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## Thesis Defense

Sorbonne Université

# Prevention of infectious diseases in the context of efficient treatment: a game theoretic approach

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Team SUMO: Communicable Diseases Surveillance and Modelling

July 5, 2021

## Interdisciplinarity statement

This thesis was conducted in the context of the interdisciplinary  
Public Health Doctoral Network coordinated by the EHESP

# Introduction

## Introduction

- General context
- General objectives
- Methods overview

## I. Vaccination

- Context
- Model
- Results

## II. PrEP

- Context
- Model
- Results

## Discussion

- Perspectives
  - Public health interventions
- Acknowledgments

## General context

Public health programs aiming to disease elimination

Efficient preventive and therapeutic interventions have decreased the overall number of new infections worldwide in the last decade.

The World Health Organization (WHO) declaration of 17 Sustainable Development Goals includes disease **prevention interventions aiming to disease elimination**, such as:

- The Immunization Agenda 2030
- The Fast Track initiative to end the AIDS epidemic



The success of prevention programs relies on the participation of the targeted population

# General context

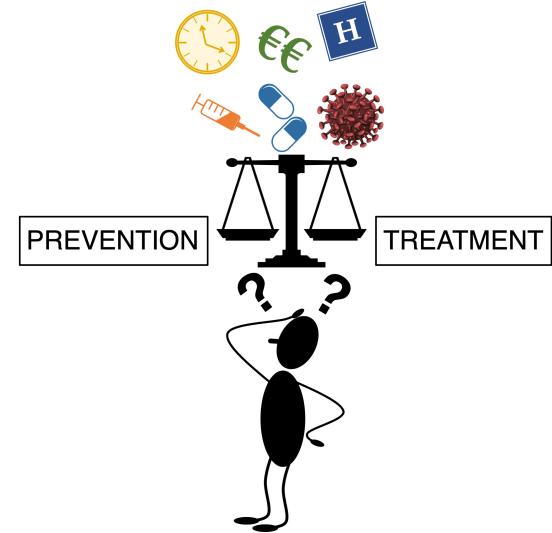
## The dilemma of prevention versus treatment

When facing the risk of an epidemic, in a context where efficient treatment is available, individuals may engage in a *prevention versus treatment dilemma*, and make the decision between adopting prevention or not, and be treated in case of infection.

### Voluntary prevention

The resolution of the dilemma of prevention versus treatment at the individual level.

Is an ounce of prevention  
worth a pound of cure?



# General objectives

## Main research question

Can voluntary prevention lead to epidemic elimination?

- Study the dilemma of prevention versus treatment from the mathematical modeling perspective
- Determine whether and under what conditions can voluntary prevention eliminate an epidemic
- Discussion
  - Public health intervention framework
  - Context of epidemic elimination goals

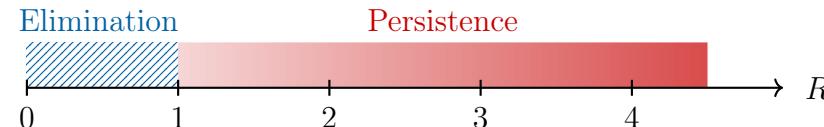
## Methods – General framework

### Epidemic elimination

#### Effective reproduction number ( $R$ ).

The expected number of secondary cases produced by a single infected individual, during his/her entire infectious period, in an uninfected population subject to control interventions.

The effective reproduction number reflects the epidemic behavior **in the long run**:



#### Epidemic elimination

Epidemic is *eliminated*, in the long run, if and only if  $R \leq 1$ .

Solving  $R = 1$  for the prevention coverage, we obtain  $p_c$ , the *herd immunity threshold*.

#### Epidemic control

We say that the epidemic is *controlled* if  $R < R_0$ , where  $R_0$  is the effective reproduction number in the absence of preventive interventions.

# Methods – General framework

## Modeling decision-making

Individual behavior and its impact on the epidemic has been addressed in behavioral epidemiology using mathematical models combining the disease transmission at the population level, with models describing the individuals' behavior before an epidemic.

In particular, **game-theoretic approaches have been used to address the individual-level decision making about prevention adoption**, by assuming that individuals choose the strategy they benefit the most from.

### Perceived cost

In a game-theoretic framework, the benefits and constraints of prevention and treatment are considered as *costs*, and may include monetary and/or non-monetary aspects such as

- price,
- quality of life,
- undesired secondary effects,
- accessibility,
- social stigma,
- reimbursement policies,
- disease morbidity,
- etc.

## Methods – Mathematical model

Individual decision-making

Epidemic dynamics

# Methods – Mathematical model

Perceived risk  
of infection

## Individual decision-making

### Game-theoretical approach

- **Decision-making between two mutually exclusive strategies:**
  - to use prevention
  - not using prevention, and be treated in case of infection
- Individual decide by considering
  - Perceived risk of infection
  - Perceived **relative cost of prevention versus treatment**
- **Maximization of the utility**

