their risk of infection when deciding whether or not to adopt PrEP. Specifically, we assumed that high-risk MSM get a sense of the risk of infection from, for instance, the rate of their high-risk MSM peers being diagnosed with HIV each year, given by

$$\tilde{\Lambda}(p,\varepsilon) \equiv \frac{\theta_P\left(I_P^{a,\mathrm{ES}} + I_P^{c,\mathrm{ES}}\right) + \theta\left(I_h^{a,\mathrm{ES}} + I_h^{c,\mathrm{ES}}\right)}{P^{\mathrm{ES}} + S_h^{\mathrm{ES}} + I_P^{a,\mathrm{ES}} + I_P^{c,\mathrm{ES}} + I_h^{a,\mathrm{ES}} + I_h^{c,\mathrm{ES}}}, \tag{S39}$$

assuming that all HIV-infected MSM disclose their serostatus.

We repeated our analyses using $\tilde{\Lambda}$ in equations (S35)–(S37) instead of Λ_h^{ES} and compared the results with those of the baseline scenario; see figure 3 of the main text. The HIV epidemiological picture regarding voluntary PrEP coverage is qualitatively similar. That is, we recover the 3-region structure and the voluntary PrEP coverage required for HIV elimination is the same. Still, the misperception of infection risk leaves less room for intervention aiming at epidemic elimination: Region I gets significantly reduced along the relative cost axis (r), compared with the baseline scenario using the force of infection for the perceived risk; see figure 3 of the main text. In particular, for a PrEP effectiveness of 86%, the cost of PrEP relative to that of ART should be lowered by a factor of ~ 2 relative to the baseline scenario, in order to reach Region I.

S3.3.2 Condom use and risk compensation

In the baseline scenario, we assumed that there is a drop in condom use among PrEP users from $\eta_h = 30\%$ to $\eta_P = 20\%$. In a worse-case scenario for condom drop (i.e., a sensitivity scenario), we considered that individuals on PrEP stop using condoms completely (i.e., $\eta_P = 0\%$) and, redoing the analyses, we compared the results

with those of the baseline scenario; see figure S5. Risk compensation among PrEP users has low impact on our results: (1) the boundary between Regions II and III shifts only slightly, and (2) only slightly higher levels of PrEP coverage are required for epidemic elimination when PrEP users completely drop condom use.

S4 Supplementary tables

Table S1: Initial values for several epidemiological indicators about the MSM population in the Paris region.

Epidemiological indicator	Value/range	[Ref.]
Total population	83 000–167 000	[18, 19]
HIV prevalence (%)	10–30	[17]
Fraction of susceptible individuals among high-risk MSM (%)	5–50	–
Fraction of HIV-infected individuals among high-risk MSM (%)	70–90	–
Fraction of individuals in chronic stage among infected MSM (%)	80	–
Fraction of individuals on treatment among infected MSM (%)	80	–

Table S2: Definition, initial value and calibrated values for the model parameters
The fourth column presents initial ranges/values used for the parameters; these ranges/values were either based on published estimates or assumed. The third column presents the mean and 95% confidence interval (CI) for the parameters values obtained through the model calibration.

Param.	Description	Calibrated value Mean (CI 95%)	Initial value/range	[Ref.]
π_i	Inflow into the population at i risk of infection[a]	–	–	–
c_h	Per-year number of partners for high-risk individuals[b]	7.4 (6.2–9.0)	1–20	[26, 27]
c_ℓ	Per-year number of partners for low-risk individuals	0.7 (0.6–0.9)	0–1	[26]
ρ_{hh}	Fraction of partnerships formed between individuals within the same risk group (%)	95 (92–97)	50–100	–
β_h^a	Per-partnership probability of HIV transmission from high-risk undiagnosed MSM, during the acute stage of infection (%)	71 (58–87)	0–100	–
β_l^a	Per-partnership probability of HIV transmission from low-risk undiagnosed MSM, during the acute stage of infection (%)	40 (16–64)	0–100	–
β_h^c	Per-partnership probability of HIV transmission from high-risk undiagnosed MSM, during the chronic stage of infection (%)	8 (7–9)	0–100	–
β_l^c	Per-partnership probability of HIV transmission from low-risk undiagnosed MSM, during the chronic stage of infection (%)	4 (2–7)	0–100	–
w	Ratio between acute and chronic stage infectivity	9.1 (8.4–9.6)	8–12	[7]
$1/\sigma$	Time spent in acute stage of infection (weeks[c])	8.2 (6.7–9.8)	6–12	[28]
$1/\theta$	Time between infection and ART initiation following diagnosis (baseline scenario; years)	3.1 (2.7–3.5)	1–4	[2, 16]
$1/\theta_P$	Time between infection and ART initiation following diagnosis for on-PrEP individuals (baseline scenario; months)	3	–	[29]
$1/\mu$	Time that individuals look for new partners (years)	30.6 (27.2–33.7)	25–50	[26]
α	Reduction in the time individuals look for new partners, once diagnosed with HIV	0.48 (0.41–0.54)	0–1	–
$1/\mu_T$	Time that individuals diagnosed with HIV look for new partners[d]	14.7 (11.2–18.2)	–	–
ξ	Condom effectiveness (%)	–	58–80	[30]
η_h	Probability of using condoms for high-risk MSM not on PrEP (baseline scenario; %)	–	30	[23]
η_P	Probability of using condoms for high-risk MSM not on PrEP (baseline scenario; %)	–	20	[8]
L_E	Life expectancy (years)	–	79.5	[31, 32]
L_{SA}	Age at which individuals start sexual activity	–	15	[26]
L	Time spent in the sexually-mixing population for individuals on treatment	–	$1/\mu_T$	–
L_T	Number of life years remaining after leaving the sexually-mixing population	–	$L_E - L - L_{SA}$	–

[a]Computed using the formula μN_i^{DFS}, where N_i^{DFS} is the number of i-risk MSM at the disease-free state (DFS).
[b]Subject to condition (S4).
[c]We approximated 1 year by 52 weeks.
[d]Can be estimated as α/μ.

Table S3: Calibration to the HIV epidemiology for MSM in the Paris region
The epidemiological indicators used for the model calibration are indicated by star (*). Other indicators are shown for additional information. The third column presents recently published estimates for the epidemiological indicators. The second column presents the mean and 95% confidence interval (CI) for these indicators, obtained through the model calibration.

Epidemiological indicator	**Calibrated estimates Mean (CI 95%)**	**Published estimates Mean (CI 95%)**	**[Ref.]**
HIV incidence rate* (%)	1.3 (1.0–1.6)	2.0 (1.0–2.6)	[16]
Per-year number of new HIV infections	1 200 (900–1 500)	1 100 (900–1 400)	[16]
HIV incidence rate among high-risk MSM* (%)	7 (4–10)	9.2	[8]
Prevalence of HIV* (%)	17 (14–20)	16 (12–20)	[17]
Proportion of undiagnosed HIV infections* (%)	17 (15–20)	18 (15–20)	[16]
Per-year number of new HIV diagnoses	1 100 (800–1 400)	1 000 (900–1 100)	[16]
Number of infected, undiagnosed MSM	3 200 (2 000–4 200)	3 400 (3 000–3 800)	[16]
Total population*	111 000 (94 000–130 000)	118 000 (83 000–167 000)	[18, 19]
Individuals eligible for PrEP[a]	14 200 (9 200–23 000)	–	–
High-risk MSM among susceptibles (%)	15 (11–23)	–	–

[a]High-risk, susceptible MSM.

Table S4: Epidemiological indicators for the HIV transmission model at the endemic state
Subscript $i \in \{h, \ell\}$ stands for the risk group (high, low) and superscript $k \in \{a, c\}$ stands for the stage of infection (acute, chronic). Superscript ES stands for endemic state.

Epidemiological indicator	**Definition**	**Formula**
Endemic HIV incidence rate	Per-year number of new infections among individuals at risk of HIV infection	$\sum_i \Lambda_i S_i^{\mathrm{ES}} \Big/ \sum_i S_i^{\mathrm{ES}}$
Endemic proportion of undiagnosed HIV infections	Fraction of infected individuals who are unaware of their infection	$\sum_{i,k} I_i^{k,\mathrm{ES}} \Big/ \left(\sum_{i,k} I_i^{k,\mathrm{ES}} + \sum_i T_i^{\mathrm{ES}}\right)$
Endemic prevalence of HIV	Fraction of the population who is infected with HIV	$\left(\sum_{i,k} I_i^{k,\mathrm{ES}} + \sum_i T_i^{\mathrm{ES}}\right) \Big/ N^{\mathrm{ES}}$

S5 Supplementary figures

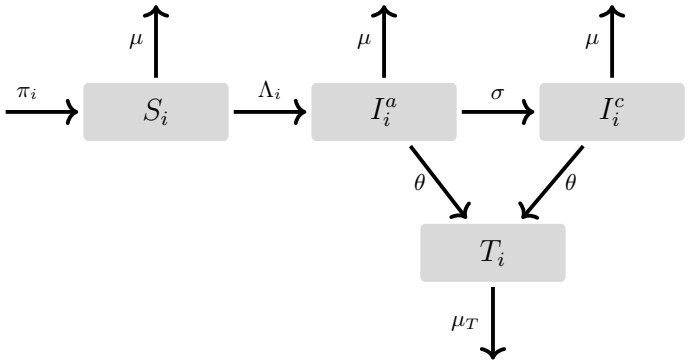

Figure S1: Flow diagram for the compartmental model of HIV transmission among MSM, when PrEP is not available as a prevention method
Sexually mixing MSM are stratified in two disjoint categories according to their risk group ($i \in \{h, \ell\}$, standing for high and low, respectively). Uninfected MSM join the i-risk-group population at a rate π_i and spend $1/\mu$ years selecting new sexual partners. Susceptible individuals, S_i, get infected with HIV at a rate Λ_i. Individuals I_i^k, where $k \in \{a, c\}$, with a standing for acute and c standing for chronic stage of infection, are infected and unaware of their infection. The progression from the acute stage of infection to the chronic stage of infection occurs at a rate σ. Infectious individuals are diagnosed at a rate θ at any stage of their infection and get immediately treated with antiretroviral therapy. Treated individuals, T_i, leave the sexually mixing population at a rate μ_T.

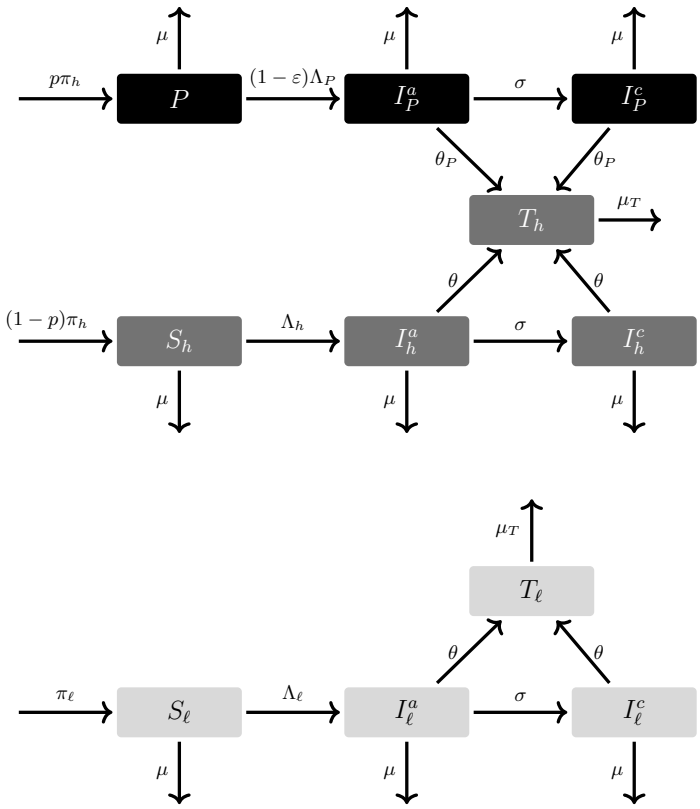

Figure S2: Flow diagram for the compartmental model of HIV transmission among MSM, when PrEP is available as a prevention method

Dark (respectively light) gray compartments depict individuals with high (respectively low) risk of HIV infection. Only uninfected individuals at high risk of infection are eligible to adopt PrEP (P). PrEP users are depicted by black compartments. PrEP coverage and PrEP effectiveness are denoted by p and ε, respectively. The HIV testing rate for on-PrEP MSM is denoted by θ_P. Individuals on PrEP get infected at a rate $(1-\varepsilon)\Lambda_P$.

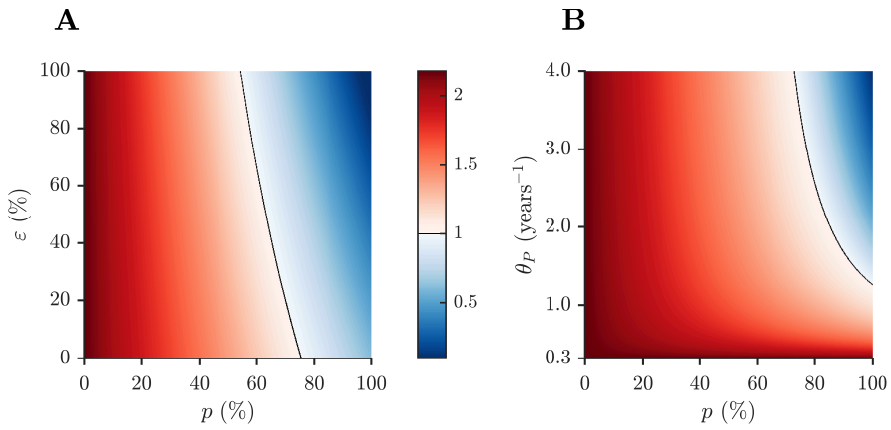

Figure S3: The effective reproduction number R as a function of the PrEP parameters
Color maps of the effective reproduction number, R, obtained for a typical parameter set calibrating our model, under the baseline scenario; i.e., high-risk MSM not on PrEP use condom with probability 30%, and if they get on PrEP, the probability drops at 20%; condom effectiveness is 70%. $R > 1$ (i.e., epidemic persistence) is shown in red shades and $R < 1$ (i.e., epidemic elimination) is shown in blue shades. The solid black line depicts $R = 1$. **A.** The effective reproduction number R versus the PrEP coverage, p, and PrEP effectiveness, ε. **B.** The effective reproduction number R versus the PrEP coverage, p, and the HIV testing rate while taking PrEP, θ_P, assuming that the PrEP effectiveness is zero (i.e., $\varepsilon = 0$). Note that HIV elimination is possible even when $\varepsilon = 0$. This intervention is equivalent to assuming that there is no PrEP, but a fraction p of the high-risk MSM get tested more frequently that the others, at a rate θ_P.