Voluntary  
prevention  
coverage

# Methods – Mathematical model

Perceived risk  
of infection

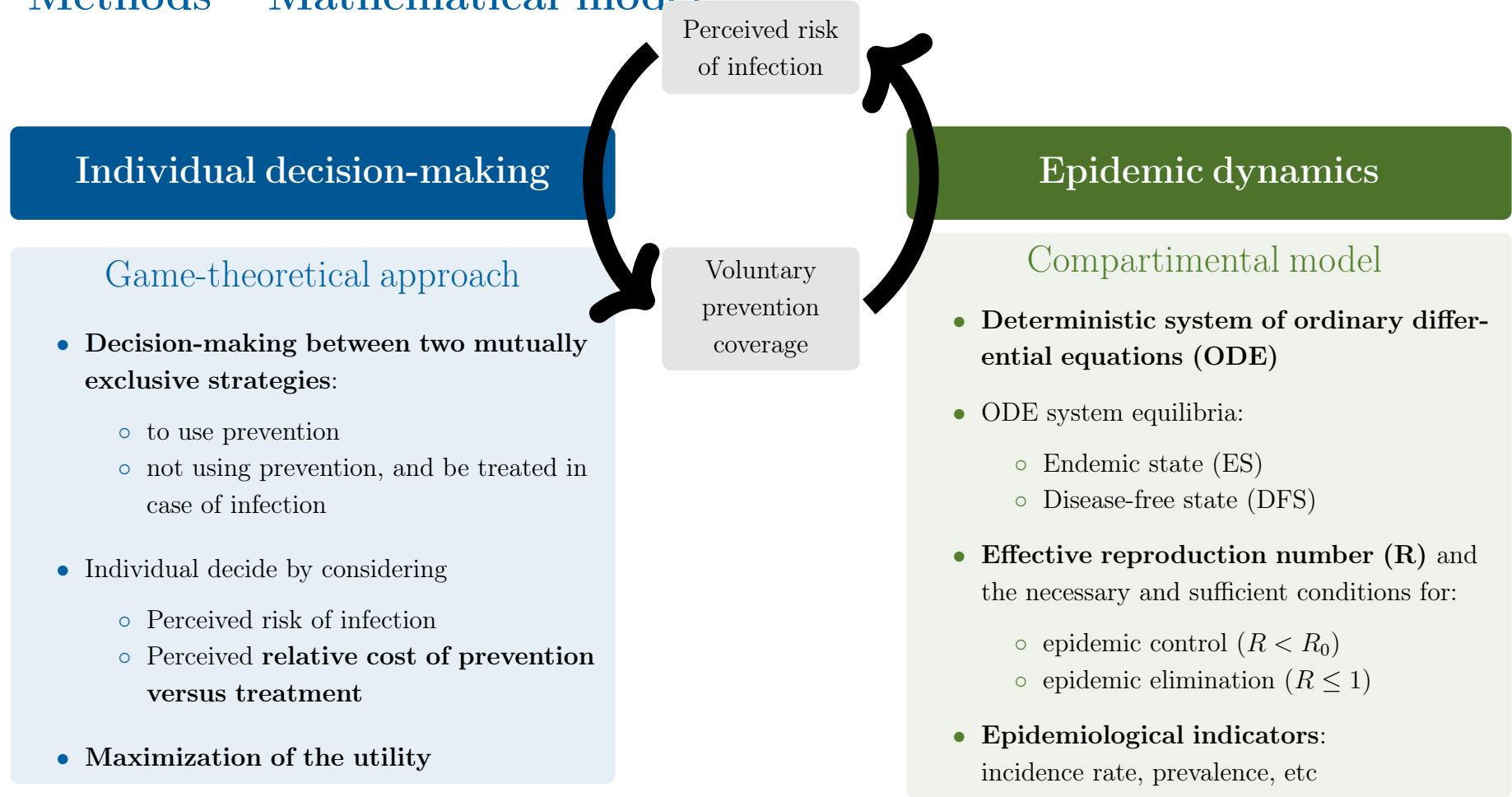
## Epidemic dynamics

Voluntary  
prevention  
coverage

### Compartmental model

- **Deterministic system of ordinary differential equations (ODE)**
- ODE system equilibria:
  - Endemic state (ES)
  - Disease-free state (DFS)
- **Effective reproduction number ( $R$ )** and the necessary and sufficient conditions for:
  - epidemic control ( $R < R_0$ )
  - epidemic elimination ( $R \leq 1$ )
- **Epidemiological indicators:**  
incidence rate, prevalence, etc

# Methods – Mathematical model



# Two projects

## I. Vaccination against childhood infectious diseases

Vaccine 35 (2017) 5339–5345

Contents lists available at ScienceDirect

Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)

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Prevention of treatable infectious diseases: A game-theoretic approach

Sofía Jijón <sup>a,\*</sup>, Virginie Supervie <sup>a</sup>, Romulus Breban <sup>b</sup>

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**ARTICLE INFO**

**Article history:**  
Received 11 May 2017  
Received in revised form 16 August 2017  
Accepted 17 August 2017  
Available online 31 August 2017

**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-



(Jijón et al., *Vaccine*, 2017)

# Two projects

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(Jijón et al., *Vaccine*, 2017)

## II. Pre-exposure prophylaxis against HIV infection

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

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(Jijón et al., *AIDS [Accepted]*, 2021)

# I. Vaccination against childhood infectious diseases

(Jijón et al., Vaccine, 2017)

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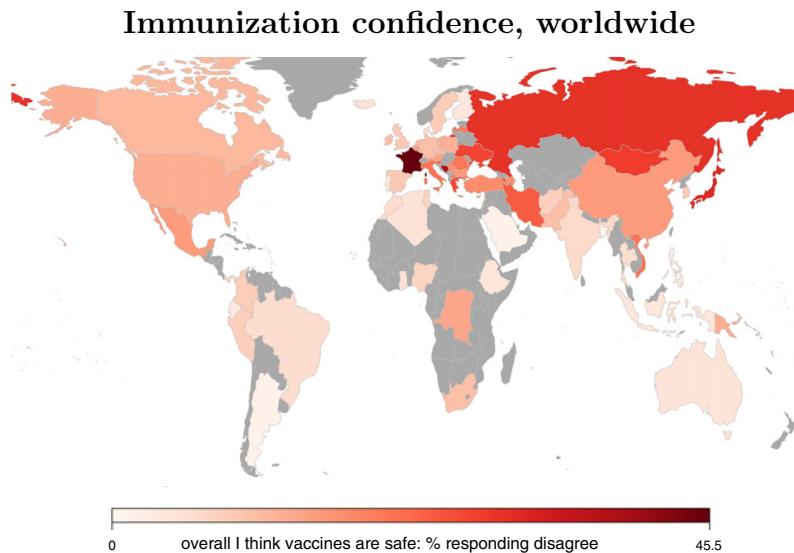
## Discussion

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## Context

Vaccine hesitancy  
(delay in acceptance or refusal)

The WHO listed vaccine hesitancy among the threats to global health in 2019

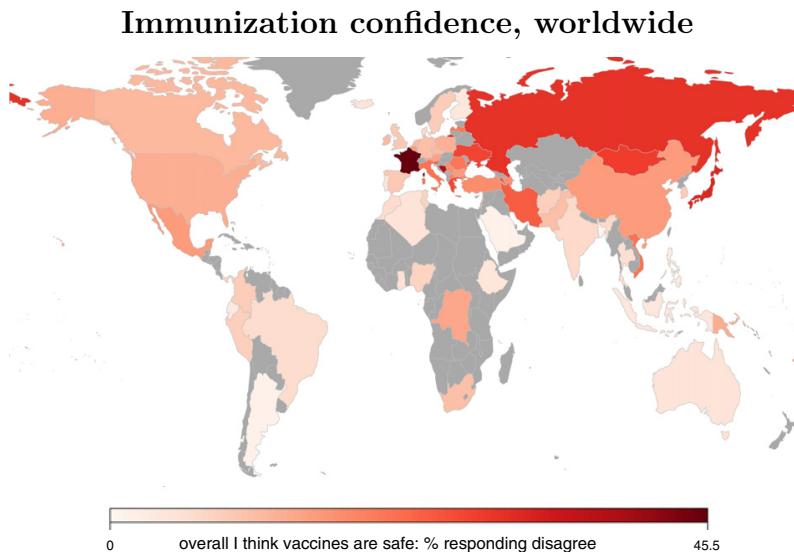


(Larson et al., *EBioMedicine*, 2016)

# Context

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The WHO listed vaccine hesitancy among the threats to global health in 2019

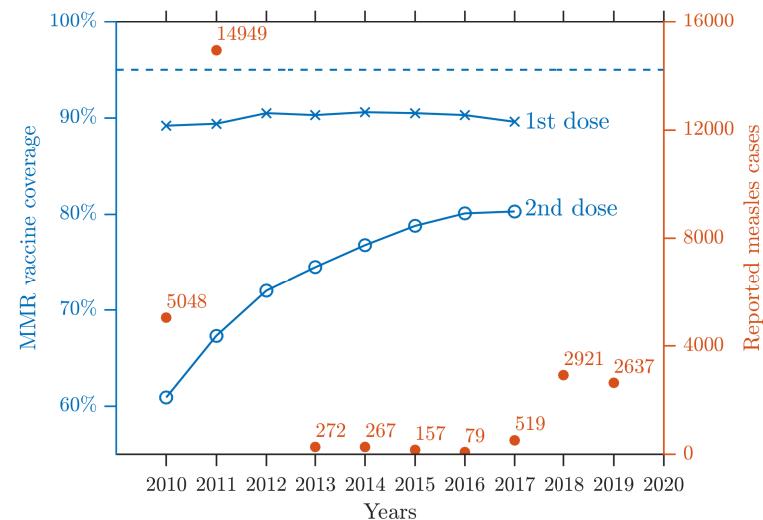


(Larson et al., *EBioMedicine*, 2016)

Vaccination against measles

In France, the coverage for the second dose of MMR vaccine is below the required level to reach herd immunity.