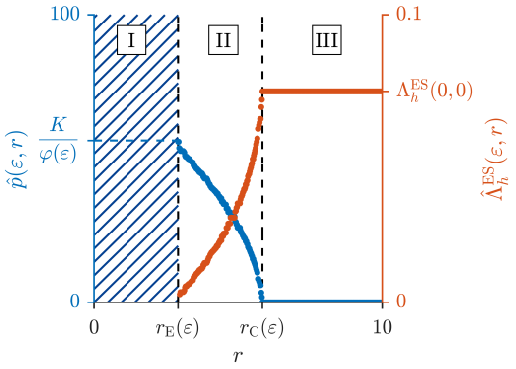

Figure S4: Impact of rollout with voluntary PrEP uptake, function of the relative cost of PrEP versus ART, when the PrEP effectiveness is 86%
We illustrate the PrEP coverage (%) reached voluntarily by high-risk MSM (left axis) and the endemic force of infection on high-risk MSM reached through voluntary PrEP use (right axis), assuming the PrEP effectiveness is $\varepsilon = 86\%$. We assumed that (i) high-risk MSM not on PrEP use condoms with 30% probability, and when they get on PrEP, the probability drops at 20%; (ii) condom effectiveness is 70%; and (iii) MSM have a fair perception of the risk of HIV infection; i.e., assumptions of the baseline scenario. The three regions correspond to the three regions identified in figure 1 of the main text. In Region III, no MSM adopts the strategy of using PrEP (i.e., $\hat{p}(\varepsilon, r) = 0$) due to high perceived cost of PrEP (i.e., $r \geq r_{\mathrm{C}}(\varepsilon)$; r_{C} denotes the threshold cost for epidemic control). Hence, in Region III, there is no impact on the course of the epidemic: the endemic force of infection among high-risk MSM remains unchanged after the introduction of PrEP; i.e., $\hat{\Lambda}_h^{\mathrm{ES}}(\varepsilon, r) = \Lambda_h^{\mathrm{ES}}(0,0) = 0.07$, where $\Lambda_h^{\mathrm{ES}}(0,0)$ is the endemic incidence rate for high-risk MSM in the absence of PrEP. In Region II, a proportion of the population decides to use PrEP (i.e., $0 < \hat{p}(\varepsilon, r) < 100\%$) at the given cost, but the PrEP coverage is not enough for epidemic elimination. Hence, the epidemic is controlled and there is a reduction in the endemic incidence. Region I, the striped area, corresponds to the case where $R\left(\hat{p}(\varepsilon, r), \varepsilon\right) \leq 1$. In Region I, the relative cost is low (i.e., $0 \leq r \leq r_{\mathrm{E}}(\varepsilon)$), so high levels of PrEP coverage — and thus, high levels of effective PrEP coverage (i.e., $\hat{p}(\varepsilon, r)\, \varphi(\varepsilon) \geq K$) — are reached, and the epidemic may be averted; i.e., the endemic force of infection can be 0. In particular, for a PrEP effectiveness of $\varepsilon = 86\%$, the minimum PrEP coverage $\hat{p}(\varepsilon, r)$ to reach Region I is $K/\varphi(\varepsilon) = 56\%$.

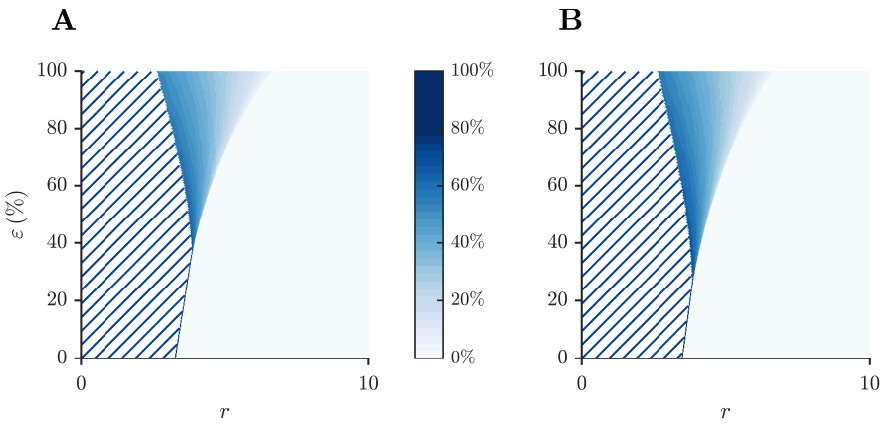

Figure S5: Impact of risk compensation on the voluntary PrEP coverage
The voluntary PrEP coverage obtained for a typical parameter set calibrating our model, **A.** assuming a complete drop in condom use among PrEP users and **B.** under the baseline scenario, where condom use drops from 30% to 20% among PrEP users.

S6 References

[1] Jacquez JA, Simon CP, Koopman J. Structured mixing: Heterogeneous Mixing by the Definition of Activity Groups. In: *Mathematical and statistical approaches to AIDS epidemiology*, 301–305. New York: Springer-Verlag New York 1989; .

[2] Dabis F. Achieving 90-90-90 – Implications for HIV epidemic control. *10th IAS Conference on HIV Science*. Mexico city, Mexico : July 2019. Available at: http://programme.ias2019.org/Programme/Session/4 [Website accessed on April 20th, 2021].

[3] Rodger AJ, Cambiano V, Bruun T, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA* 2016; **316**(2): 171–181. doi:10.1001/jama.2016.5148.

[4] Jacquez JA, Simon CP, Koopman J, Sattenspiel L, Perry T. Modeling and analyzing HIV transmission: the effect of contact patterns. *Mathematical Biosciences* 1988; **92**(2): 119–199. doi:10.1016/0025-5564(88)90031-4.

[5] Koopman J, Simon CP, Jacquez JA, Joseph J, Sattenspiel L, Park T. Sexual partner selectiveness effects on homosexual HIV transmission. *Journal of Acquired Inmune Deficiency Syndromes* 1988; **1**: 486–504.

[6] Gupta S, Anderson RM, May RM. Networks of sexual contacts: implications for the pattern of spread of HIV. *AIDS* 1989; **3**(12): 807–817. doi:10.1097/00002030-198912000-00005.

[7] Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk. *AIDS* 2014; **28**(10): 1509–1519. doi:10.1097/QAD.0000000000000298.

[8] Molina JM, Ghosn J, Béniguel L, et al. Incidence of HIV-infection in the ANRS Prevenir study in the Paris region with daily or on demand PrEP with TDF/FTC. *22nd International AIDS Conference*, Amsterdam, Netherlands, July 23–27, 2018.

[9] Anderson RM, May RM. Infectious diseases of humans: dynamics and control. *Oxford University Press* 1991; 757.

[10] van den Driessche P, Watmough J. Further notes on the basic reproduction number. In: Brauer F, van den Driessche P, Wu J, eds. *Mathematical Epidemiology*, Vol. 1945 of *Lecture Notes in Mathematics*, 159–178. Berlin, Heidelberg: Springer Berlin Heidelberg 2008; doi:10.1007/978-3-540-78911-6.

[11] Arnold EA, Steward WT. HIV transmission in MSM: considerations for PrEP scale-up. *The Lancet HIV* 2016; **3018**(15): 9–10. doi:10.1016/S2352-3018(15)00060-0.

[12] Gilson RI, Clutterbuck DJ, Chen ZE. Demand for pre-exposure prophylaxis for HIV and the impact on clinical services: Scottish men who have sex with men perspectives. *International Journal of STD & AIDS* 2018; **29**(3): 273–277. doi:10.1177/0956462417723817.

[13] Thomann M, Grosso A, Zapata R, Chiasson MA. 'WTF is PrEP?': attitudes towards pre-exposure prophylaxis among men who have sex with men and transgender women in New York City. *Culture, Health and Sexuality* 2017; **20**(7): 772–786. doi:10.1080/13691058.2017.1380230.

[14] Brooks RA, Nieto O, Landrian A, Donohoe TJ. Persistent stigmatizing and negative perceptions of pre-exposure prophylaxis (PrEP) users: implications for PrEP adoption among Latino men who have sex with men. *AIDS Care - Psychological and Socio-Medical Aspects of AIDS/HIV* 2019; **31**(4): 427–435. doi:10.1080/09540121.2018.1499864.

[15] Santé Publique France. 2019. Surveillance de l'infection à VIH (dépistage et déclaration obligatoire), 2010-2017. Available at: https://www.santepubliquefrance.fr/maladies-et-traumatismes/infections-sexuellement-transmissibles/vih-sida/documents/bulletin-national/bulletin-de-sante-publique-infection-a-vih.-mars-2019 [Website accessed on April 20, 2021].

[16] Marty L, Cazein F, Panjo H, Pillonel J, Costagliola D, Supervie V. Revealing geographical and population heterogeneity in HIV incidence, undiagnosed HIV prevalence and time to diagnosis to improve prevention and care: estimates for France. *Journal of the International AIDS Society* 2018; **21**(3): e25100. doi: 10.1002/jia2.25100. [Data updated for 2016].

[17] Saboni L, Sauvage C, Trouiller-Gerfaux P, et al. Rapport Prevagay 2015, Paris. Enquête de séroprévalence du VIH menée auprès des hommes ayant des relations sexuelles avec les hommes fréquentant les lieux de convivialité gay. Saint-Maurice, Santé Publique France, 2017.

[18] Bajos N, Rahib D, Lydié N. Genre et sexualité. D'une décennie à l'autre. Baromètre santé 2016. Saint-Maurice : Santé publique France, 2018.

[19] Insee. Dossier Complet – Région Île de France. Population par sexe et âge en 2015. Available at: https://www.insee.fr/fr/statistiques/2011101?geo=REG-11#tableau-POP_T3. [Website accessed on April 20, 2021].

[20] CNS, ANRS. Prise en charge médicale des personnes vivant avec le VIH 2018. Available at: https://cns.sante.fr/actualites/prise-en-charge-du-vih-recommandations-du-groupe-dexperts/ [Website accessed on April 20, 2021].

[21] Kretzschmar ME, Schim van der Loeff MF, Birrell PJ, De Angelis D, Coutinho RA. Prospects of elimination of HIV with test-and-treat strategy. *Proc Natl Acad Sci U S A* 2013; **110**(39): 15538–43. doi:10.1073/pnas.1301801110.

[22] WHO. Prevent HIV, test and treat all 2016. Available at: https://www.who.int/hiv/pub/progressreports/2016-progress-report/en/ [Website accessed on April 20, 2021].

[23] Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *The New England Journal of Medicine* 2015; **373**(23): 2237–2246. doi:10.1056/NEJMoa1506273.

[24] Jijón S, Supervie V, Breban R. Prevention of treatable infectious diseases: a game-theoretic approach. *Vaccine* 2017; **35**(40): 5339–5345. doi:10.1016/j.vaccine.2017.08.040.

[25] Blumenthal J, Jain S, Mulvihill E, et al. Perceived versus calculated HIV risk: implications for pre-exposure prophylaxis uptake in a randomized trial of men who have sex with men. *Journal of Acquired Immune Deficiency Syndromes* 2019; **80**(2): e23–e29. doi:10.1097/QAI.0000000000001888.

[26] Velter A, Saboni L, Sommen C, Bernillon P, Bajos N, Semaille C. Sexual and prevention practices in men who have sex with men in the era of combination HIV prevention: results from the Presse Gays et Lesbiennes survey, France, 2011. *Eurosurveillance : Bulletin Européen sur les Maladies Transmissibles* 2015; **20**(14).

[27] Sagaon-Teyssier L, Suzan-Monti M, Demoulin B, et al. Uptake of PrEP and condom and sexual risk behavior among MSM during the ANRS IPERGAY trial. *AIDS care* 2016; **28: Supp1**: 48–55. doi:10.1080/09540121.2016.1146653.

[28] Lodi S, Phillips A, Touloumi G, et al. Time from human immunodeficiency virus seroconversion to reaching CD4+ cell count thresholds <200, <350, and <500 cells/mm^3: assessment of need following changes in treatment guidelines. *Clinical Infectious Diseases* 2011; **53**(8): 817–825. doi:10.1093/cid/cir494.

[29] CNS et ANRS. Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe d'experts. Actualisation 2015 prophylaxie pré-exposition. Sous la direction du Pr. Philippe Morlat et sous l'égide du CNS et de l'ANRS. Available at: https://cns.sante.fr/wp-content/uploads/2015/10/experts-vih_prep2015.pdf [Website accessed on April 20, 2021].

[30] Smith DK, Herbst JH, Zhang X, Rose CE. Condom effectiveness for HIV prevention by consistency of use among men who have sex with men in the United States. *Journal of Acquired Inmune Deficiency Syndromes* 2015; **68**(3): 337–344. doi:10.1097/QAI.0000000000000461.

[31] World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach 2016. Available at: https://www.who.int/hiv/pub/arv/arv-2016/en/ [Website accessed on April 20, 2021].

[32] French Institut of Demographic Studies (INED). Life expectancy 2017. Available at: https://www.ined.fr/en/everything_about_population/data/france/deaths-causes-mortality/life-expectancy/. [Website accessed: April 20, 2021].

3.3 Additional material

Section 3.3.1 presents the computations and proofs of the results shown in section 3.2.3. Namely, the explicit computations of some epidemiological indicators, using the ODE system (see item a) to c)), the thresholds for the PrEP effectiveness and the perceived relative cost yielding epidemic control and elimination (see items d), e) and h)), and a description of the numerical approximation of the voluntary PrEP coverage (see g)).

Section 3.3.2 contains some additional figures that where not included in the paper submission, but may help visualizing the system behavior from other perspectives. For instance, we present the values of the reproduction number before PrEP introduction for the calibrated model 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. 3.10). Additional results for the scenario where on-PrEP MSM do not follow the recommendations on frequently testing for HIV are presented as well.

3.3.1 Computations and proofs of our analytical results

a) The effectiveness of PrEP

PrEP effectiveness has been estimated at 86% (95% CI: 40%–98%) in two clinical trials conducted 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 reduced version of our HIV transmission model (cf. eq.(S6) of section 3.2.3) adapted to describe 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 the force of infection. Then, the following ODE system models the HIV infections dynamics that occur during the study:

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

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

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:

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

Using the number of participants and the number of seroconversions that took place during the *IPERGAY* study (Molina and Earn, 2015),

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

we obtain $\varepsilon = 0.86$. Hence, we found the same value as the efficacy estimated in from the *IPERGAY* trial, thus corroborating our modeling choices in section 3.2.3.

b) The disease-free equilibrium

The equations for the disease-free state (DFS) of the ODE system (S6), section 3.2.3, are given by

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

and

$$I_i^{k,\mathrm{DFS}} = T_i^{\mathrm{DFS}} = 0, \qquad \text{for all } i \in \{h, \ell\}, k \in \{a, c\}. \tag{3.7}$$

The total population at i risk of infection at the DFS is thus given by $N_i^{\mathrm{DFS}} = \pi_i/\mu$, for

$i \in \{h, \ell\}$. Then, the total population at the DFS is given by

$$N^{\mathrm{DFS}} = N_h^{\mathrm{DFS}} + N_\ell^{\mathrm{DFS}} = \frac{\pi_h + \pi_\ell}{\mu}. \tag{3.8}$$

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

c) Computing the effective reproduction number

To compute the effective reproduction number for the ODE system (S6), we follow the methods and notation developed by van den Driessche and Watmough (2002), where $R(p, \varepsilon)$ is defined as the largest eigenvalue of the *next generation matrix* (van den Driessche and Watmough, 2008; Diekmann et al., 1990).

We start with the state vector of our ODE system,

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

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

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

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 $V_{mn} = \partial \mathscr{V}_m / \partial X_n \Big|_{\text{DFS}}$, where $n, m = 1, \ldots, 8$, is given by

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

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

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

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

and

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

where

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

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

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

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 $\partial\Lambda_i/\partial I_j^k\Big|_{\text{DFS}} = \lambda_{ji}^k \, \mu/\pi_j$. Therefore,

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

and

$$\frac{\partial}{\partial I_j^k} \Lambda_\ell S_\ell \Big|_{\text{DFS}} = \frac{\lambda_{j\ell}^k \, \pi_\ell}{\pi_j}. \tag{3.16}$$

The matrix F is thus given by

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

where

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

The effective reproduction number R is given by the largest eigenvalue of the next generation matrix, $G = FV^{-1}$.

d) The PrEP effectiveness threshold for epidemic control

Epidemic control induced by PrEP uptake is defined as a reduction on the effective reproduction number due to PrEP adoption, i.e., $R(p, \varepsilon) < R(0, \varepsilon)$; see section 3.2.3. Here, we study the monotonicity 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 $R(p, \varepsilon) < R(0, \varepsilon)$.