**Measles vaccination in France**



(WHO, 2020)

# Model – Population-level disease transmission

## Main hypotheses

- Imperfect vaccine
  - limited duration of vaccine-induced immunity
  - takes in a proportion of vaccinees
- Imperfect treatment (works on a proportion of treated individuals)

## ODE system

$$\frac{dV}{dt} = \varepsilon p \pi - (\rho + \mu) V,$$

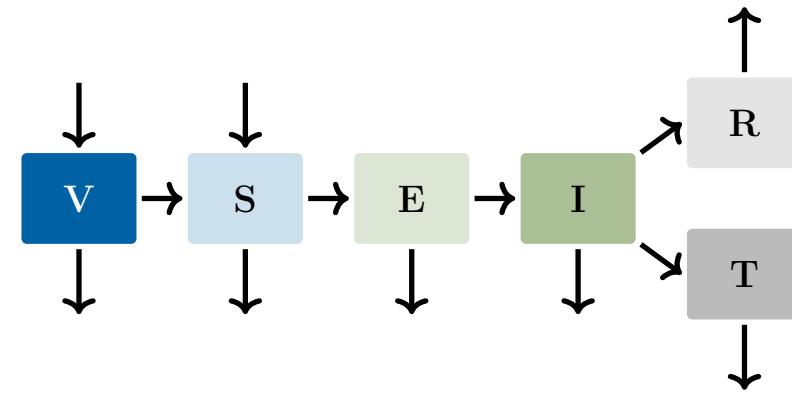
$$\frac{dS}{dt} = (1 - \varepsilon p) \pi + \rho V - \frac{\beta I}{N} S - \mu S,$$

$$\frac{dE}{dt} = \frac{\beta I}{N} S - (\nu + \mu) E,$$

$$\frac{dI}{dt} = \nu E - (\sigma + \gamma + \mu) I,$$

$$\frac{dR}{dt} = (1 - \xi) \sigma I + \gamma I - \mu R,$$

$$\frac{dT}{dt} = \xi \sigma I - \mu T.$$



## Model – Studying the ODE system

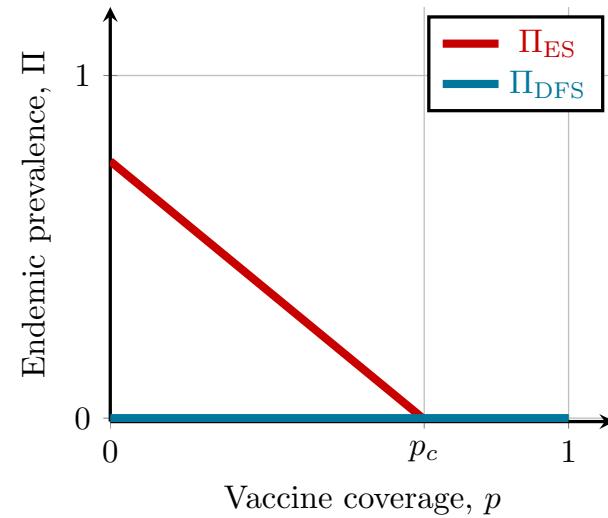
The endemic prevalence ( $\Pi$ )

$$\Pi(\varepsilon, p) = \begin{cases} \Pi_{\text{DFS}}, & \text{if } R \leq 1, \\ \Pi_{\text{ES}}, & \text{if } R > 1; \end{cases}$$

where

$$\Pi_{\text{DFS}} = 0$$

$$\Pi_{\text{ES}} = \frac{\mu}{\beta} \left( 1 + \frac{\sigma + \gamma + \mu}{\nu} \right) (R(\varepsilon, p) - 1)$$



## Model – Studying the ODE system

The endemic prevalence ( $\Pi$ )

$$\Pi(\varepsilon, p) = \begin{cases} \Pi_{\text{DFS}}, & \text{if } R \leq 1, \\ \Pi_{\text{ES}}, & \text{if } R > 1; \end{cases}$$

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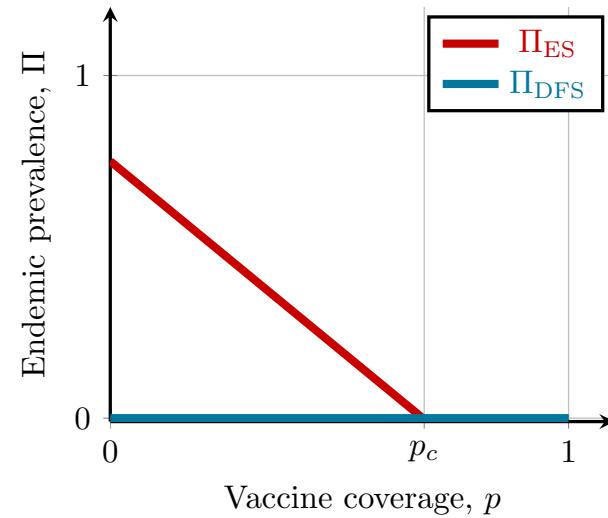
$$\Pi_{\text{ES}} = \frac{\mu}{\beta} \left( 1 + \frac{\sigma + \gamma + \mu}{\nu} \right) (R(\varepsilon, p) - 1)$$

The effective reproduction number ( $R$ )

$$R(\varepsilon, p) = \left( 1 - \varepsilon p \frac{\mu}{\rho + \mu} \right) R_0$$

where

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



Herd immunity threshold

$$\varepsilon p_c = \left( 1 + \frac{\rho}{\mu} \right) \left( 1 - \frac{1}{R_0} \right)$$

## Model – Individual-level decision-making

### Main hypothesis

- Individuals assess their risk of infection by acknowledging the endemic prevalence,  $\Pi(p)$
- Individuals maximize their utility

### Individual utility

The **total perceived cost** expected for an individual is given by

$$C \equiv p C_V + (1 - \varepsilon p) \Pi(p) C_T$$

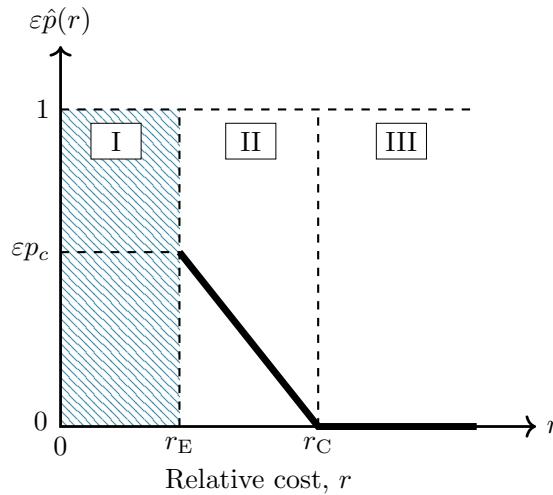
Introducing the **relative cost of vaccination versus treatment**,  $r \equiv C_V/C_T$ ,

#### Utility function

$$U(p; r) \equiv -p r - (1 - \varepsilon p) \Pi(p) \equiv -C$$

## Results – Maximizing the utility

By solving  $\partial U/\partial p = 0$  for  $p$ , we obtain the **effective, voluntary vaccine coverage** ( $\varepsilon\hat{p}$ )



where

$$p_c = \hat{p}(r_E)$$

$r_E$ : threshold for epidemic elimination

$r_C$ : threshold for epidemic control

### Epidemic elimination

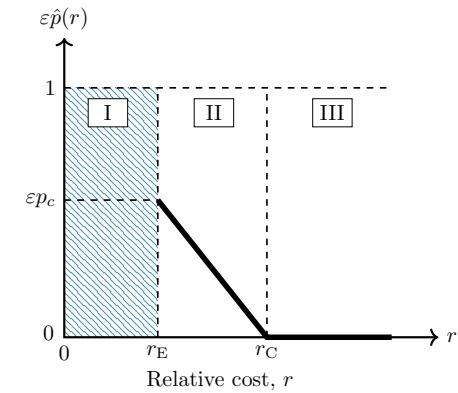
We found that there is no equilibrium coverage for voluntary vaccination in region I.

In addition,

$$r_E > 0 \text{ if and only if } \frac{1}{\rho} > \frac{1}{\mu} (R_0 - 1)$$

# Conclusions

- We obtain the **voluntary vaccination coverage** expressed as a function of the relative cost of vaccination versus treatment perceived by individuals
- We found, analytically, the **thresholds for the relative cost yielding epidemic control ( $R < R_0$ ) and epidemic elimination ( $R \leq 1$ )**, which delimit the domain of the voluntary vaccination coverage in **three regions**
- Epidemic elimination may only be temporary
- The relative cost thus becomes the parameter to be tuned to increase the voluntary vaccination coverage and to maintain elimination in the long run



## II. Pre-exposure prophylaxis (PrEP) against HIV infection

(Jijón et al., AIDS [Accepted], 2021)

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## Context

- In many high-income settings, **men who have sex with men (MSM) are the most affected by HIV**
- Highly effective anti-retroviral treatments (ART) are available
- According to two clinical trials, **PrEP can reduce HIV incidence among MSM by 86%:**
  - IPERGAY (France and Canada)
  - PROUD (England)
- According to **modeling studies**, PrEP can curtail and even **eliminate HIV epidemics**:

Country	PrEP coverage	Time period	Result	Reference
United States	40%	10 years	33% reduction in number of infections	(Jenness et al., <i>J Infect Dis</i> , 2016)
Netherlands	82%	5 years	Elimination	(Rozhnova et al., <i>AIDS</i> , 2018)

Can these high levels of PrEP coverage be achieved voluntarily?

# Model – Compartmental model

## Main hypotheses

### Sexual behavior

- Structured mixing (low and high risk of infection, mainly defined by a higher per-year number of sexual partners)
- No change in sexual behavior
- Mixing occurs preferentially within the same risk group
- High-risk MSM drive the epidemic ( $R \leq 1$  if no transmission by high-risk MSM)

### Treatment

- ART recommended at any stage of the HIV infection
- Individuals on ART no longer transmit HIV

### PrEP

- PrEP is recommended for high risk MSM
- on-PrEP MSM use condom less frequently
- PrEP prescription renewal requires a negative HIV test every 3 months

## Model – Compartmental model

HIV transmission among MSM, subject to PrEP interventions

$$dP/dt = p\pi_h - \left( (1 - \varepsilon)\Lambda_P + \mu \right)P$$

$$dI_P^a/dt = (1 - \varepsilon)\Lambda_P P - (\sigma + \theta_P + \mu) I_P^a$$

$$dI_P^c/dt = \sigma I_P^a - (\theta_P + \mu) I_P^c$$

$$dS_h/dt = (1 - p)\pi_h - (\Lambda_h + \mu) S_h$$

$$dI_h^a/dt = \Lambda_h S_h - (\sigma + \theta + \mu) I_h^a$$

$$dI_h^c/dt = \sigma I_h^a - (\theta + \mu) I_h^c$$

$$dT_h/dt = \theta_P (I_P^a + I_P^c) + \theta (I_h^a + I_h^c) - \mu_T T_h$$

$$dS_\ell/dt = \pi_\ell - (\Lambda_\ell + \mu) S_\ell$$

$$dI_\ell^a/dt = \Lambda_\ell S_\ell - (\sigma + \theta + \mu) I_\ell^a$$

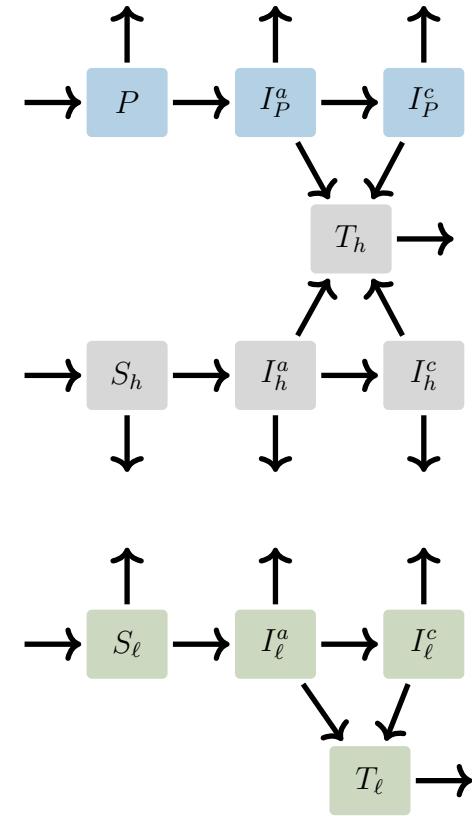
$$dI_\ell^c/dt = \sigma I_\ell^a - (\theta + \mu) I_\ell^c$$

$$dT_\ell/dt = \theta (I_\ell^a + I_\ell^c) - \mu_T T_\ell$$

High risk  
On-PrEP  
MSM

High risk  
Off-PrEP  
MSM

Low risk  
MSM



## Model – Compartmental model

### ODE system equilibria

- Disease-free state (DFS).
- Endemic state (ES), computed numerically.

### Endemic force of infection

For low-risk and high-risk off-PrEP MSM:

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

Endemic force of infection for high-risk on-PrEP MSM:

$$(1 - \varepsilon)\Lambda_P^{\text{ES}} = (1 - \varepsilon) \left( \frac{1 - \xi\eta_P}{1 - \xi\eta_h} \right) \Lambda_h^{\text{ES}}$$

### Effective reproduction number

We obtained  $R(p, \varepsilon)$  analytically, where  $p$  denotes PrEP coverage and  $\varepsilon$  denotes PrEP effectiveness, and we found the conditions for **epidemic elimination** (i.e.,  $R \leq 1$ , and thus the system reaches the DFS).