Monotonicity with respect to PrEP effectiveness

Recall the definition of $R(\varepsilon, p)$; see section 3.2.3, eqs. (S14)–(S20). Since $A > 0$, the function $R(p, \varepsilon)$ verifies $\partial R(p, \varepsilon)/\partial\varepsilon \leq 0$ if and only if

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

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

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

Therefore, $\partial R(p, \varepsilon)/\partial\varepsilon \leq 0$. That is, the higher the level of PrEP effectiveness, the bigger the reduction of the effective reproduction number.

Monotonicity with respect to PrEP coverage

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

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

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

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

Hence, $\partial R(p,\varepsilon)/\partial p \leq 0$ if and only if $\varepsilon \geq \varepsilon_{\mathrm{C}}$, where

$$\varepsilon_{\mathrm{C}} \equiv 1-\left(\frac{1-\xi\eta_h}{1-\xi\eta_P}\right)\left(\frac{H_h}{H_P}\right). \tag{3.22}$$

e) The PrEP effectiveness threshold for epidemic elimination

Epidemic elimination is defined by $R(p,\varepsilon)\leq 1$; see section S1.2.3. That is,

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

Therefore, $R(p,\varepsilon)\leq 1$ can be rewritten as $p\,\varphi(\varepsilon)\leq K$, where

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

is a function of PrEP and condom effectiveness, and

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

is independent of the PrEP parameters.

In addition, assuming $p=1$, $R(1,\varepsilon)\leq 1$ can be rewritten as $\varphi(\varepsilon)\leq K$, which is equivalent to $\varepsilon > \varepsilon_{\mathrm{E}}$, where

$$\varepsilon_{\mathrm{E}} \equiv 1-\left(1-\frac{K}{H_h}\right)(1-\varepsilon_{\mathrm{C}}). \tag{3.26}$$

In other words, ε_{E} is the minimum value of PrEP effectiveness for which epidemic elimination

is possible, provided that PrEP coverage verifies $p\,\varphi(\varepsilon) \leq K$. We say that ε_{E} is the threshold for the PrEP effectiveness above which epidemic elimination is possible. Note that eq. (3.22) can also be obtained from looking to conditions on ε for which $\varphi(\varepsilon) \geq 0$. Hence, $\varphi(\varepsilon)$ can be interpreted as the combined effectiveness of PrEP and condoms.

f) The rescaled perceived costs for the PrEP-adoption strategies

We expanded analytically the costs defined by integrals in eqs. (S26)–(S27) of section 3.2.3

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

and

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

These equations were used to compute the expected utility directly and efficiently, rather than their integral form; cf. algorithm 3.1.

g) Numerical approximation of the voluntary PrEP coverage

The voluntary PrEP coverage was obtained numerically, as detailed in 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, $\hat{p}(\varepsilon, r)$

procedure ENDEMIC FORCE OF INFECTION, $\Lambda_i^{\mathrm{ES}}(p, \varepsilon)$ for $i \in \{h, P\}$ ▷ We used parallel computation.
  for $0 \leq p \leq 1$ **do**
    for $0 \leq \varepsilon \leq 1$ **do**
      Compute $R(p, \varepsilon)$; cf. eqs. (S14)–(S20)
      if $R(p, \varepsilon) > 1$ **then**
        Set T
        while $\log\left(\left|\left(N(t) - N(t-1)\right)/N(t-1)\right|\right) > \delta$ **do**
          Increase T
          Solve ODE system (S6) until $t = T$
        end while
        Endemic state (ES) $\leftarrow$ ODE system at $t = T$
        Compute $\Lambda_h^{\mathrm{ES}}(p, \varepsilon)$; see eq. (S9)
      else
        $\Lambda_h^{\mathrm{ES}}(p, \varepsilon) = 0$
      end if
    end for
  end for
  Compute $\Lambda_P^{\mathrm{ES}}(p, \varepsilon)$; see eq. (S13)
end procedure

procedure UTILITY MAXIMIZATION, $\max_p U(p; \varepsilon, r)$
  Compute $U(p; \varepsilon, r)$; cf. eq. (S25) and eqs. (3.27)–(3.28)
  for $0 \leq r \leq 1$ **do**
    for $0 \leq \varepsilon \leq 1$ **do**
      $\hat{p} \leftarrow$ The value of p for which $U(p, \varepsilon, r)$ attains its maximum
    end for
  end for
end procedure
Return $\hat{p}(\varepsilon, r)$

h) 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 3.2.3), were numerically extracted from $\hat{p}(\varepsilon, r)$, by identifying the boundaries between the regions I, II and III; see fig. 3.9. On one hand, $r_C(\varepsilon)$ is the boundary between region III and region II: we defined $r_C(\varepsilon)$ 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 set in our algorithm. See algorithm 3.2 below for the numerical implementation and fig. 3.9 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

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

Return $r_C(\varepsilon)$ and $r_E(\varepsilon)$

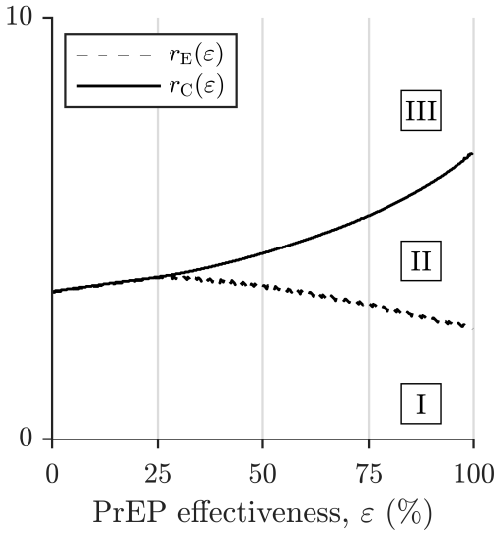

Figure 3.9 – The relative cost thresholds for epidemic control and elimination

The thresholds in relative cost 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 section 3.2.3. $r_C(\varepsilon)$ is the boundary between region III and region II, while $r_E(\varepsilon)$ is the boundary between region II and region I.

3.3.2 Additional results

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 ~ 500 simulations calibrating our model. A mean value of 2.2 (95% CI: 1.7–2.6) resulted from our model calibration, which is broadly in agreement with the results from Anderson and May (1991), where R_0 has been estimated at 2–5 among MSM.

The number of new HIV infections despite PrEP uptake

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. 3.10, which shows the number of new infections among on-PrEP MSM at the endemic

state (ES), given by $(1-\varepsilon)\Lambda_P^{\mathrm{ES}} P^{\mathrm{ES}} = (1-\varepsilon)(1-\xi\eta_P)\Lambda_h^{\mathrm{ES}} P^{\mathrm{ES}}/(1-\xi\eta_h)$, where Λ_P^{ES} and P^{ES} are functions of p and ε; cf. eq. (S13).

Given a fixed value for the 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, and PrEP offers protection despite risk compensation. The number of new infections reduces with PrEP coverage, reaching zero when herd immunity threshold is reached.

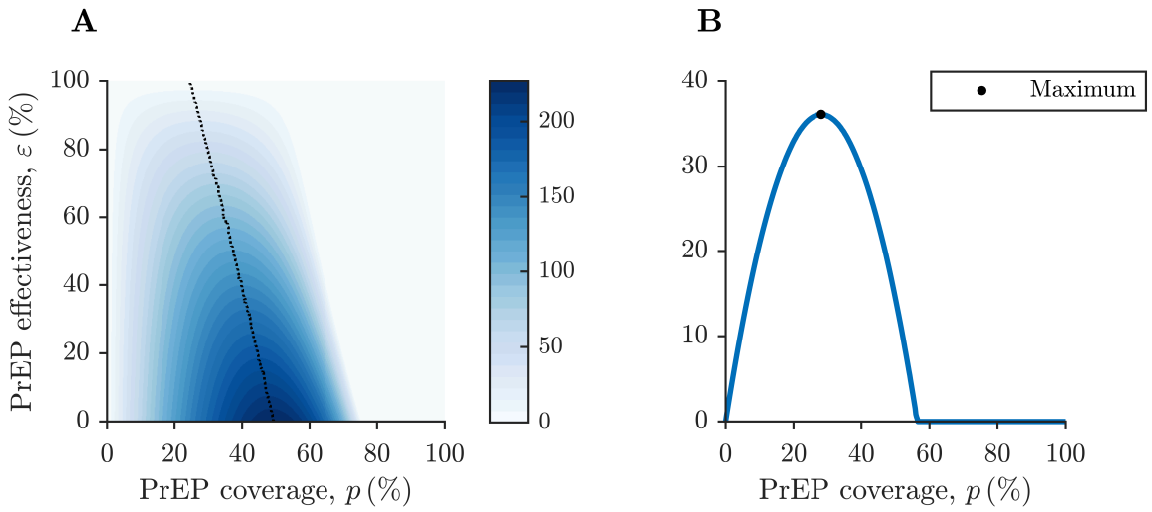

Figure 3.10 – Number of new HIV infections despite PrEP uptake
The number of new infections among on-PrEP MSM for the baseline scenario, at the endemic state, **(A)** as a function of PrEP coverage (p) and PrEP effectiveness (ε), and **(B)** for $\varepsilon = 86\%$. For low levels of PrEP coverage, 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.

3.4 Further discussion

3.4.1 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 that including PrEP into routine prevention healthcare and thus, allowing all sexually active adults to decide whether or not adopt PrEP, may improve PrEP adoption by reducing PrEP-related stigma and access inequalities (Calabrese et al., 2017).

From the modeling perspective, we found that targeting high-risk MSM allowed to control and eventually eliminate the epidemic at the population level. However, comparing the results between targeted and universal PrEP interventions remains to be studied. In our model, the HIV epidemic is driven by high-risk MSM (we hypothesized that there is no epidemic at the population level if HIV transmission no longer occurs among high-risk MSM) and thus, PrEP-induced epidemic elimination relies heavily on the MSM population at high risk of infection to adopt PrEP. It might be interesting to study universal PrEP access to evaluate the contribution of low-risk MSM to epidemic elimination.

Decreasing the perceived cost of PrEP in the French context

According to our results, not enough MSM have adopted PrEP to eliminate the HIV epidemic in the Paris region, and that decreasing the cost perceived for PrEP is essential to increase PrEP coverage.

Since PrEP is fully reimbursed by the social security system, low PrEP coverage reflects that French MSM value non-monetary aspects when deciding about this PrEP uptake for HIV prevention. Therefore, some difficulties regarding PrEP adoption still need to be addressed in the French context. For instance, the social security system covers ∼70% of the fees of

medical visits. In addition, the first PrEP prescription and the yearly renewal must still be done by HIV-specialized practitioners working in hospitals or HIV-specialized health centers (Haute Autorité de Santé, 2019; EPI-PHARE, 2020). This may perpetuate social stigma and discourage individuals. Training general practitioners and allowing them to prescribe PrEP may facilitate and, thus, broaden PrEP access.

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. Some healthcare providers may be reluctant to prescribe PrEP, due to concerns about risk compensation and potential increase in STI transmission (Caumes, 2018). As of the end of 2017, STI diagnoses among MSM 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 the acceptability of PrEP, by breaking the misperceived link between PrEP uptake and risk compensation.

3.4.2 Modeling limitations and perspectives

Delay in HIV testing for on-PrEP MSM

Our baseline scenario accounts for the current HIV-testing guidelines, where 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) and thus, frequent HIV testing may not be guaranteed in the long run. Hence, to study the impact of on-PrEP MSM testing less frequently for HIV, concerns about drug resistance arise (Supervie et al., 2011; Gibas et al., 2019).

Our model could be extended by taking into account an additional compartment for individuals undergoing late second line ART after HIV infection despite PrEP use, which may not be virally suppressed for a period of time and thus, may contribute to HIV transmission. Further stratification of the infected population by drug-susceptibility (drug-sensitive vs. drug resistant —transmitted or PrEP-induced) may also be necessary to describe the epidemic dynamics and study the impact of PrEP-induced drug resistance (Glaubius et al., 2019).

Modeling other PrEP-uptake patterns

Our model relies on the assumption that, in the long term, high-risk MSM use PrEP for as long as they select new partners; cf. Table S2. This assumption may not represent current reality in the Paris region, where about 15% of PrEP users did not get a prescription renewal the following year, since PrEP rollout (EPI-PHARE, 2019, 2020). Hence, modeling recurrent decision-making or the drop of PrEP while being sexually active may thus be interesting to study. Still, our results may be useful for understanding how could PrEP programs place HIV epidemic in the path of epidemic elimination, as well as future tools of prevention against HIV, which may be perceived as less costly by individuals, such as long-lasting injectable PrEP (Marshall et al., 2018) and vaccination against HIV (Burton, 2019).

Obtaining data on sexual behavior

Including heterogeneity in sexual behavior in modeling studies allows to account for essential behavioral data to which the epidemiology might be very sensitive. In our model, we accounted for the number of sexual contacts and the proportion of condomless interactions. 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.

However, data on sexual behavior rely heavily on self-reporting[8], resulting in high variation of results among some papers (Hess et al., 2017). 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) and thus, there may be some difficulties in obtaining data about the individuals' sexual practices which give the population stratification by risk of infection (Marcus et al., 2013; Baral et al., 2018).

These difficulties point not only 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 surveys may help overcoming these

[8]It 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)

difficulties and thus, obtaining more and accurate data on sexual behavior (Velter et al., 2015; Baral et al., 2018).

Targeting other subpopulations

Modeling explicitly condom use among individuals at low risk of infection and, in particular, modeling risk compensation among non-PrEP users (Phanuphak and Phanuphak, 2018) is left for future research. In addition, considering an age-structured model might help better understanding wether and under what conditions could targeting other high-risk subpopulations, such as young MSM (Siguier and Molina, 2018; WHO, 2016b), lead to epidemic elimination.

Considering heterogeneity in the risk and cost perception

In our model, we assumed 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 for 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.

Chapter 4

General discussion

4.1 Summary

4.1.1 Reaching epidemic elimination through voluntary adoption of prevention

We modeled the individual response to an epidemic threat through the resolution of a prevention-versus-treatment dilemma, and studied its impact on epidemic dynamics. We assumed that 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 individual-level risk assessment, we assumed that individuals acknowledge, directly or indirectly, some epidemiological data (e.g., the disease prevalence (Jijón et al., 2017) and the incidence rate (Jijón et al., 2021)) 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 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 programming 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 Jijón et al. (2021)). For the HIV model, 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 for 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, causing the system dynamics to return to its endemic status.

Another key outcome of our model is the effective reproduction number, which we obtained analytically. 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 an HIV epidemic may be eliminated by targeting the prevention interventions at those who identify themselves most at risk of infection. We study epidemic elimination as a function of the level of

risk compensation incurred by on-PrEP high-risk MSM. In addition, we considered alternative scenarios where individuals misperceive their risk of infection, by acknowledging only the proportion of diagnosed individuals among their peers as being infected with HIV, and where MSM dropped condom use. Our results suggest that risk misperception had a more negative impact on epidemic elimination programs, than a drop in condom use by on-PrEP MSM.