## Model – Decision model

Modeling the resolution of the PrEP versus ART dilemma among high-risk MSM

Total expected cost

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

where

- $p$  is the probability of using PrEP
- $\varepsilon$  is PrEP effectiveness
- $r = c_P/c_T > 0$  is the relative cost of PrEP versus ART perceived by high-risk MSM
- $C_{\text{PrEP}}(p; \varepsilon, r)$  is the cost perceived for the strategy of using PrEP
- $C_{\text{No-PrEP}}(p; \varepsilon)$  is the cost perceived for the strategy of not using PrEP

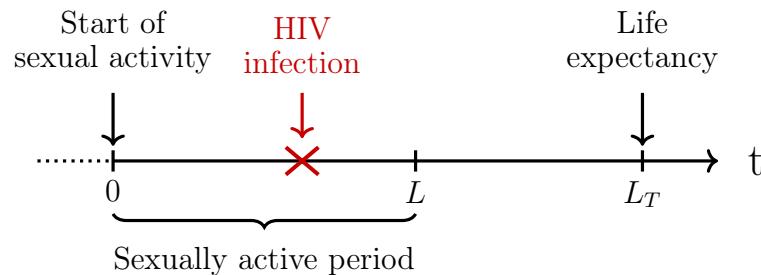
The maximization of the utility  $U(p; \varepsilon, r) \equiv -C(p; \varepsilon, r)$  yields the voluntary PrEP coverage

# Model – Decision model

## Perceived costs for the strategies

Let

- $c_T$  be the cost of ART
- $c_P$  be the cost of PrEP



### Cost of not using PrEP

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

### Cost of using PrEP

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

## Perceived risk of HIV infection (assuming fair perception)

### Off-PrEP MSM

$$\lambda \equiv \begin{cases} \Lambda_h^{\text{ES}}, & \text{if } R > 1 \\ \Lambda_h^{\text{DFS}}, & \text{if } R \leq 1 \end{cases}$$

### On-PrEP MSM

$$\lambda_P \equiv \begin{cases} (1 - \varepsilon) \Lambda_P^{\text{ES}}, & \text{if } R > 1 \\ \Lambda_P^{\text{DFS}}, & \text{if } R \leq 1 \end{cases}$$

## Results – Model calibration for MSM in the Paris region

Our model was calibrated to reproduce the epidemiological situation in the Paris region (Ile-de-France).

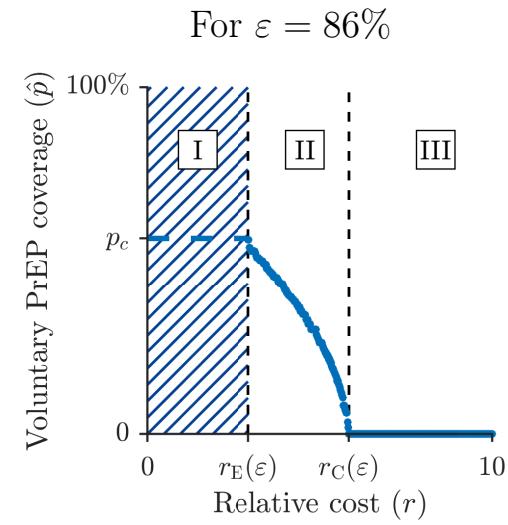
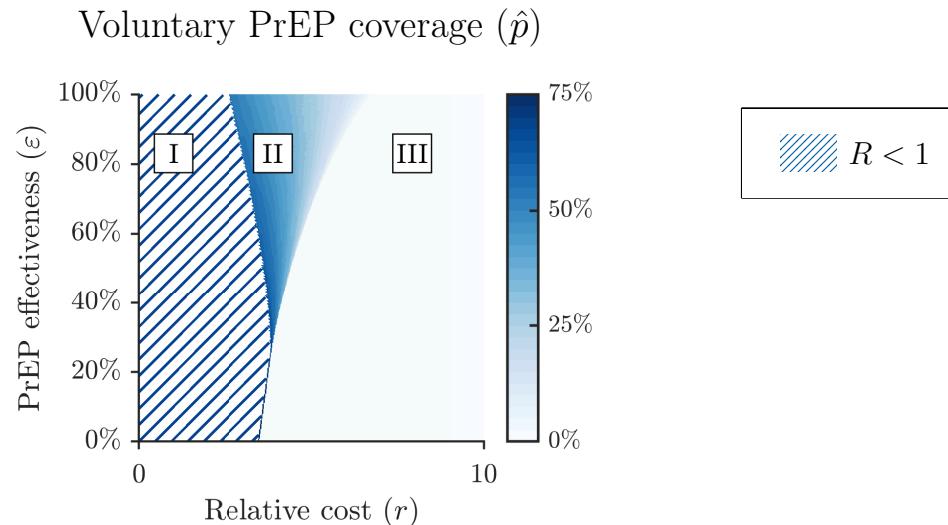
We obtained  $\sim 500$  parameters sets calibrating the ES of the ODE system.

Epidemiological indicator	Calibrated estimates	Published estimates
	Mean (CI 95%)	Mean (CI 95%)
HIV incidence rate (%)	1.3 (1.0–1.6)	2.0 (1.0–2.6)
HIV incidence rate among high-risk MSM (%)	7 (4–10)	9.2
Prevalence of HIV (%)	17 (14–20)	16 (12–20)
Proportion of undiagnosed HIV infections (%)	17 (15–20)	18 (15–20)
Total population	111 000 (94 000–130 000)	118 000 (83 000–167 000)

# Results – The voluntary PrEP coverage ( $\hat{p}$ )

Baseline scenario: Assuming fair risk perception

For one typical parameter set calibrating our model



### Three-region structure

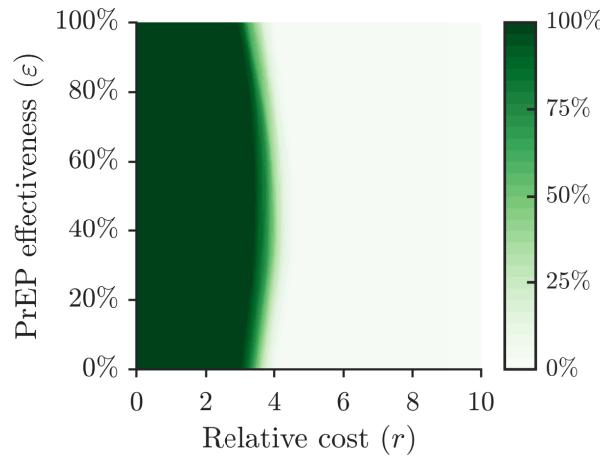
Region I	$R \leq 1$	PrEP-induced epidemic elimination
Region II	$R < R(0, 0)$	PrEP-induced epidemic control
Region III	$R = R(0, 0)$	No PrEP adoption

## Results – Bootstrap

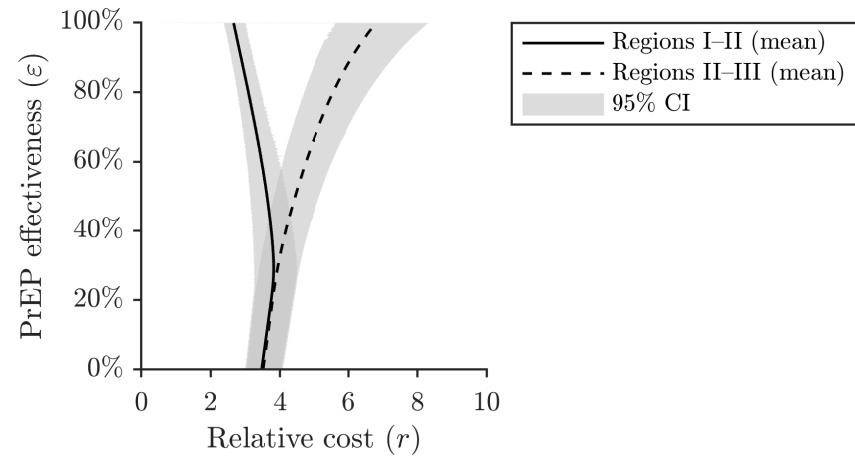
Baseline scenario: Assuming fair risk perception

For the  $\sim 500$  calibrated parameter sets

Probability of HIV elimination



Boundary uncertainty for the three-region structure

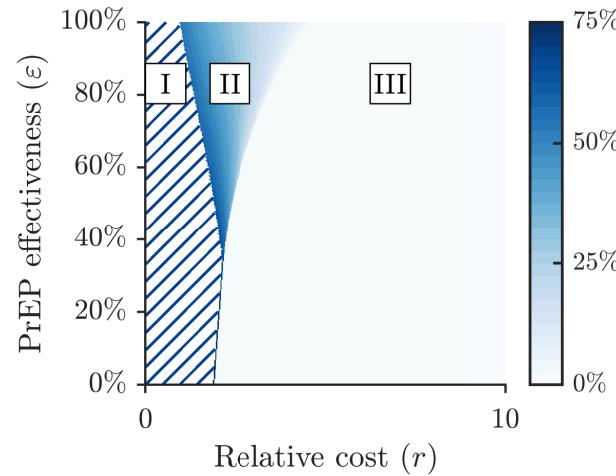


## Sensitivity scenario: risk misperception among high-risk MSM

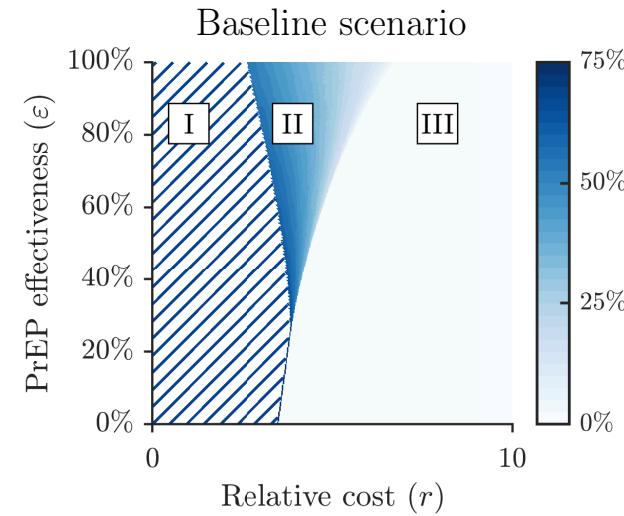
Risk perceived given by the proportion of high-risk MSM diagnosed with HIV

For one typical parameter set calibrating our model

Risk misperception



Baseline scenario



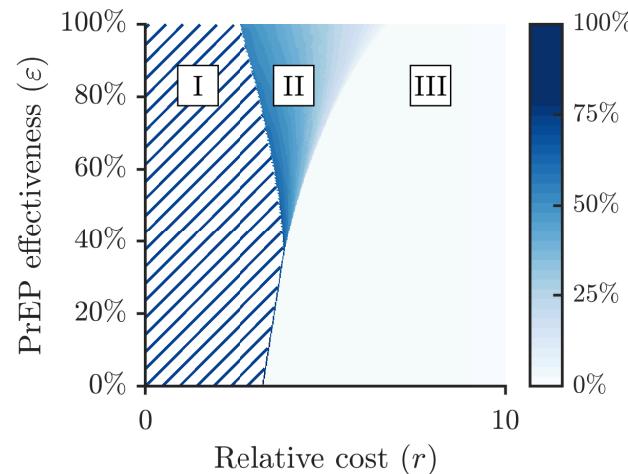
- Enlargement of Region III (no willingness to adopt PrEP)
- Reduction of Region I, despite high levels of PrEP effectiveness

## Sensitivity scenario: risk compensation among on-PrEP MSM

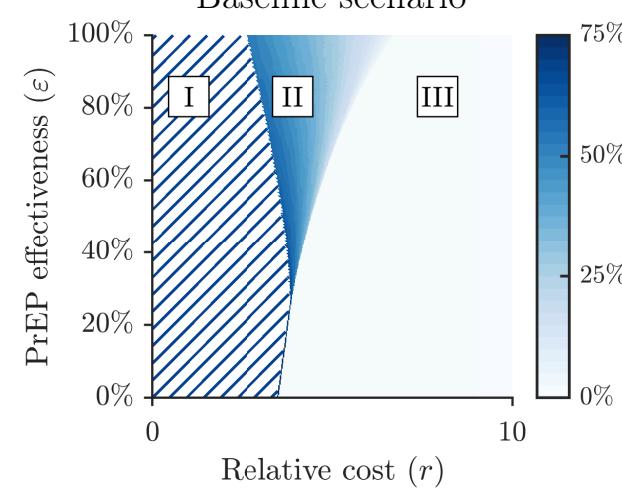
Total drop in condom use among on-PrEP MSM:  $\eta_P = 0$  (instead of a drop from 30% to 20%)

For one typical parameter set calibrating our model

Risk compensation



Baseline scenario



Similar results to the baseline scenario



Risk compensation among on-PrEP MSM does not threaten epidemic elimination

# Conclusions

- **Main outcome.** We obtained the **voluntary PrEP coverage among high-risk MSM** as a function of the PrEP effectiveness and the perceived relative cost of PrEP versus ART
- **Epidemic elimination.** Prevention interventions relying on the voluntary participation of most-at-risk MSM can eliminate HIV epidemic, but elimination may only be temporary.
- **Sensitivity scenarios**
  - Risk underestimation yields a lower cost of PrEP is required for elimination
  - Risk compensation may not play an essential role against epidemic elimination
- **PrEP uptake in the Paris region.** The PrEP coverage among high-risk MSM was estimated to be less than 47%, which is below the herd-immunity threshold 55%. We conclude that **the current PrEP rollout protocol in the Paris region has not reached the prevention coverage for epidemic elimination.**

# General discussion

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- Perspectives
- Public health interventions

## Acknowledgments

## Limitations and perspectives

- Interpreting the relative cost. Our approach does not focus on monetary aspects only, so **the interpretation of the relative cost of prevention versus treatment remains qualitative**. However, this may allow to account for non-monetary barriers for prevention uptake.
- Assuming fair perception may result in overestimation. Assuming misperception under full disclosure of diagnosed peers (PrEP project), may also be an overestimation.
- Including perception heterogeneity. Individuals may perceive costs and risk of infection differently and the utility function may also thus be defined to explicitly account for heterogeneity in risk and cost perception.
- Studying the system dynamics near region I. Our model does not allow to study the system behavior around  $R = 1$ , due to the absence of an equilibrium for the voluntary coverage when  $R < 1$ .
- Considering other behavioral models might be interesting to study in the context of PrEP adoption, such as modeling couples explicitly, including decision-making and/or sexual mixing based on the PrEP-status of the sexual partner and free-riding.