In both projects, we found that the perception of the risk of infection plays a major role in achieving epidemic elimination: the higher the risk perceived, the wider the area in the parameter space where epidemic elimination can be reached. That is, if the perceived risk decreases, the cost that individuals are willing to pay to adopt prevention decreases as well, regardless of the level of prevention effectiveness. In other words, if individuals do not perceive themselves as being at 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 adoption of prevention and epidemic dynamics in the long 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, 2020). Assuming that individuas make their choice on whether or not to adopt prevention, based on the individual-level perception of the risk of infection and the relative cost of prevention versus treatment, reaching and maintaining epidemic elimination in the long run would require active efforts to keep the cost of prevention perceived as low, as well as ensuring that individuals have access 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 out 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) (thus lowering the cost perceived for vaccination); while PrEP programs have identified the need 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 strategies could be established by public health policies aiming at disease elimination. 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. In the case of epidemic elimination, maintaining high levels of prevention coverage by ensuring accessibility, but also by sharing information about the achievements of preventive programs and the epidemic severity previous to their implementation.

In addition, our results may add new perspectives into the discussion about voluntary versus mandatory prevention, by supporting individual informed decision-making, which may join public efforts towards epidemic elimination.

4.2 Limitations and perspectives

4.2.1 The complexity of modeling human behavior

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 some factors reflecting the complexity of human behavior. Notably, we use a system of ordinary differential equations to model disease transmission, which may fail to take into account all individual-level heterogeneity: fixed parameters are assigned for each subpopulation to transit from one compartment to another; that is, all individual behaviors are summarized into an average behavior that is assumed to be the same for all individuals within a compartment. We tried to overcome this potential limitation in the application concerning PrEP and HIV by accounting for two subpopulations (high- and low-risk MSM), represented by additional compartments.

In addition, we modeled decision-making as a maximization of utility, which was mainly based on individuals' perception of the relative cost and the risk of infection, which was assumed to be the same for every individual. However, individuals may perceive these factors differently and the utility function may also thus be defined to explicitly account for heterogeneity in risk and cost perception. Accounting for heterogeneity in the perception of infection risk and cost among individuals, and thus in the utility, may help better understanding dynamics in terms of population heterogeneity and developing targeted prevention programs.

4.2.2 Determining and interpreting the relative cost of prevention versus treatment

In our model, 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 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 by individuals and/or cost reduction may be easier to interpret and to aim for. Hence estimating the relative cost may not be strictly needed to increase prevention coverage. Indeed, interventions may be proposed, which intuitively increase the accessibility and affordability of prevention and thus contributing to reduce the cost perceived by individuals. Then, the reduction in cost can be indirectly appreciated by monitoring the increase in prevention coverage. If feasible, estimating the relative cost would make it possible to predict the resulting prevention coverage, depending on the intervention.

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 and, more importantly, to maintain the objective of cost reduction.

4.2.3 Information dissemination and interpretation

During an epidemic, individuals may also face an *infodemic*[1], an "excessive amount of information about a problem, which makes it difficult to identify a solution" (WHO, 2020a). The dissemination of information about epidemics and disease burden may shape individuals' perception of their risk of infection, as well as the cost related to the available preventive and therapeutic tools. In a perception-based decision-making framework, such as our model, these perceptions impact significantly the outcomes of prevention rollout programs.

[1]The term was first used in the context of the SARS outbreak and more recently for the COVID-19 epidemic.

For individuals to make well-informed decisions, it is essential for individuals not only to have access to accurate and clear information, but also for them to trust these sources of information. This may be achieved through intervention from many different fronts: notably, by reducing the spreading of misinterpreted research results through mass media (Haneef et al., 2015); by making scientific results broadly accessible by explaining the meaning of prevention-parameters estimations such as effectiveness (Underhill et al., 2016); by reassessing the algorithmic curation of mass-media information to prioritize the sharing of transparent and quality information (Lorenz-Spreen et al., 2020); by revisiting and relativizing website statistics (such as the number of readers, shares, 'likes', etc.) to counteract the false perception of consensus (Lorenz-Spreen et al., 2020); by encouraging healthcare providers to share information and their experiences through mass media (Hernandez et al., 2021); by promoting collaborations between the general population and health authorities (WHO, 2020a); and by making data available through open source and open data (Kobayashi et al., 2021), among others.

From the modeling perspective, as mentioned above, accounting for the heterogeneity in the perception of risk and cost of prevention may help evaluating the impact on the voluntary adoption of prevention. In addition, modeling tools such as network models may be useful to further couple the epidemic spreading and the individual-level decision-making, with information spreading (Chang et al., 2020).

4.2.4 Considering other behavioral models

In our model, we considered a single-player game, where individuals act in their own interest to solve their own prevention vs. treatment dilemma. This can be interpreted as a game between the individuals and the public health authorities aiming at epidemic elimination. Individuals are not playing against each other, nor considering explicitly others' strategies. Hence, the game resolution should not be interpreted as a Nash equilibrium.

Considering multi-player games would take into account the interactions between individuals. For instance, accounting for individuals' acknowledgment of herd immunity and other players' decisions would allow to model explicitly *free riders*, individuals who adopt the strategy of delaying or not using prevention. Free-riding behaviors may be conscious, with individuals

expecting explicitly to benefit from others' preventive behaviors (herd immunity)[2], or a result of complacency. 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. Complacent free-riders may be modeled by considering the heterogeneity in the risk of infection and its related costs, as previously mentioned.

Considering altruism into the model by including a component for the collective utility may allow to study if voluntary prevention coverage may reach levels that optimize the payoff at the collective level (Shim et al., 2012a). In addition, social learning (Bauch and Bhattacharyya, 2012) could also be considered to take into account individuals mimicking their peers behavior, if they are perceived as having adopted a more beneficial strategy regarding prevention.

4.2.5 Studying epidemics in other socio-economical settings

Our results point to prevention 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, especially involving the individuals' acceptability of the preventive methods. However, in low-income settings, the consequences of infections may be 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). Hence, the MMR vaccine is often well accepted in low-income countries (Larson et al., 2016) but availability issues persist: as of August 2019, 23 countries had yet to introduce the second dose of MMR vaccine in the national vaccination schedules (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 but highly

[2]In the context of vaccination against influenza, Parker et al. (2013) found that conscious free-riding may be a strategy adopted only by a small proportion of the population.

desirable given high incidence levels (UNAIDS, 2019a). Hence, context-specific strategies to facilitate access to PrEP should be considered and implemented (Rebe et al., 2019).

4.2.6 Epidemic dynamics at low prevalence

Since we found no equilibrium for the voluntary prevention coverage in that region, our model does not allow to study the infectious disease transmission once $R < 1$, and our simulations encounter somme difficulties when the epidemic is close to elimination. Therefore, it remains to understand the infectious disease transmission at low prevalence (i.e., around the threshold $R = 1$) subject to the individuals' voluntary adoption of prevention. Including stochasticity[3] in our model constitutes a problem worth to be explored in the future. This could shed light on how the epidemic state ($R > 1$) could be reached again, as a consequence of low prevention coverage induced by the low risk perceived by individuals.

4.2.7 The impact of the COVID-19 pandemic on prevention interventions against measles and HIV

The COVID-19 epidemic provoked a sanitary crisis worldwide, also impacting public health programs aiming for disease elimination. For instance, the COVID-19 epidemic impacted childhood immunization, with 37 countries delaying immunization activities during the first wave of the epidemic (WHO, 2020b). Thus, public health authorities around the world will need to address the decrease in prevention coverage that the COVID-19 epidemic provoked during the year 2020, to maintain measles on the path of epidemic elimination. The COVID-19 epidemic also impacted HIV care and prevention accessibility, including PrEP uptake. For instance, the increase in PrEP use in France was slower during the first semester of 2020 (cf. fig. 3.3). A survey conducted among $\sim 8\,350$ French MSM regarding their sexual behaviors during the period June–July 2020 found that 60% of respondents had declared a complete drop in casual sexual encounters, and that 59% of PrEP users had stopped using PrEP due to a decrease in sexual activity (Velter et al., 2020).

Hence, the epidemic dynamics of the infectious diseases that are studied in this thesis are

[3]Stochastic models are used to describe disease transmission when the number of infectious individuals is low, and thus, the assumption of mass action is no longer tenable and stochastic effects are taken into account instead (Brauer, 2008).

currently perturbed. The completion of our research project took place before the emergence of the COVID-19 pandemic; still, our results remain relevant, since we analyze the system at the equilibrium, in the long term, which is not impacted by perturbations (i.e., relatively small, short-term changes in epidemic dynamics).

4.3 Conclusion

The methods developed in this doctoral research 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 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.

Our results thus suggest that individual-level risk and cost perception are essential for placing epidemics in the path towards elimination through preventive programs based on informed decision-making. Hence, the accurate and broad communication of scientific results, including epidemiological data, disease parameters estimations, and the efficacy, side effects of both preventive and therapeutic tools, as well as their impact on the epidemic, becomes a crucial focus of health programs on infectious disease prevention; especially in the current context where individuals are exposed to massive and fast spreading information.

Appendices

A Behavioral epidemiology and the COVID-19 pandemic

As of March 31, 2021, around 128 million cases of SARS-CoV-2[4] infections were reported to the WHO worldwide, and resulted in $\sim$ 2.8 million deaths (WHO, 2021a). Public health authorities have established a variety of mandatory non-pharmaceutical interventions aiming to control the still ongoing epidemic, successfully reducing the number of new infections worldwide (Bo et al., 2021). However, heavy interventions such as national-level lockdowns and closing schools and stores are not tenable in the long run, so the development of immunization tools has been of great interest. Since mid-December 2020, several vaccines were put on the market (WHO, 2021b), and vaccination campaigns started around the world. As of March 31, 2021, $\sim$ 338 million people had received at least one dose of COVID-19 vaccine worldwide (Our World in Data, 2021). The discussion on ending the COVID-19 epidemic at the European region started with a petition in Germany in January 2021 (ZeroCovid, 2021), provoking debates in other European countries, such as France (Tribune, 2021) and UK (Nuki, 2021).

Mathematical models have assisted public-health decision-making by estimating disease parameters (such as the duration of the different stages of disease progression, and the basic and the effective reproduction numbers), as well as predicting the impact of intervention measures on the COVID-19 pandemic (Xiang et al., 2021). In particular, behavioral epidemiology has been used to study the impact of epidemic control interventions requiring the voluntary partici-

[4]Severe acute respiratory syndrome coronavirus 2, the causative agent of COVID-19, the severe coronavirus disease. See the review by Salzberger et al. (2021) for more details on the epidemiology of SARS-CoV-2.

pation of individuals, such as social distancing (Gupta et al., 2020), stay-at-home interventions (Kabir and Tanimoto, 2020) and vaccination (Choi and Shim, 2020) and its interplay with control restrictions (Jentsch et al., 2021)[5].

Our approach may give insights into the subject of voluntary vaccination against COVID-19 and health programs aiming at epidemic elimination, by highlighting that increasing vaccination coverage requires for individuals to have an accurate perception of their risk of infection and to perceive a low cost of preventing SARS-CoV-2 infection. On the one hand, individuals' perception of the risk of SARS-CoV-2 infection has shown to be strongly related to their direct experience with the virus and the local epidemic situation (Domínguez et al., 2020; Elharake et al., 2021). A recent study found that 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 remain to be ensured. Official, governmental sources may help increasing individuals' trust in information, which may translate in the successful adoption of preventive behaviors (Lim et al., 2021) by reducing misinformation spreading through mass media (Lorenz-Spreen et al., 2020). In addition, the participation of the general population may help increasing people's trust in health authorities (WHO, 2020a). On the other hand, attitudes towards vaccination against COVID-19 vary widely between countries and between individuals, despite evidence of efficacy against severe forms of the disease and preliminary results showing a reduction in onward transmission (WHO, 2021b). A survey about vaccine acceptability (Wouters et al., 2021) found that only 44% of the French respondents would potentially get vaccinated, versus 81% of the UK responders. Hence, vaccine hesitancy remains to be addressed to control the COVID-19 pandemic. The cost perceived for vaccination may be reduced by increasing transparent and accurate communication about vaccine safety and effectiveness, as well as ensuring broad availability and accessibility (Wouters et al., 2021).

[5]Last search of bibliography related to behavioral epidemiology and COVID-19: April 15th, 2021.

B Résumé détaillé

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

B.1. 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 developper 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.

B.2. 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.

B.2.1. 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 determiner si une couverture de la prévention permettant d'obtenir $R < 1$ peut être atteints volontairement.

B.2.2. 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'accessibilité, la morbidité de la maladie, etc.

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 prevention pour un individu typique et ainsi, détermine à la fois la *couverture volontaire de la prévention* au niveau populationnel.

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 prevention inférieur à 1).

B.3. Travaux de recherche

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 (Jijón et al., 2021).

B.3.1. 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 témoignée 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 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 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, 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 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 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 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 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 perception du coût bas et donc une motivation pour se faire vacciner. Par exemple, des incentives (monétaires et non monétaires) on 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 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 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 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 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.

B.3.2. 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; Beyrer 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).

Des études de modélisation ont estimé que la PrEP pourrait conduire à une réduction considérable du nombre de nouvelles infections (Punyacharoensin 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.

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

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 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 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 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 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 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 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 :

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 (au lieu de seulement diminuer leur utilisation).

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.

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 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.

B.4. 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.

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.

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, 2020). 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 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.

Bibliography

A. Aghaizu, D. Mercey, A. Copas, A. M. Johnson, G. Hart, and A. Nardone. Who would use PrEP? Factors associated with intention to use among MSM in London: a community survey. *Sexually transmitted infections*, 89(3):207–11, 2013. doi: 10.1136/sextrans-2012-050648.

S. H. Ali, J. Foreman, Y. Tozan, A. Capasso, A. M. Jones, and R. J. DiClemente. Trends and predictors of COVID-19 information sources and their relationship with knowledge and beliefs related to the pandemic: Nationwide cross-sectional study. *JMIR Public Health and Surveillance*, 6(4):1–15, 2020. doi: 10.2196/21071.

A. Amendola, L. Bubba, A. Piralla, S. Binda, A. Zanetti, E. Pariani, et al. Surveillance and vaccination coverage of measles and rubella in Northern Italy. *Human Vaccines & Immunotherapeutics*, 11(1):206–213, 2015. doi: 10.4161/hv.35865.

R. Anderson and R. May. Immunisation and herd immunity. *The Lancet*, 335(8690):641–645, 1990. doi: 10.1016/0140-6736(90)90420-A.

R. M. Anderson. The concept of herd immunity and the design of community-based immunization programmes. *Vaccine*, 10(13):928–935, 1992. doi: 10.1016/0264-410X(92)90327-G.

R. M. Anderson and R. M. May. *Infectious diseases of humans: dynamics and control*. Oxford University Press, 1991. ISBN 9780198540403.

J. K. Andrus, C. A. de Quadros, C. Castillo Solórzano, M. Roses Periago, and D. A. Henderson. Measles and rubella eradication in the Americas. *Vaccine*, 29(SUPPL. 4):D91–D96, 2011. doi: 10.1016/j.vaccine.2011.04.059.

ANRS. Actualisation des recommandations concernant la prophylaxie pré-exposition (PrEP). Prise en charge médicale des personnes vivant avec le VIH. Recommandations du groupe

d'experts. Sous la direction du Pr. Philippe Morlat et sous l'égide du CNS et de l'ANRS, 2015.

D. Antona, D. Lévy-Bruhl, C. Baudon, F. Freymuth, M. Lamy, C. Maine, D. Floret, and I. P. du Chatelet. Measles elimination efforts and 2008-2011 outbreak, France. *Emerging Infectious Diseases*, 19(3):357–364, 2013. doi: 10.3201/eid1903.121360.

E. A. Arnold and W. T. Steward. HIV transmission in MSM : considerations for PrEP scale-up. *The Lancet HIV*, 3018(15):9–10, 2016. doi: 10.1016/S2352-3018(15)00060-0.

M. C. Auld. Choices, beliefs, and infectious disease dynamics. *Journal of Health Economics*, 22 (3):361–377, 2003. doi: 10.1016/S0167-6296(02)00103-0.

Australian Government Department of Health. No jab, no pay ? New immunisation requirements for family assistance payments, 2015.

N. Bajos and M. Bozon. Enquête sur la sexualité en France: pratiques, genre et santé. *La Découverte*, page 609, 2008.

S. Baral, R. M. Turner, C. E. Lyons, S. Howell, B. Honermann, A. Garner, R. Hess III, D. Diouf, G. Ayala, P. S. Sullivan, and G. Millett. Population size estimation of gay and bisexual men and other men who have sex with men using social media-based platforms. *JMIR Public Health and Surveillance*, 4(1):e15, 2018. doi: 10.2196/publichealth.9321.

F. Barré-Sinoussi, A. L. Ross, and J. F. Delfraissy. Past, present and future: 30 years of HIV research. *Nature Reviews Microbiology*, 11(12):877–883, 2013. doi: 10.1038/nrmicro3132.

C. Bauch and D. Earn. Vaccination and the theory of games. *Proceedings of the National Academy of Sciences of the United States of America*, 101(36):13391–4, 2004. doi: 10.1073/pnas.0403823101.

C. Bauch, A. D'Onofrio, and P. Manfredi. Behavioral epidemiology of infectious diseases: an overview. In *Modeling the Interplay Between Human Behavior and the Spread of Infectious Diseases*, pages 1–19. Springer New York, NY, 2013. ISBN 9781461454748. doi: 10.1007/978-1-4614-5474-8.

C. T. Bauch and S. Bhattacharyya. Evolutionary game theory and social learning can determine how vaccine scares unfold. *PLoS Computational Biology*, 8(4):e1002452, apr 2012. doi: 10.1371/journal.pcbi.1002452.

C. T. Bauch, A. P. Galvani, and D. J. D. Earn. Group interest versus self-interest in smallpox vaccination policy. *Proceedings of the National Academy of Sciences*, 100(18):10564–10567, 2003. doi: 10.1073/pnas.1731324100.

A. Bechini, S. Boccalini, A. Ninci, P. Zanobini, G. Sartor, G. Bonaccorsi, M. Grazzini, and P. Bonanni. Childhood vaccination coverage in Europe: impact of different public health policies. *Expert Review of Vaccines*, 18(7):693–701, 2019. doi: 10.1080/14760584.2019.1639502.

D. Bernoulli. Essai d'une nouvelle analyse de la mor- talite causee par la petite verole. *Mem Math Phy Acad Roy Sci*, 1766. (English translation entitled 'An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it' In Smallpox Inoculation: An Eighteenth Century Mathematical Controversy, Bradley L. Adult Education Department: Nottingham, 1971, 21).

C. Beyrer, S. D. Baral, F. Van Griensven, S. M. Goodreau, S. Chariyalertsak, A. L. Wirtz, and R. Brookmeyer. Global epidemiology of HIV infection in men who have sex with men. *The Lancet*, 380(9839):367–377, 2012. doi: 10.1016/S0140-6736(12)60821-6.

S. Bhattacharyya and C. T. Bauch. A game dynamic model for delayer strategies in vaccinating behaviour for pediatric infectious diseases. *Journal of Theoretical Biology*, 267(3):276–282, 2010. doi: 10.1016/j.jtbi.2010.09.005.

S. Blower and D. Bernoulli. An attempt at a new analysis of the mortality caused by smallpox and of the advantages of inoculation to prevent it. *Reviews in medical virology*, 14:275–288, 2004. doi: 10.1002/rmv.443.

J. Blumenthal, S. Jain, E. Mulvihill, S. Sun, M. Hanashiro, E. Ellorin, S. Graber, R. Haubrich, and S. Morris. Perceived versus calculated HIV risk. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, 80(2):e23–e29, 2019. doi: 10.1097/QAI.0000000000001888.

Y. Bo, C. Guo, C. Lin, Y. Zeng, H. B. Li, Y. Zhang, M. S. Hossain, J. W. Chan, D. W. Yeung, K. O. Kwok, S. Y. Wong, A. K. Lau, and X. Q. Lao. Effectiveness of non-pharmaceutical interventions on COVID-19 transmission in 190 countries from 23 January to 13 April 2020. *International Journal of Infectious Diseases*, 102:247–253, 2021. doi: 10.1016/j.ijid.2020.10.066.

M. Bonneton, D. Antona, K. Danis, F. Aït-Belghiti, and D. Levy-Bruhl. Are vaccinated measles cases protected against severe disease? *Vaccine*, 38(29):4516–4519, 2020. doi: 10.1016/j.vaccine.2020.05.005.

R. Bosworth, T. A. Cameron, and J. R. DeShazo. Is an ounce of prevention worth a pound of cure? Comparing demand for public prevention and treatment policies. *Medical Decision Making*, 30(4):E40–E56, 2010. doi: 10.1177/0272989X10371681.

F. Brauer. Compartmental models in epidemiology. *Lecture Notes in Mathematics*, 1945:19–79, 2008. doi: 10.1007/978-3-540-78911-6_2.

F. Brauer. Mathematical epidemiology: Past, present, and future. *Infectious Disease Modelling*, 2(2):113–127, 2017. doi: 10.1016/j.idm.2017.02.001.

R. Breban. Health newscasts for increasing influenza vaccination coverage: An inductive reasoning game approach. *PLoS One*, 6(12):e28300–10, 2011.

R. Breban, R. Vardavas, and S. Blower. Mean-field analysis of an inductive reasoning game: Application to influenza vaccination. *Phys. Rev. E*, 76:031127, 2007. doi: 10.1103/PhysRevE.76.031127.

A. E. Brown, S. Nash, N. Connor, P. D. Kirwan, D. Ogaz, S. Croxford, D. De Angelis, and V. C. Delpech. Towards elimination of HIV transmission, AIDS and HIV-related deaths in the UK. *HIV Medicine*, 19(8):505–512, 2018. doi: 10.1111/hiv.12617.

K. F. Brown, J. S. Kroll, M. J. Hudson, M. Ramsay, J. Green, S. J. Long, et al. Factors underlying parental decisions about combination childhood vaccinations including MMR: A systematic review. *Vaccine*, 28(26):4235–4248, 2010. doi: 10.1016/j.vaccine.2010.04.052.

D. R. Burton. Advancing an HIV vaccine; advancing vaccinology. *Nature Reviews Immunology*, 19(2):77–78, 2019. doi: 10.1038/s41577-018-0103-6.

S. K. Calabrese, M. Magnus, K. H. Mayer, D. S. Krakower, A. I. Eldahan, L. A. Gaston Hawkins, et al. Putting PrEP into practice: Lessons learned from early-adopting U.S. providers' first-hand experiences providing HIV pre-exposure prophylaxis and associated care. *PLoS ONE*, 11(6):1–16, 2016. doi: 10.1371/journal.pone.0157324.

S. K. Calabrese, D. S. Krakower, and K. H. Mayer. Integrating HIV preexposure prophylaxis (PrEP) into routine preventive health care to avoid exacerbating disparities. *American Journal of Public Health*, 107(12):1883–1889, 2017. doi: 10.2105/AJPH.2017.304061.

V. Cambiano, A. Miners, D. Dunn, S. McCormack, K. J. Ong, O. N. Gill, et al. Cost-effectiveness of pre-exposure prophylaxis for HIV prevention in men who have sex with men in the UK: A modelling study and health economic evaluation. *The Lancet Infectious Diseases*, 18(1):85–94, 2017. doi: 10.1016/S1473-3099(17)30540-6.

C. Castillo-Chavez. Mathematical and statistical approaches to AIDS epidemiology. In C. Castillo-Chavez, editor, *Lecture Notes in Biomathematics*, volume 83. Springer - Verlag Berlin, 1989. ISBN 9783540521747.

E. Caumes. Réémergence inquiétante des infections sexuellement transmissibles dans un contexte de promotion de la PrEP. Pourquoi ne pas en revenir au safer sex ? *La Presse Médicale*, 47 (9):719–721, 2018. doi: 10.1016/j.lpm.2018.09.007.

CDC. Measles eradication: recommendations from a meeting cosponsored by the WHO, the Pan American Health Organization, and CDC. *MMWR.*, 46(RR-11):1–20, 1997.

CDC. Vaccinia (smallpox) vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*, 50(RR-10):1–20, 2001.

CDC. Smallpox fact sheet, 2015. URL http://www.cdc.gov/agent/smallpox/vaccination/pdf/vaccine-overview.pdf.

CDC. HIV Basics, 2020. URL https://www.cdc.gov/hiv/basics/index.html.

CDC. Measles Cases in 2019, August 2019. URL https://www.cdc.gov/measles/cases-outbreaks.html.

S. L. Chang, M. Piraveenan, P. Pattison, and M. Prokopenko. Game theoretic modelling of infectious disease dynamics and intervention methods: a review. *Journal of Biological Dynamics*, 14(1):57–89, 2020. doi: 10.1080/17513758.2020.1720322.

Y. H. Chen, W. McFarland, H. F. Raymond, H. M. Scott, E. Vittinghoff, and T. C. Porco. Distribution of behavioral patterns before infection among San Francisco men who have sex with men newly infected with HIV in 2014. *Journal of Acquired Immune Deficiency Syndromes*, 75(5):528–534, 2017. doi: 10.1097/QAI.0000000000001439.

W. Choi and E. Shim. Optimal strategies for vaccination and social distancing in a game-theoretic epidemiologic model. *Journal of Theoretical Biology*, 505:110422, 2020. doi: 10.1016/j.jtbi.2020.110422.

R. Coleman and M. Prins. Options for affordable pre-exposure prophylaxis (PrEP) in national HIV prevention programmes in Europe. *Eurosurveillance*, pages 1–4, 2017.

P. S. Corso, J. K. Hammitt, J. D. Graham, R. C. Dicker, and S. J. Goldie. Assessing preferences for prevention versus treatment using willingness to pay. *Medical Decision Making*, 22(Suppl5): S92–S101, 2002. doi: 10.1177/027298902237713.

D. Costagliola, J. Ghosn, B. Spire, D. R. Castro, L. Beniguel, M. Algarte-Genin, et al. PrEP persistence and associated factors: an analysis from the ANRS Prevenir study. *HIV Medicine*, 20(S9):33, 2019.

I. Cremin, R. Alsallaq, M. Dybul, P. Piot, G. Garnett, and T. B. Hallett. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. *AIDS*, 27 (3):447–458, 2013. doi: 10.1097/QAD.0b013e32835ca2dd.

C. A. De Quadros. Can measles be eradicated globally? *Bulletin of the World Health Organization*, 82(2):134–138, 2004. doi: 10.1126/science.156.3778.1029.

K. Desai, S. L. Sansom, M. L. Ackers, S. R. Stewart, H. I. Hall, D. J. Hu, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. *Aids*, 22(14):1829–1839, 2008. doi: 10.1097/QAD.0b013e32830e00f5.

M. Desai, N. Field, R. Grant, and S. McCormack. Recent advances in pre-exposure prophylaxis for HIV. *BMJ (Clinical research ed.)*, 359:j5011, 2018.

O. Diekmann, J. A. P. Heesterbeek, and J. A. J. Metz. On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology*, 28(4):365–382, 1990. doi: 10.1007/BF00178324.

K. Dietz and J. Heesterbeek. Daniel Bernoulli's epidemiological model revisited. *Mathematical Biosciences*, 180(1-2):1–21, 2002. doi: 10.1016/S0025-5564(02)00122-0.

D. Dimitrov, J. R. Moore, D. Wood, K. M. Mitchell, M. Li, J. P. Hughes, et al. Predicted effectiveness of daily and nondaily preexposure prophylaxis for men who have sex with men based

on sex and pill-taking patterns from the Human Immuno Virus Prevention Trials Network 067/ADAPT Study. *Clinical Infectious Diseases*, 1024(Xx):1–7, 2019. doi: 10.1093/cid/ciz799.

J. M. M. Domínguez, I. F. Jiménez, A. B. Eraso, D. P. Otero, D. D. Pérez, and A. M. R. Vivas. Risk perception of COVID-19 community transmission among the spanish population. *International Journal of Environmental Research and Public Health*, 17(23):1–15, 2020. doi: 10.3390/ijerph17238967.

A. D'Onofrio, P. Manfredi, and E. Salinelli. Vaccinating behaviour, information, and the dynamics of SIR vaccine preventable diseases. *Theoretical Population Biology*, 71(3):301–317, 2007. doi: 10.1016/j.tpb.2007.01.001.

E. F. Drabo, J. W. Hay, R. Vardavas, Z. R. Wagner, and N. Sood. A cost-effectiveness analysis of preexposure prophylaxis for the prevention of HIV among Los Angeles county men who have sex with men. *Clinical Infectious Diseases*, 63(11):1495–1504, dec 2016. doi: 10.1093/cid/ciw578.

L. Drew. The case for mandatory vaccination. *Nature*, 575(7784):S58–S60, 2019. doi: 10.1038/d41586-019-03642-w.

E. Dubé, C. Laberge, M. Guay, P. Bramadat, R. Roy, and J. A. Bettinger. Vaccine hesitancy. *Human Vaccines & Immunotherapeutics*, 9(8):1763–1773, 2013. doi: 10.4161/hv.24657.

E. Dubé, D. Gagnon, N. MacDonald, A. Bocquier, P. Peretti-Watel, and P. Verger. Underlying factors impacting vaccine hesitancy in high income countries: a review of qualitative studies. *Expert Review of Vaccines*, 17(11):989–1004, 2018. doi: 10.1080/14760584.2018.1541406.

I. Durand-Zaleski, P. Mutuon, I. Charreau, C. Tremblay, D. Rojas, G. Pialoux, et al. Costs and benefits of on-demand HIV preexposure prophylaxis in MSM. *Aids*, 32(1):95–102, 2018. doi: 10.1097/QAD.0000000000001658.

J. W. Eaton, L. F. Johnson, J. A. Salomon, T. Bärnighausen, E. Bendavid, et al. HIV treatment as prevention: Systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Medicine*, 9(7), 2012. doi: 10.1371/journal.pmed.1001245.

ECDC. Evidence Brief: Pre-Exposure Prophylaxis for HIV prevention in Europe, 2016.

ECDC. Surveillance Report: Monthly measles and rubella monitoring report, April 2019.

M. Eichner and K. Dietz. Eradication of poliomyelitis: When can one be sure that polio virus transmission has been terminated? *American Journal of Epidemiology*, 143(8):816–822, 1996. doi: 10.1093/oxfordjournals.aje.a008820.

J. A. Elharake, M. Shafiq, S. M. McFadden, A. A. Malik, and S. B. Omer. The association of COVID-19 risk perception, county death rates, and voluntary health behaviors among U.S. adult population. *The Journal of Infectious Diseases*, pages 1–31, 2021. doi: 10.1093/infdis/jiab131.

EPI-PHARE. Suivi de l'utilisation de Truvada® ou génériques pour une prophylaxie pré-exposition (PrEP) au VIH à partir des données du Système National des Données de Santé (SNDS), 2019. URL https://ansm.sante.fr/content/download/169903/2220521/version/2/file/Rapport_Truvada_PrEP+2019_Epiphare.pdf.