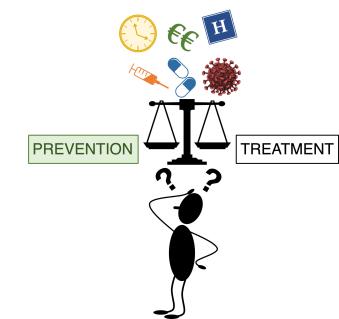
# Challenges for public health interventions aiming to epidemic elimination

- **Facilitating the access to information** on scientific results, infectious disease epidemiology, disease morbidity, and the efficacy and consequences of using the available preventive and therapeutic tools

- Public local and worldwide epidemiological status
- Broad and accessible scientific communication
- Managing infodemics

- **Reducing the perceived cost of prevention** involves monetary and non-monetary interventions

- reducing the price of prevention
- facilitating access to preventive programs
- reducing stigma of individuals at high risk of infection
- developing easier prevention protocols  
(one-shot vaccines, injectable PrEP)



# Acknowledgments

## Advisors

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Virginie SUPERVIE

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MESuRS – Cnam

## Support system

Friends

Family



# Supplementary slides

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# Scientific production

## 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

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## 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.

# Scientific production

## 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.

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 and the EHESP Interdisciplinary Doctoral Network seminar, Rennes, France on March, 2017.

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.

## Vulgarization of science

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

# I. Vaccination – Supplementary information

Key data on vaccination against some preventable childhood infectious

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

<sup>a</sup>After four spaced doses between 2 and 18 months old.

<sup>b</sup>After two shortly separated doses.

<sup>c</sup>After three doses of inactivated poliovirus vaccine.

<sup>d</sup>Corresponding to three doses.

\* Eradication declared in 1980 WHO, 1980

# I. Vaccination – Supplementary results

The effective, voluntary vaccination coverage

$$\varepsilon \hat{p}(r) = \begin{cases} \frac{r_C - r}{\tilde{r}}, & \text{if } r_E < r < r_C, \\ 0, & \text{if } r \geq r_C, \end{cases}$$

where

$$\tilde{r} = \frac{2\varepsilon\mu^2}{(\nu + \mu)(\rho + \mu)} \left( 1 + \frac{\nu}{\sigma + \gamma + \mu} \right) \quad \text{and} \quad r_C = \tilde{r} \left[ 1 - \frac{1}{2R_0} + \frac{\rho}{2\mu} \left( 1 - \frac{1}{R_0} \right) \right]$$

Critical vaccination coverage

The restriction  $R(\hat{p}) > 1$  yields  $r > r_E$ , where  $r_E = \tilde{r} \left[ \frac{1}{2R_0} - \frac{\rho}{2\mu} \left( 1 - \frac{1}{R_0} \right) \right]$

Existence of the three regions

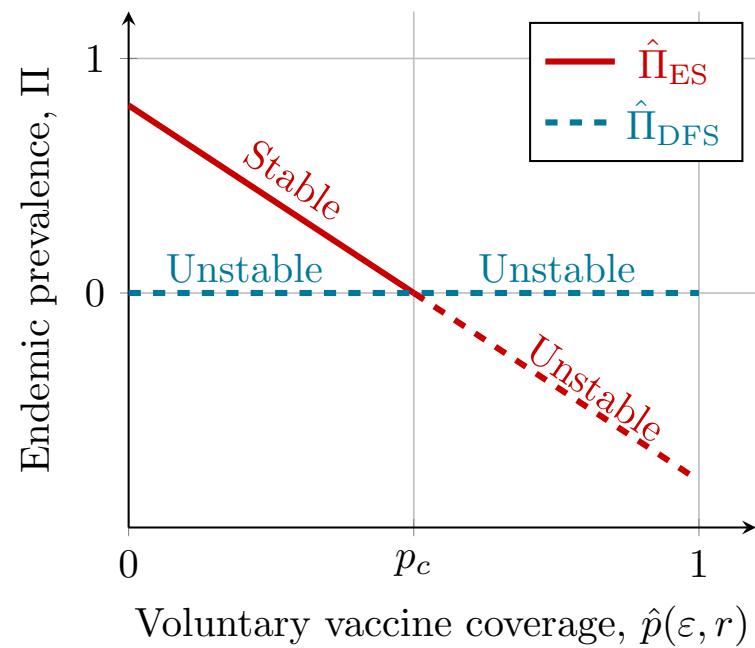
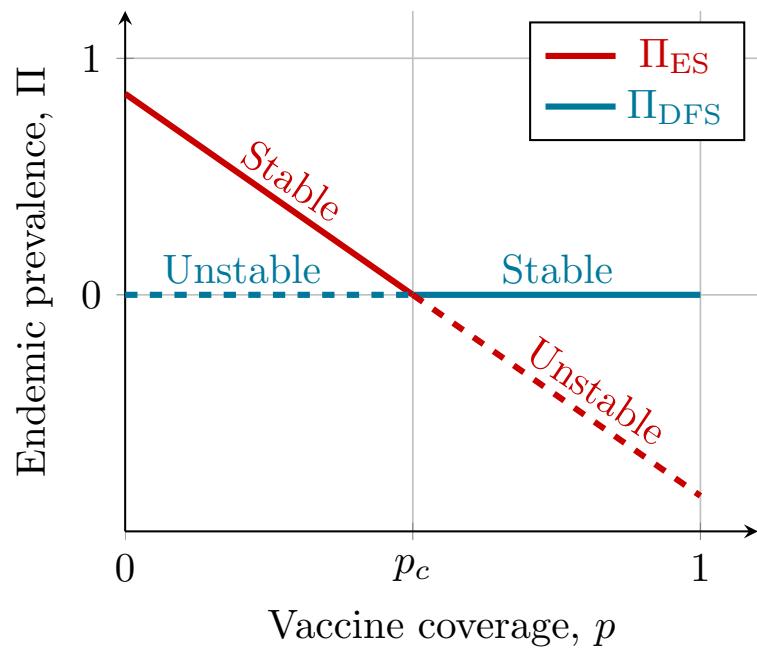
We note that  $r_E < r_C$  whenever  $R_0 > 1$ . In addition,  $r_E > 0$  if and only if  $\frac{1}{\rho} > \frac{1}{\mu} \left( R_0 - 1 \right)$ .