EPI-PHARE. Suivi de l'utilisation de Truvada® ou génériques pour une prophylaxie pré-exposition (PrEP) au VIH à partir des données du Système National des Données de Santé (SNDS), 2020. URL https://www.epi-phare.fr/rapports-detudes-et-publications/prep-vih-2020/.

L. Ferrer, C. Folch, P. Fernandez-Davila, A. Garcia, A. Morales, J. Belda, A. R. Susperregui, and J. Casabona. Awareness of pre-exposure prophylaxis for HIV, willingness to use it and potential barriers or facilitators to uptake among men who have sex with men in Spain. *AIDS and Behavior*, 20(7):1423–1433, 2016. doi: 10.1007/s10461-016-1379-9.

P. Fine, K. Eames, and D. L. Heymann. "Herd immunity": A rough guide. *Clinical Infectious Diseases*, 52(7):911–916, 2011. doi: 10.1093/cid/cir007.

J. Frankis, I. Young, P. Flowers, and L. McDaid. Who will use pre-exposure prophylaxis (PrEP) and why?: Understanding PrEP awareness and acceptability amongst men who have sex with men in the UK - A mixed methods study. *PLoS ONE*, 11(4):1–15, 2016. doi: 10.1371/journal.pone.0151385.

S. Funk, M. Salathé, and V. A. Jansen. Modelling the influence of human behaviour on the spread of infectious diseases: A review. *Journal of the Royal Society Interface*, 7(50):1247–1256, 2010. doi: 10.1098/rsif.2010.0142.

R. C. Gallo and L. Montagnier. The discovery of HIV as the cause of AIDS. *New England Journal of Medicine*, 349(24):2283–2285, 2003. doi: 10.1056/nejmp038194.

A. P. Galvani, T. C. Reluga, and G. B. Chapman. Long-standing influenza vaccination policy is in accord with individual self-interest but not with the utilitarian optimum. *Proceedings of the National Academy of Sciences*, 104(13):5692–5697, 2007. doi: 10.1073/pnas.0606774104.

P. Gastanaduy, P. Haber, P. A. Rota, and M. Patel. Measles. In *Epidemiology and Prevention of Vaccine-Preventable Diseases, 13th Edition*, pages 209–229. CDC, 2015.

K. M. Gibas, P. van den Berg, V. E. Powell, and D. S. Krakower. Drug resistance during HIV pre-exposure prophylaxis. *Drugs*, 79(6):609–619, apr 2019. doi: 10.1007/s40265-019-01108-x.

R. Glaubius, Y. Ding, K. J. Penrose, G. Hood, E. Engquist, J. W. Mellors, U. M. Parikh, and U. L. Abbas. Dapivirine vaginal ring for HIV prevention: modelling health outcomes, drug resistance and cost-effectiveness. *Journal of the International AIDS Society*, 22(5):e25282, may 2019. doi: 10.1002/jia2.25282.

Global Public Health Achievements Team. Ten great public health achievements — Worldwide, 2001–2010. *Morbidity and Mortality Weekly Report*, 60(24):814–818, 2011.

S. A. Golub. Tensions between the epidemiology and psychology of HIV risk: Implications for pre-exposure prophylaxis. *AIDS and Behavior*, 18(9):1686–1693, 2014. doi: 10.1007/s10461-014-0770-7.

G. B. Gomez, A. Borquez, C. F. Caceres, E. R. Segura, R. M. Grant, G. P. Garnett, and T. B. Hallett. The potential impact of pre-exposure prophylaxis for HIV prevention among men who have sex with men and transwomen in Lima, Peru: A mathematical modelling study. *PLoS Medicine*, 9(10), 2012. doi: 10.1371/journal.pmed.1001323.

M. Graham, A. K. Winter, M. Ferrari, B. Grenfell, W. J. Moss, A. S. Azman, C. J. E. Metcalf, and J. Lessler. Measles and the canonical path to elimination. *Science*, 364(6440):584–587, 2019. doi: 10.1126/science.aau6299.

R. M. Granich, C. F. Gilks, C. Dye, K. M. De Cock, and B. G. Williams. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *The Lancet*, 373(9657):48–57, 2009. doi: 10.1016/S0140-6736(08)61697-9.

R. M. Grant, J. R. Lama, P. L. Anderson, V. McMahan, A. Y. Liu, L. Vargas, et al. Preexposure

Chemoprophylaxis for HIV Prevention in men who have sex with men. *New England Journal of Medicine*, 363(27):2587–2599, 2010. doi: 10.1056/NEJMoa1109071.

C. Grov, H. J. Rendina, T. H. Whitfield, A. Ventuneac, and J. T. Parsons. Changes in familiarity with and willingness to take preexposure prophylaxis in a longitudinal study of highly sexually active gay and bisexual Men. *LGBT Health*, 3(4):252–257, 2016. doi: 10.1089/lgbt.2015.0123.

A. E. Grulich, R. Guy, J. Amin, F. Jin, C. Selvey, J. Holden, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. *The Lancet HIV*, 3018(18):1–9, 2018. doi: 10.1016/S2352-3018(18)30215-7.

F. M. Guerra, S. Bolotin, G. Lim, J. Heffernan, S. L. Deeks, Y. Li, and N. S. Crowcroft. The basic reproduction number (R0) of measles: a systematic review. *The Lancet Infectious Diseases*, 17(12):e420–e428, 2017. doi: 10.1016/S1473-3099(17)30307-9.

A. B. Gumel, C. C. McCluskey, and P. van den Driessche. Mathematical study of a staged-progression HIV model with imperfect vaccine. *Bulletin of Mathematical Biology*, 68(8):2105–28, 2006. doi: 10.1007/s11538-006-9095-7.

S. Gupta, R. M. Anderson, and R. M. May. Networks of sexual contacts: implications for the pattern of spread of HIV. *AIDS (London, England)*, 3(12):807–817, 1989. doi: 10.1097/00002030-198912000-00005.

S. Gupta, K. Simon, and C. Wing. Mandated and voluntary social distancing during the COVID-19 epidemic: A review. Technical report, National Bureau of Economic Research, Cambridge, MA, 2020. URL http://www.nber.org/papers/w28139.pdf.

J. Hamborsky, A. Kroger, and W. S. Wolfe, editors. *Epidemiology and prevention of vaccine-preventable diseases*. CDC. Public Health Foundation, Washington D.C., 13 edition, 2015.

R. Haneef, C. Lazarus, P. Ravaud, A. Yavchitz, and I. Boutron. Interpretation of results of studies evaluating an intervention highlighted in google health news: A cross-sectional study of news. *PLOS ONE*, 10(10):1–15, 10 2015. doi: 10.1371/journal.pone.0140889.

D. Hansson, S. Stromdahl, K. Y. Leung, and T. Britton. Introducing pre-exposure prophylaxis to prevent HIV acquisition among men who have sex with men in Sweden: in-

sights from a mathematical pair formation model. *BMJ open*, 10(2):e033852, 2020. doi: 10.1136/bmjopen-2019-033852.

Haute Autorité de Santé. La prophylaxie pré-exposition (PrEP) au VIH par TRUVADA®, 2019.

J. A. Heesterbeek. A brief history of R0 and a recipe for its calculation. *Acta Biotheoretica*, 50 (3):189–204, 2002. doi: 10.1023/A:1016599411804.

J. M. Heffernan, R. J. Smith, and L. M. Wahl. Perspectives on the basic reproductive ratio. *Journal of the Royal Society, Interface / the Royal Society*, 2(4):281–293, 2005. doi: 10.1098/rsif.2005.0042.

R. G. Hernandez, L. Hagen, K. Walker, H. O'Leary, and C. Lengacher. The COVID-19 vaccine social media infodemic : healthcare providers' missed dose in addressing misinformation and vaccine hesitancy. *Human Vaccines & Immunotherapeutics*, pages 1–3, apr 2021. doi: 10.1080/21645515.2021.1912551.

K. L. Hess, N. Crepaz, C. Rose, D. Purcell, and G. Paz-Bailey. Trends in sexual behavior among men who have sex with men (MSM) in high-income countries, 1990–2013: A systematic review. *AIDS and Behavior*, 21(10):2811–2834, 2017. doi: 10.1007/s10461-017-1799-1.

H. W. Hethcote. The mathematics of infectious diseases. *SIAM Review*, 42(4):599–653, 2000. doi: 10.1137/S0036144500371907.

I. Hodges-Mameletzis, S. Dalal, B. Msimanga-Radebe, M. Rodolph, and R. Baggaley. Going global: the adoption of the World Health Organization's enabling recommendation on oral pre-exposure prophylaxis for HIV. *Sexual Health*, 15(6):489, 2018. doi: 10.1071/SH18125.

M. Holt, T. Lea, L. Mao, J. Kolstee, I. Zablotska, T. Duck, et al. Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney, Australia: results of repeated behavioural surveillance in 2013-17. *The Lancet HIV*, 3018(18):1–9, 2018. doi: 10.1016/S2352-3018(18)30072-9.

D. R. Hopkins, J. P. Koplan, A. R. Hinman, and J. M. Lane. The case for global measles eradication. *The Lancet*, 319(8286):1396–1398, 1982. doi: 10.1016/S0140-6736(82)92510-7.

Y. Ibuka, M. Li, J. Vietri, G. B. Chapman, and A. P. Galvani. Free-riding behavior in vaccination decisions: an experimental study. *PLoS One*, 9(1):e87164, 2014. doi: 10.1371/journal.pone.0087164.

J. A. Jacquez, C. P. Simon, J. Koopman, L. Sattenspiel, and T. Perry. Modeling and analyzing HIV transmission: the effect of contact patterns. *Mathematical Biosciences*, 92(2):119–199, 1988. doi: 10.1016/0025-5564(88)90031-4.

J. A. Jacquez, C. P. Simon, and J. Koopman. Structured mixing: heterogeneous mixing by the definition of activity groups. In *Mathematical and Statistical Approaches to AIDS Epidemiology*, pages 301–305. Springer-Verlag New York, New York, 1989.

S. M. Jenness, S. M. Goodreau, E. Rosenberg, E. N. Beylerian, K. W. Hoover, D. K. Smith, and P. Sullivan. Impact of the Centers for Disease Control's HIV preexposure prophylaxis guidelines for men who have sex with men in the United States. *J. Infect. Dis.*, 214(12): 1800–1807, 2016. doi: 10.1093/infdis/jiw223.

P. C. Jentsch, M. Anand, and C. T. Bauch. Prioritising COVID-19 vaccination in changing social and epidemiological landscapes: a mathematical modelling study. *The Lancet Infectious Diseases*, 3099(21), 2021. doi: 10.1016/S1473-3099(21)00057-8.

S. Jijón, V. Supervie, and R. Breban. Prevention of treatable infectious diseases: A game-theoretic approach. *Vaccine*, 35(40):5339–5345, 2017. doi: 10.1016/j.vaccine.2017.08.040.

S. Jijón, J.-M. Molina, D. Costagliola, V. Supervie, and R. Breban. Can HIV epidemics among men who have sex with men be eliminated through participation in PrEP rollouts?. Published ahead of print. *AIDS*, jul 2021. ISSN 0269-9370. doi: 10.1097/QAD.0000000000003012.

W. D. Johnson, L. V. Hedges, G. Ramirez, S. Semaan, L. R. Norman, E. Sogolow, et al. HIV prevention research for men who have sex with men: A systematic review and meta-analysis. *Journal of Acquired Immune Deficiency Syndromes*, 30(SUPPL. 1):118–129, 2002. doi: 10.1097/00042560-200207011-00011.

J. L. Juusola, M. L. Brandeau, D. K. Owens, and E. Bendavid. The cost-effectiveness of preexposure prophylaxis for HIV prevention in men who have sex with men in the United States. *NIH Public Access Author Manuscript*, 2013. doi: 10.1059/0003-4819-156-8-201204170-00001.

K. M. Kabir and J. Tanimoto. Evolutionary game theory modelling to represent the behavioural dynamics of economic shutdowns and shield immunity in the COVID-19 pandemic: Economic shutdowns and shield immunity. *Royal Society Open Science*, 7(9), 2020. doi: 10.1098/rsos.201095rsos201095.

S. C. Kalichman and L. Eaton. Alcohol-antiretroviral interactive toxicity beliefs as a potential barrier to HIV pre-exposure prophylaxis among men who have sex with men. *Journal of the International AIDS Society*, 20(1), 2017. doi: 10.7448/IAS.20.1.21534.

A. Keenan, S. Ghebrehewet, R. Vivancos, D. Seddon, P. MacPherson, and D. Hungerford. Measles outbreaks in the UK, is it when and where, rather than if? A database cohort study of childhood population susceptibility in Liverpool, UK. *BMJ Open*, 7(3):e014106, 2017. doi: 10.1136/bmjopen-2016-014106.

Q. J. Khan and D. Greenhalgh. Hopf bifurcation in epidemic models with a time delay in vaccination. *IMA journal of mathematics applied in medicine and biology*, 16(2):113–142, jun 1999.

S. B. Kim, M. Yoon, N. S. Ku, M. H. Kim, J. E. Song, J. Y. Ahn, et al. Mathematical modeling of HIV prevention measures including pre-exposure prophylaxis on HIV incidence in South Korea. *PLoS ONE*, 9(3):1–9, 2014. doi: 10.1371/journal.pone.0090080.

S. Kobayashi, L. Falcón, H. Fraser, J. Braa, P. Amarakoon, A. Marcelo, and C. Paton. Using open source, open data, and civic technology to address the COVID-19 pandemic and infodemic. *Yearbook of Medical Informatics*, apr 2021. doi: 10.1055/s-0041-1726488.

H. Larson, A. de Figueiredo, E. Karafillakis, and M. Rawal. State of vaccine confidence un the EU 2018. A report for the European Commission, 2018. doi: 10.2875/241099.

H. J. Larson, C. Jarrett, E. Eckersberger, D. M. D. Smith, and P. Paterson. Understanding vaccine hesitancy around vaccines and vaccination from a global perspective: A systematic review of published literature, 2007–2012. *Vaccine*, 32(19):2150–2159, 2014. doi: http://dx.doi.org/10.1016/j.vaccine.2014.01.081.

H. J. Larson, A. de Figueiredo, Z. Xiahong, W. S. Schulz, P. Verger, I. G. Johnston, A. R. Cook, and N. S. Jones. The state of vaccine confidence 2016: Global insights through a 67-country survey. *EBioMedicine*, 12:295–301, 2016. doi: 10.1016/j.ebiom.2016.08.042.

M. T. LeVasseur, N. D. Goldstein, L. P. Tabb, B. L. Olivieri-Mui, and S. L. Welles. The effect of PrEP on HIV incidence among men who have sex with men in the context of condom use, treatment as prevention, and seroadaptive practices. *Journal of acquired immune deficiency syndromes (1999)*, 77(1):31–40, 2018. doi: 10.1097/QAI.0000000000001555.

V. Lim, R. Lim, Y. Tan, A. Soh, M. Tan, N. Othman, S. Dickens, T.-L. Thein, M. Lwin, R. Ong, Y.-S. Leo, V. Lee, and M. Chen. Government trust, perceptions of COVID-19 and behaviour change: cohort surveys, Singapore, 2021.

C. Lions, O. Cabras, L. Cotte, T. Huleux, A. Gagneux-Brugnon, A. Makinson, et al. Missed opportunities of HIV pre-exposure prophylaxis in France: a retrospective analysis in the French DAT'AIDS cohort. *BMC Infectious Diseases*, 19(1):278, 2019. doi: 10.1186/s12879-019-3915-5.

J. Liu, B. F. Kochin, Y. I. Tekle, and A. P. Galvani. Epidemiological game-theory dynamics of chickenpox vaccination in the USA and Israel. *Journal of the Royal Society, Interface / the Royal Society*, 9(66):68–76, 2012. doi: 10.1098/rsif.2011.0001.

P. Lorenz-Spreen, S. Lewandowsky, C. R. Sunstein, and R. Hertwig. How behavioural sciences can promote truth, autonomy and democratic discourse online. *Nature Human Behaviour*, 4 (11):1102–1109, nov 2020. doi: 10.1038/s41562-020-0889-7.

J. Luyten, R. Kessels, P. Goos, and P. Beutels. Public preferences for prioritizing preventive and curative health care interventions: A discrete choice experiment. *Value in Health*, 18(2): 224–233, 2015. doi: 10.1016/j.jval.2014.12.007.

P. Manfredi and A. D'Onofrio, editors. *Modeling the interplay between human behavior and the spread of infectious diseases*. Springer New York, New York, NY, 2013. ISBN 978-1-4614-5473-1. doi: 10.1007/978-1-4614-5474-8.

P. Manfredi, P. Della Posta, A. D'Onofrio, E. Salinelli, F. Centrone, C. Meo, and P. Poletti. Optimal vaccination choice, vaccination games, and rational exemption: an appraisal. *Vaccine*, 28(1):98–109, 2009. doi: 10.1016/j.vaccine.2009.09.109.

U. Marcus, F. Hickson, P. Weatherburn, and A. J. Schmidt. Estimating the size of the MSM populations for 38 European countries by calculating the survey-surveillance discrepancies (SSD) between self-reported new HIV diagnoses from the European MSM internet survey (EMIS) and surveillance-reported HIV diagnoses am. *BMC Public Health*, 13(1):1, 2013. doi: 10.1186/1471-2458-13-919.

B. D. Marshall, W. C. Goedel, M. R. King, A. Singleton, D. P. Durham, P. A. Chan, J. P. Townsend, and A. P. Galvani. Potential effectiveness of long-acting injectable pre-exposure

prophylaxis for HIV prevention in men who have sex with men: a modelling study. *The Lancet HIV*, 3018(18):1–8, 2018. doi: 10.1016/S2352-3018(18)30097-3.

L. Marty, F. Cazein, H. Panjo, J. Pillonel, D. Costagliola, and V. Supervie. Revealing geographical and population heterogeneity in HIV incidence, undiagnosed HIV prevalence and time to diagnosis to improve prevention and care: estimates for France. *Journal of the International AIDS Society*, 21(3):e25100, 2018. doi: 10.1002/jia2.25100.

S. McCormack, D. T. Dunn, M. Desai, D. I. Dolling, M. Gafos, R. Gilson, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): Effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *The Lancet*, 387(10013):53–60, 2016. doi: 10.1016/S0140-6736(15)00056-2.

W. McFarland, Y.-H. Chen, H. F. Raymond, B. Nguyen, G. Colfax, J. Mehrtens, et al. HIV seroadaptation among individuals, within sexual dyads, and by sexual episodes, men who have sex with men, San Francisco, 2008. *AIDS Care*, 23(3):261–268, 2011. doi: 10.1080/09540121.2010.507748.

R. M. Meertens, V. M. J. de Gaar, M. Spronken, and N. K. de Vries. Prevention praised, cure preferred: results of between-subjects experimental studies comparing (monetary) appreciation for preventive and curative interventions. *BMC Medical Informatics and Decision Making*, 13 (1):136, 2013.

Ministère des Solidarités et de la Santé. *Calendrier des vaccinations et recommandations vaccinales 2019*. Paris, 2019.

C. Molina and D. J. D. Earn. Game theory of pre-emptive vaccination before bioterrorism or accidental release of smallpox. *Journal of the Royal Society Interface*, 12:20141387, 2015. doi: 10.1098/rsif.2014.1387.

J. M. Molina, I. Charreau, B. Spire, L. Cotte, J. Chas, C. Capitant, et al. Efficacy, safety, and effect on sexual behaviour of on-demand pre-exposure prophylaxis for HIV in men who have sex with men: an observational cohort study. *The Lancet HIV*, 4(9):e402–e410, 2017. doi: 10.1016/S2352-3018(17)30089-9.

J.-M. Molina, J. Ghosn, L. Béniguel, D. Rojas-Castro, M. Algarte-Genin, and G. o. Pialoux. Incidence of HIV-infection in the ANRS Prevenir Study in the Paris Region with Daily or On Demand PrEP with TDF/FTC. In *AIDS 2018 Conference*, 2018.

D. Mortimer and L. Segal. Is the value of a life or life-year saved context specific? Further evidence from a discrete choice experiment. *Cost Effectiveness and Resource Allocation : C/E*, 6:8, 2008. doi: 10.1186/1478-7547-6-8.

B. E. Nichols, C. A. Boucher, M. van der Valk, B. J. Rijnders, and D. A. van de Vijver. Cost-effectiveness analysis of pre-exposure prophylaxis for HIV-1 prevention in the Netherlands: a mathematical modelling study. *The Lancet Infectious Diseases*, 16(12):1423–1429, 2016. doi: 10.1016/S1473-3099(16)30311-5.

H. Nishiura. Methods to Determine the End of an Infectious Disease Epidemic: A Short Review. In G. Chowell and J. M. Hyman, editors, *Mathematical and Statistical Modeling for Emerging and Re-emerging Infectious Diseases*, pages 291–301. Springer International Publishing, Cham, 2016. ISBN 978-3-319-40413-4. doi: 10.1007/978-3-319-40413-4_17.

P. Nuki. Zero covid strategy is impossible... the future of the virus is more likely to follow the flu or measles. *The Telegraph*, 2021. URL https://www.telegraph.co.uk/global-health/science-and-disease/zero-covid-strategy-impossible-future-virus-likely-follow-flu/.

E. Ouellet, M. Durand, J. R. Guertin, J. LeLorier, and C. L. Tremblay. Cost effectiveness of 'on demand' HIV pre-exposure prophylaxis for non-injection drug-using men who have sex with men in Canada. *The Canadian Journal of Infectious Diseases & Medical Microbiology*, 26(1): 23, 2015. doi: 10.1155/2015/964512.

Our World in Data. Cumulative COVID-19 vaccination doses administered, 2021. URL https://ourworldindata.org/covid-vaccinations.

L. Palk, J. Gerstoft, N. Obel, and S. Blower. A modeling study of the Danish HIV epidemic in men who have sex with men: travel, pre-exposure prophylaxis and elimination. *Scientific Reports*, 8(1):16003, 2018. doi: 10.1038/s41598-018-33570-0.

A. M. Parker, R. Vardavas, C. S. Marcum, and C. A. Gidengil. Conscious Consideration of Herd Immunity in Influenza Vaccination Decisions. *American Journal of Preventive Medicine*, 45 (1):118–121, jul 2013. doi: 10.1016/j.amepre.2013.02.016.

M. Peck, M. Gacic-dobo, M. S. Diallo, Y. Nedelec, S. S. Sodha, and A. S. Wallace. Global routine vaccination coverage, 2016. *Releve epidemiologique hebdomadaire*, 92(46):701–707, 2017. doi: 10.15585/mmwr.mm6842a1.

P. Peng, S. Su, C. K. Fairley, M. Chu, S. Jiang, X. Zhuang, and L. Zhang. A Global Estimate of the Acceptability of Pre-exposure Prophylaxis for HIV Among Men Who have Sex with Men: A Systematic Review and Meta-analysis. *AIDS and Behavior*, 22(4):1063–1074, 2018. doi: 10.1007/s10461-017-1675-z.

R. E. Pérez-Figueroa, F. Kapadia, S. C. Barton, J. A. Eddy, and P. N. Halkitis. Acceptability of PrEP uptake among racially/ethnically diverse young men who have sex with men: The P18 study. *AIDS Education and Prevention*, 27(2):112–125, 2015. doi: 10.1521/aeap.2015.27.2.112.

N. Phanuphak and P. Phanuphak. Time to focus more on condomless anal sex in non-PrEP users. *The Lancet HIV*, 3018(18):17–18, 2018. doi: 10.1016/S2352-3018(18)30100-0.

A. N. Phillips, V. Cambiano, F. Nakagawa, A. E. Brown, F. C. Lampe, A. Rodger, et al. Increased HIV Incidence in men who have sex with men Despite High Levels of ART-Induced Viral Suppression: Analysis of an Extensively Documented Epidemic. *PLoS ONE*, 8(2):15–16, 2013. doi: 10.1371/journal.pone.0055312.

S. A. Plotkin, W. A. Orenstein, and P. A. Offit. *Vaccines: Sixth Edition*. Elsevier, University of Pennsylvania, Philadelphia, United States, 2012. ISBN 978-1-4557-0090-5.

M. Porta, editor. *A dictionary of epidemiology*. Oxford University Press, New York, 6 edition, 2013. ISBN 978–0–19–997672–0.

N. Punyacharoensin, W. J. Edmunds, D. De Angelis, and R. G. White. Mathematical models for the study of HIV spread and control amongst men who have sex with men. *European Journal of Epidemiology*, 26(9):695–709, 2011. doi: 10.1007/s10654-011-9614-1.

N. Punyacharoensin, W. J. Edmunds, D. D. Angelis, V. Delpech, G. Hart, J. Elford, A. E. Brown, and N. Gill. Effect of pre-exposure prophylaxis and combination HIV prevention for men who have sex with men in the UK : a mathematical modelling study. *The Lancet HIV*, 3018(15):1–11, 2016. doi: 10.1016/S2352-3018(15)00056-9.

S. C. Quinn, A. M. Jamison, and V. S. Freimuth. Measles outbreaks and public attitudes towards vaccine exemptions: some cautions and strategies for addressing vaccine hesitancy. *Human Vaccines & Immunotherapeutics*, 0(0):21645515.2019.1646578, 2019. doi: 10.1080/21645515.2019.1646578.

K. Rebe, N. Hoosen, and J. A. McIntyre. Strategies to improve access for MSM in low-income and middle-income countries. *Current opinion in HIV and AIDS*, 14(5):387–392, 2019. doi: 10.1097/COH.0000000000000568.

T. C. Reluga and J. Li. Games of age-dependent prevention of chronic infections by social distancing. *Journal of Mathematical Biology*, 66(7):1527–1553, 2013. doi: 0.1007/s00285-012-0543-8.

P. Revill and E. Dwyer. Pre-exposure prophylaxis is cost-effective for HIV in the UK. *The Lancet Infectious Diseases*, 3099(17):6–7, 2017. doi: 10.1016/S1473-3099(17)30594-7.

B. Ridenhour, J. M. Kowalik, and D. K. Shay. Unraveling R0: Considerations for public health applications. *American Journal of Public Health*, 108(2):S445–S454, 2018. doi: 10.2105/AJPH.2013.301704.

O. Robineau, A. Velter, F. Barin, and P. Y. Boelle. HIV transmission and pre-exposure prophylaxis in a high risk MSM population: A simulation study of location-based selection of sexual partners. *PLoS ONE*, 12(11):1–15, 2017. doi: 10.1371/journal.pone.0189002.

A. Rodger, V. Cambiano, T. Bruun, et al. Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. *JAMA*, 316(2):171–181, 2016.

M. Roser and H. Ritchie. HIV / AIDS. *Our World in Data*, 2020. Available at: https://ourworldindata.org/hiv-aids.

G. Rozhnova, J. Heijne, D. Bezemer, A. van Sighem, A. Presanis, D. De Angelis, and M. Kretzschmar. Elimination prospects of the Dutch HIV epidemic among men who have sex with men in the era of preexposure prophylaxis. *Aids*, 32(17):2615–2623, 2018. doi: 10.1097/QAD.0000000000002050.

G. Rozhnova, J. Heijne, M. Basten, C. den Daas, A. Matser, and M. Kretzschmar. Impact of sexual trajectories of men who have sex with men on the reduction in HIV transmission by pre-exposure prophylaxis. *Epidemics*, 28:1–9, 2019. doi: 10.1016/j.epidem.2019.03.003.

B. Salzberger, F. Buder, B. Lampl, B. Ehrenstein, F. Hitzenbichler, T. Holzmann, B. Schmidt, and F. Hanses. Epidemiology of SARS-CoV-2. *Infection*, 49:233–239, 2021. doi: 10.1007/s15010-020-01531-3.

S. Salzman. What does PrEP cost outside the United States? *The Body*, 2019.

Santé Publique France. Infection par le VIH et IST bactériennes. Bilan épidémiologique 2017, 2018. URL https://www.corevih-na.fr/sites/default/files/bilan_epidemiologique_2017_-_bulletin_vih-ist.pdf.

Santé Publique France. Données de couverture vaccinale rougeole, rubéole, oreillons par groupe d'âge, 2019a. URL https://www.santepubliquefrance.fr/determinants-de-sante/vaccination/articles/donnees-de-couverture-vaccinale-rougeole-rubeole-oreillons-par-groupe-d-age.

Santé Publique France. Surveillance de l'infection à VIH (dépistage et déclaration obligatoire), 2010–2017, 2019b. URL https://www.santepubliquefrance.fr/content/download/128428/1957006.

L. Sattenspiel, J. Koopman, C. Simon, and J. A. Jacquez. The effects of population structure on the spread of the HIV infection. *American Journal of Physical Anthropology*, 82:421–429, 1990.

D. L. B. Schwappach. The equivalence of numbers: The social value of avoiding health decline: An experimental web-based study. *BMC Medical Informatics and Decision Making*, 2:3, 2002. doi: 10.1186/1472-6947-2-3.

N. Scott, M. Stoové, S. L. Kelly, D. P. Wilson, and M. E. Hellard. Achieving 90-90-90 human immunodeficiency virus (HIV) targets will not be enough to achieve the HIV incidence reduction target in Australia. *Clin Infect Dis*, 66(7):1019–1023, 2018. doi: 10.1093/cid/cix939.

A. E. Sever, J. J. Rainey, E. R. Zell, K. Hennessey, A. Uzicanin, C. Castillo-Solórzano, and V. Dietz. Measles elimination in the Americas: A comparison between countries with a one-dose and two-dose routine vaccination schedule. *Journal of Infectious Diseases*, 204(SUPPL. 2), 2011. doi: 10.1093/infdis/jir445.

E. Shim, G. B. Chapman, J. P. Townsend, and A. P. Galvani. The influence of altruism on influenza vaccination decisions. *Journal of The Royal Society Interface*, 9(74):2234–2243, 2012a. doi: 10.1098/rsif.2012.0115.

E. Shim, J. J. Grefenstette, S. M. Albert, B. E. Cakouros, and D. S. Burke. A game dynamic model for vaccine skeptics and vaccine believers: Measles as an example. *Journal of Theoretical Biology*, 295:194–203, 2012b. doi: 10.1016/j.jtbi.2011.11.005.

D. Sidebottom, A. M. Ekström, and S. Strömdahl. A systematic review of adherence to oral pre-exposure prophylaxis for HIV - How can we improve uptake and adherence? *BMC Infectious Diseases*, 18(1):1–14, 2018. doi: 10.1186/s12879-018-3463-4.

M. Siguier and J. M. Molina. HIV preexposure prophylaxis: An essential, safe and effective prevention tool for sexual health. *Medecine et Maladies Infectieuses*, 48(5):318–326, 2018. doi: 10.1016/j.medmal.2018.01.009.