Threshold for the effective vaccination coverage

$$\varepsilon \hat{p}(r_E) = \left( 1 + \frac{\rho}{\mu} \right) \left( 1 - \frac{1}{R_0} \right)$$

## I. Vaccination – Supplementary results

Endemic prevalence



## Supplementary definitions – PrEP

The mixing matrix

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

where

$$0 < \rho_{ij} < 1, \quad \sum_j \rho_{ij} = 1.$$

We assume that individuals mix preferentially (but not exclusively) with same-risk MSM

$$\rho_{ii} > 1/2.$$

The total number of partnerships is balanced ( $\rho_{ij}c_iN_i = \rho_{ji}c_jN_j$ ), which yields an upper bound for the number of contacts for high-risk MSM arises:

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

## II. PrEP – Supplementary results

### Model calibration to the HIV epidemiology for MSM in the Paris region

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)	(Marty et al., <i>JIAS</i> , 2018)
Per-year number of new HIV infections	1 200 (900–1 500)	1 100 (900–1 400)	(Marty et al., <i>JIAS</i> , 2018)
HIV incidence rate among high-risk MSM* (%)	7 (4–10)	9.2	(Molina et al., <i>AIDS 2018 Conf</i> , 2018)
Prevalence of HIV* (%)	17 (14–20)	16 (12–20)	(Saboni et al., 2017)
Proportion of undiagnosed HIV infections* (%)	17 (15–20)	18 (15–20)	(Marty et al., <i>JIAS</i> , 2018)
Per-year number of new HIV diagnoses	1 100 (800–1 400)	1 000 (900–1 100)	(Marty et al., <i>JIAS</i> , 2018)
Number of infected, undiagnosed MSM	3 200 (2 000–4 200)	3 400 (3 000–3 800)	(Marty et al., <i>JIAS</i> , 2018)
Total population*	111 000 (94 000–130 000)	118 000 (83 000–167 000)	(Bajos et al., 2018) (Insee, 2015)
Individuals eligible for PrEP <sup>1</sup>	14 200 (9 200–23 000)	–	–
High-risk MSM among susceptibles (%)	15 (11–23)	–	–

**Table:** 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.

<sup>1</sup>High-risk, susceptible MSM.

## II. PrEP – Supplementary results

The effective reproduction number

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

where

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

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

$$M \equiv (\theta_P + \mu)(\sigma + \theta_P + \mu) \left[ (\theta + \mu)c_\ell\rho_{\ell\ell}\beta_\ell^a + \sigma c_\ell\rho_{\ell\ell}\beta_\ell^c \right],$$

are independent of the PrEP parameters; while

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

with

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

and

$$H_P \equiv (\theta + \mu)(\sigma + \theta + \mu) \left[ (\theta_P + \mu)c_h\rho_{hh}\beta_h^a + \sigma c_h\rho_{hh}\beta_h^c \right].$$

## II. PrEP – Supplementary results

### The epidemic control threshold

$R(p, \varepsilon) < R(0, \varepsilon)$  if and only if  $\varepsilon \geq \varepsilon_C$ , where

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

### The epidemic elimination threshold

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

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

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

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

$R(p = 1, \varepsilon) \leq 1$  if and only if  $\varepsilon \geq \varepsilon_E$ , where

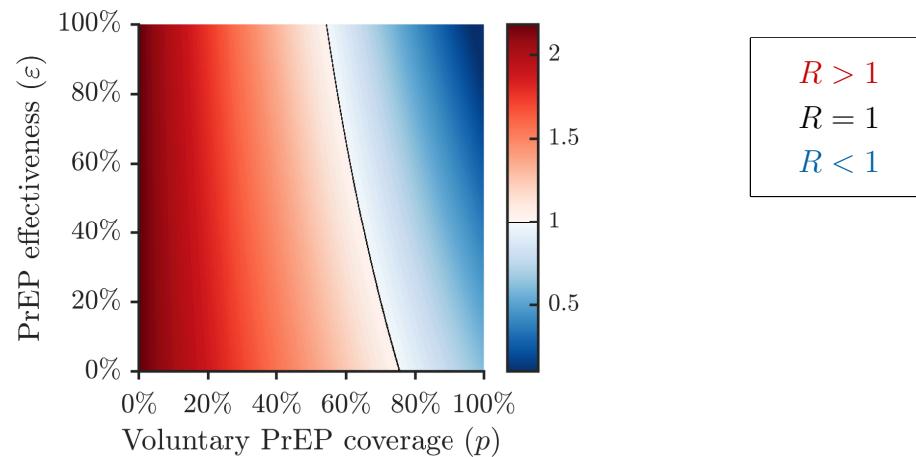
$$\varepsilon_E \equiv 1 - \left( 1 - \frac{K}{H_h} \right) (1 - \varepsilon_C).$$

## II. PrEP – Supplementary results

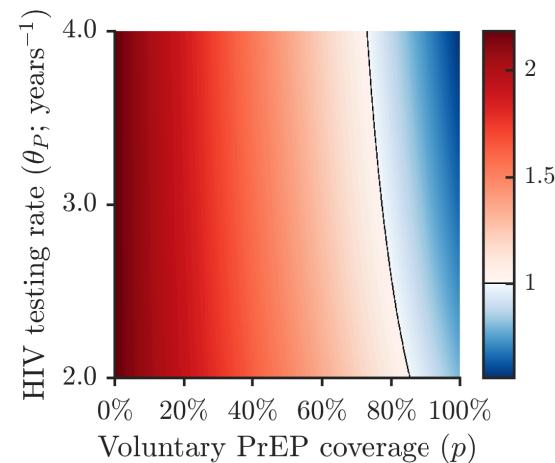
Baseline scenario: Assuming fair risk perception

For one typical parameter set calibrating our model

Effective reproduction number ( $R$ )



For  $\varepsilon = 0\%$



	$\varepsilon$	$p$
$R(\varepsilon, p) = 1 \iff$		
	0%	75%
	86%	57%
	100%	54%

Test-and-treat effect

## Sensitivity scenario: risk misperception among high-risk MSM

Risk perceived given by the proportion of high-risk MSM diagnosed with HIV at the ES:

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

where  $\theta$  and  $\theta_P$  are the HIV testing rates for off- and on- PrEP high-risk MSM, respectively.

## II. PrEP – Supplementary results

### PrEP rollout in the Paris region

For 86% PrEP effectiveness and a number of PrEP-eligible MSM in the Paris region estimated at 14 200 (95%CI: 9 200–23 000):

	Estimated	Observed
Herd immunity threshold <sup>2</sup>	55% (95%CI: 43%–64%)	< 47% <sup>3</sup>
On-PrEP MSM	7 700 (95%CI: 5 800–10 100)	~ 6 700 <sup>4</sup>

If all the MSM currently on PrEP remained on PrEP for the long term, our model predicted a reduction of 90% (95%CI: 81%–100%) in HIV incidence at the new endemic state.

<sup>2</sup>Within the high-risk MSM population.

<sup>3</sup>Assuming that all men on PrEP were indeed high-risk MSM, which is probably an overestimation.

<sup>4</sup>As of mid-2019. However, the 30-month dropout rate was ~32%.

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