Sigve. HIV timecourse. URL: https://commons.wikimedia.org/w/index.php?curid=15383502, 2011.

A. L. Singleton, B. D. Marshall, X. Zang, A. S. Nunn, and W. C. Goedel. Added benefits of pre-exposure prophylaxis use on HIV incidence with minimal changes in efficiency in the context of high treatment engagement among men who have sex with men. *AIDS Patient Care and STDs*, 34(12):506–515, 2020. doi: 10.1089/apc.2020.0151.

N. Sood, Z. Wagner, A. Jaycocks, E. Drabo, and R. Vardavas. Test-and-treat in Los Angeles: A mathematical model of the effects of test-and-treat for the population of men who have sex with men in Los Angeles county. *Clinical Infectious Diseases*, 56(12):1789–1796, 2013. doi: 10.1093/cid/cit158.

P. M. Strebel, M. J. Papania, A. P. Fiebelkorn, and N. A. Halsey. 20 - Measles vaccine. In S. A. Plotkin, W. A. Orenstein, and P. A. Offit, editors, *Vaccines (Sixth Edition)*, pages 352–387. W.B. Saunders, sixth edition, 2013. ISBN 978-1-4557-0090-5. doi: 10.1016/B978-1-4557-0090-5.00028-8.

V. Supervie, J. G. García-Lerma, W. Heneine, and S. Blower. HIV, transmitted drug resistance, and the paradox of preexposure prophylaxis. *Proceedings of the National Academy of Sciences of the United States of America*, 107(27):12381–12386, 2010. doi: 10.1073/pnas.1006061107.

V. Supervie, M. Barrett, J. S. Kahn, G. Musuka, T. L. Moeti, L. Busang, and S. Blower. Modeling dynamic interactions between pre-exposure prophylaxis interventions and treatment programs: predicting HIV transmission and resistance. *Scientific Reports*, 1:1–11, 2011. doi: 10.1038/srep00185.

S. W. Taylor, K. H. Mayer, S. M. Elsesser, M. J. Mimiaga, C. O'Cleirigh, and S. A. Safren. Optimizing content for pre-exposure prophylaxis (PrEP) counseling for men who have sex

with men: Perspectives of PrEP used and high-rise PrEP naïve men. *AIDS and behavior*, 18 (5):871–879, 2014. doi: 10.1007/s10461-013-0617-7.

Tribune. Viser l'objectif zéro covid constitue un moyen clair de traverser la pandémie en minimisant les dégâts. *Le Monde*, 2021. URL https://www.lemonde.fr/idees/article/2021/02/15/viser-l-objectif-zero-covid-constitue-un-moyen-clair-de-traverser-la-pandemie-en-minimisan 6070045_3232.html.

A. Trickey, M. T. May, J.-J. Vehreschild, N. Obel, M. J. Gill, H. M. Crane, et al. Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies. *The Lancet HIV*, 4(8):e349–e356, 2017. doi: 10.1016/S2352-3018(17) 30066-8.

S. Tully, M. Cojocaru, and C. T. Bauch. Coevolution of risk perception, sexual behaviour, and HIV transmission in an agent-based model. *Journal of Theoretical Biology*, 337:125–132, 2013. doi: 10.1016/j.jtbi.2013.08.014.

S. Tully, M. Cojocaru, and C. T. Bauch. Sexual behavior, risk perception, and HIV transmission can respond to HIV antiviral drugs and vaccines through multiple pathways. *Scientific Reports*, 5(November 2014):1–16, 2015. doi: 10.1038/srep15411.

S. Tully, M.-G. Cojocaru, and C. T. Bauch. Multiplayer games and HIV transmission via casual encounters. *Mathematical Biosciences and Engineering*, 13(6):1–1, 2016. doi: 10.3934/mbe. 2017023.

P. A. Ubel, M. D. Spranca, M. L. Dekay, J. C. Hershey, and D. A. Asch. Public preferences for prevention versus cure: What if an ounce of prevention is worth only an ounce of cure? *Medical Decision Making*, 18(2):141–148, 1998. doi: 10.1177/0272989X9801800202.

UNAIDS. On the Fast-Track to end AIDS, 2011. URL https://www.fast-trackcities.org/sites/default/files/UNAIDS%202016-2021%20Strategy%20-%20On%20the%20Fast-Track%20to%20end%20AIDS%20%282015%29.pdf.

UNAIDS. Fast-Track: Ending the AIDS epidemic by 2030, 2014. URL https://www.unaids.org/en/resources/documents/2014/JC2686_WAD2014report.

UNAIDS. Ending AIDS progress towards the 90–90–90 targets. *Global AIDS Update*, page 198, 2017. URL http://rstesa.unaids.org/publications/global-publications/2017/item/81-ending-aids-progress-towards-the-90-90-90-targets.

UNAIDS. Data 2018. pages 1–376, 2018. URL https://www.unaids.org/en/resources/documents/2018/unaids-data-2018.

UNAIDS. Data 2019. pages 1–476, 2019a. URL https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf.

UNAIDS. Fact Sheet – Global Update AIDS 2019, 2019b. URL https://www.unaids.org/en/resources/fact-sheet.

UNAIDS. Data 2020. pages 1–436, 2020a. URL https://www.unaids.org/sites/default/files/media{_}asset/2020{_}{%}0Aglobal-aids-report{_}en.pdf.

UNAIDS. HIV estimates with uncertainty bounds 1990–2019. Global HIV & AIDS statistics — 2020 fact sheet, 2020b. URL https://www.unaids.org/en/resources/documents/2020/HIV_estimates_with_uncertainty_bounds_1990-present.

K. Underhill, K. M. Morrow, C. Colleran, S. K. Calabrese, D. Operario, P. Salovey, and K. H. Mayer. Explaining the efficacy of pre-exposure prophylaxis (PrEP) for HIV prevention: A qualitative study of message framing and messaging preferences among US men who have sex with men. *AIDS and Behavior*, 20(7):1514–1526, 2016. doi: 10.1007/s10461-015-1088-9.

A. J. Valleron. Les roles de la modelisation en epidemiologie. *Comptes Rendus de l'Academie des Sciences - Serie III*, 323(5):429–433, 2000. doi: 10.1016/S0764-4469(00)00153-0.

F. van Aar, Y. van Weert, R. Spijker, H. Götz, E. Op de Coul, M. Hulstein, D. van Veldhuizen, J. Rodriquez, L. Vasen, F. van Aar, and R. Spijker. Partner notification among men who have sex with men and heterosexuals with STI/HIV: different outcomes and challenges. *International Journal of STD and AIDS*, 26(8):565–573, 2015. doi: 10.1177/0956462414547398.

P. Van Den Driessche and J. Watmough. A simple SIS epidemic model with a backward bifurcation. *Journal of Mathematical Biology*, 40(6):525–540, 2000. doi: 10.1007/s002850000032.

P. van den Driessche and J. Watmough. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Mathematical Biosciences*, 180: 29–48, 2002. doi: 10.1016/S0025-5564(02)00108-6.

P. van den Driessche and J. Watmough. Further notes on the basic reproduction number. In F. Brauer, P. van den Driessche, and J. Wu, editors, *Mathematical Epidemiology*, volume 1945 of *Lecture Notes in Mathematics*, chapter 6, pages 159–178. Springer Berlin Heidelberg, Berlin, Heidelberg, 2008. ISBN 978-3-540-78910-9. doi: 10.1007/978-3-540-78911-6.

R. Vardavas, R. Breban, and S. Blower. Can influenza epidemics be prevented by voluntary vaccination? *PLoS Computational Biology*, 3(5):0796–0802, 2007. doi: 10.1371/journal.pcbi.0030085.

A. Velter, L. Saboni, C. Sommen, P. Bernillon, N. Bajos, and C. Semaille. Sexual and prevention practices in men who have sex with men in the era of combination HIV prevention: results from the 'Presse Gays et Lesbiennes' survey, France, 2011. *Eurosurveillance*, 20(14), 2015.

A. Velter, K. Champenois, D. Rojas Casto, and N. Lydié. Impact perçu de l'épidémie de COVID-19 des hommes ayant des rapports sexuels avec des hommes en france. Enquête eras COVID-19, 30 juin–15 juillet 2020. *Bulletin Epidémiologique Hebdomanaire*, 2020(33–34):666–672, 2020.

F. Verelst, L. Willem, and P. Beutels. Behavioural change models for infectious disease transmission: a systematic review (2010–2015). *Journal of The Royal Society Interface*, 13(125): 20160820, 2016. doi: 10.1098/rsif.2016.0820.

W. Wang and S. Ruan. Bifurcations in an epidemic model with constant removal rate of the infectives. *Journal of Mathematical Analysis and Applications*, 291(2):775–793, 2004. doi: 10.1016/j.jmaa.2003.11.043.

Z. Wang, M. A. Andrews, Z. X. Wu, L. Wang, and C. T. Bauch. Coupled disease-behavior dynamics on complex networks: A review. *Physics of Life Reviews*, 15:1–29, 2015. doi: 10.1016/j.plrev.2015.07.006.

Z. Wang, C. T. Bauch, S. Bhattacharyya, A. D'Onofrio, P. Manfredi, M. Perc, N. Perra, M. Salathé, and D. Zhao. Statistical physics of vaccination. *Physics Reports*, 664:1–113, 2016. doi: 10.1016/j.physrep.2016.10.006.

WHO. Declaration of global eradication of smallpox. *Weekly epidemiology records*, 55(20):148, 1980. URL https://apps.who.int/iris/handle/10665/155528.

WHO. *Global measles and rubella strategic plan 2012–2020*. 2012. URL https://www.who.int/publications/i/item/9789241503396.

WHO. *Strategies for addressing vaccine hesitancy – A systematic review.* 2014. URL https://www.who.int/immunization/sage/meetings/2014/october/3_SAGE_WG_Strategies_addressing_vaccine_hesitancy_2014.pdf.

WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV, 2015. ISBN 9789241509565. URL https://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/.

WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. *World Health Organization*, page 155 p., 2016a. URL https://www.who.int/hiv/pub/guidelines/keypopulations-2016/en/.

WHO. HIV Prevention, Diagnosis, Treatment and Care for Key Populations (2016 Update). *World Health Organization*, page 155, 2016b. URL https://apps.who.int/iris/bitstream/handle/10665/258967/WHO-HIV-2017.05-eng.pdf;sequence=1.

WHO. Global health sectors strategy on sexually transmitted infections 2016–2021. Towards ending STIs., 2016a. URL https://www.who.int/reproductivehealth/ghs-strategies/en/.

WHO. Smallpox vaccines, 2016b. URL https://www.who.int/csr/disease/smallpox/vaccines/en/.

WHO. 2018 Assessment report of the Global Vaccine Action Plan. Strategic Advisory Group of Experts on Immunization. Geneva: World Health Organization, 2018a. URL https://www.who.int/immunization/global_vaccine_action_plan/SAGE_GVAP_Assessment_Report_2018_EN.pdf?ua=1.

WHO. *World Health Statistics 2018: monitoring health for the SDGs, sustainable development goals.* Geneva, 2018b. ISBN 978-92-4-156558-5. URL https://apps.who.int/iris/handle/10665/272596.

WHO. Ten threats to global health in 2019, 2019. URL https://www.who.int/news-room/feature-stories/ten-threats-to-global-health-in-2019.

WHO. HIV/AIDS factsheet, 2019a. URL https://www.who.int/en/news-room/fact-sheets/detail/hiv-aids.

WHO. Measles factsheet, 2019b. URL https://www.who.int/en/news-room/fact-sheets/detail/measles.

WHO. Polio factsheet, 2019c. URL https://www.who.int/en/news-room/fact-sheets/detail/poliomyelitis.

WHO. Immunisation agenda 2030: A global strategy to leave no one behind, 2019. URL https://www.who.int/publications/m/item/immunization-agenda-2030-a-global-strategy-to-leave-no-one-behind.

WHO. Measles in Europe: record number of both sick and immunized, 2019. URL http://www.euro.who.int/en/media-centre/sections/press-releases/2019/measles-in-europe-record-number-of-both-sick-and-immunized.

WHO. GVAP 2011-2020, Review and lessons learned. Strategic Advisory Group of Experts on immunization, 2020. URL https://apps.who.int/iris/bitstream/handle/10665/329097/WHO-IVB-19.07-eng.pdf?ua=1.

WHO. Sustainable development goals. Goal 3: Ensure healthy lives and promote well-being for all at all ages, 2020. URL https://sdgs.un.org/goals/goal3. Website accessed: November 22, 2020.

WHO. Department of global communications. un tackles 'infodemic' of misinformation and cybercrime in covid-19 crisis, 2020a.

WHO. More than 117 million children at risk of missing out on measles vaccines, as COVID-19 surges, 2020b. URL https://www.who.int/immunization/diseases/measles/statement_missing_measles_vaccines_covid-19/en/.

WHO. Immunization coverage, 2020c. URL https://www.who.int/news-room/fact-sheets/detail/immunization-coverage.

WHO. 1st WHO Infodemic Manager training. URL: https://www.who.int/teams/risk-communication/infodemic-management/1st-who-training-in-infodemic-management, 2020a.

WHO. Vaccine-preventable diseases: monitoring system. 2020 global summary, 2020b. URL https://apps.who.int/immunization_monitoring/globalsummary/countries?countrycriteria%5Bcountry%5D%5B%5D=FRA&commit=OK. Website accessed: November 22, 2020.

WHO. Coronavirus Disease (COVID-19) Dashboard, 2021a. URL https://covid19.who.int.

WHO. Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process, 2021b. URL https://www.who.int/emergencies/diseases/novel-coronavirus-2019/covid-19-vaccines.

WHO. New measles surveillance data from WHO, August 2019. URL https://www.who.int/immunization/newsroom/new-measles-data-august-2019/en/.

O. J. Wouters, K. C. Shadlen, M. Salcher-Konrad, A. J. Pollard, H. J. Larson, Y. Teerawattananon, and M. Jit. Challenges in ensuring global access to COVID-19 vaccines: production, affordability, allocation, and deployment. *The Lancet*, 6736(21):1–12, 2021. doi: 10.1016/S0140-6736(21)00306-8.

B. Wu, F. Fu, and L. Wang. Imperfect vaccine aggravates the long-standing dilemma of voluntary vaccination. *PLoS ONE*, 6(6), 2011. doi: 10.1371/journal.pone.0020577.

Y. Xiang, Y. Jia, L. Chen, L. Guo, B. Shu, and E. Long. COVID-19 epidemic prediction and the impact of public health interventions: A review of COVID-19 epidemic models. *Infectious Disease Modelling*, 6(24):324–342, 2021. doi: 10.1016/j.idm.2021.01.001.

I. Young, P. Flowers, and L. M. McDaid. Barriers to uptake and use of pre-exposure prophylaxis (PrEP) among communities most affected by HIV in the UK: Findings from a qualitative study in Scotland. *BMJ Open*, 4(11), 2014. doi: 10.1136/bmjopen-2014-005717.

ZeroCovid. The aim is zero infections! for a european shutdown in solidarity. 2021. URL https://zero-covid.org/language/en/.

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LaTeX packages

- `algorithmx` (available at: https://ctan.org/pkg/algorithmicx)
- `fancyhdr` (available at: https://www.ctan.org/pkg/fancyhdr)
- `pdfpages` (available at: https://ctan.org/pkg/pdfpages)
- `pseudocode` (available at: https://ctan.org/pkg/pseudocode)

Matlab packages

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

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