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

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1 **Abstract**

2 **Objectives:** To study the conditions under which PrEP coverage can eliminate HIV

3 among men who have sex with men (MSM) in the Paris region.

4

5 **Design:** Mathematical modeling.

6

7 **Methods:** We propose an innovative approach, combining a transmission model with a

8 game-theoretic model, for decision-making about PrEP use. Individuals at high risk of

9 HIV infection decide to use PrEP, depending on their perceived risk of infection and the

10 relative cost of using PrEP versus antiretroviral treatment (ART), which includes

11 monetary and/or non-monetary aspects, such as price and access model of PrEP,

12 consequences of being infected and lifelong ART.

13

14 **Results:** If individuals assessed correctly their infection risk, and the cost of using PrEP

15 were sufficiently low, then the PrEP rollout could lead to elimination. Specifically,

16 assuming 86% PrEP effectiveness, as observed in two clinical trials, a minimum PrEP

17 coverage of 55% (95% CI:43%–64%) among high-risk MSM would achieve elimination

18 in the Paris region. A complete condom drop by MSM using PrEP slightly increases the

19 minimum PrEP coverage required for elimination, by ~1%, while underestimation of their

20 own HIV infection risk could demand PrEP programs reduce the cost of using PrEP by a

21 factor ~2 to achieve elimination.

22

23 **Conclusions:** Elimination conditions are not yet met in the Paris region, where at most

24 47% of high-risk MSM were using PrEP as of mid-2019. Further lowering the cost of

25   PrEP and promoting a fair perception of HIV risk are required and should be maintained

26   in the long run, to maintain elimination status.

27

28

29   **Keywords:** Pre-exposure prophylaxis; HIV; men who have sex with men; behavioral

30   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,

55 to determine whether and under what conditions certain PrEP coverage levels can be

56 reached voluntarily. Particularly, we study the potential impact of PrEP among MSM in

57 the Paris region of France, where universal antiretroviral treatment (ART) is in place, and

58 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 adherence. The PrEP coverage, p, was not fixed; rather, it was obtained through the decision-making game model (see below).

82 We computed the effective reproduction number for the epidemic model, R, defined as

83 the expected number of secondary cases caused by one infected individual, during his

84 entire infectious period, in an uninfected population subject to control interventions

85 [17,18]. PrEP use may change individuals' preference for other prevention tools, turning

86 R into a function of PrEP parameters. $R(p,\varepsilon) > 1$ indicates epidemic persistence,

87 meaning that an endemic state will be reached. Elimination requires $R(p,\varepsilon) < 1$, such

88 that the disease-free state will be reached. Elimination implies that incidence is reduced

89 to zero in the studied population, but HIV can re-emerge in absence of control

90 interventions, as it does not imply eradication. We say the epidemic is controlled using

91 PrEP if $R(p,\varepsilon)$ decreases with the PrEP parameters, although the decrease is not below

92 1. Our model shows that epidemic control and elimination can occur through PrEP,

93 provided that two thresholds in PrEP effectiveness are exceeded; $\varepsilon \geq \varepsilon_C$ is required for

94 epidemic control and $\varepsilon \geq \varepsilon_E$ for epidemic elimination (see SM section 1.2.3). These

95 thresholds are called the epidemic control and the epidemic elimination thresholds,

96 respectively.

97

98 **The decision-making game model**

99 During an epidemic, individuals may adopt PrEP according to their perceived HIV risk

100 [19], price [20] and access model of PrEP [21], adverse effects [22], social stigma [23],

101 consequences of being infected, which includes potential HIV-related stigma, regular

102 clinical visits, lifelong ART, and other pros and cons. These factors, summarizing

103 monetary and/or non-monetary aspects, are expressed in our decision-making model as

104 costs perceived by the individual.

105

106   We assume that all high-risk MSM choose between two mutually-exclusive strategies. If

107   an MSM decides not to use PrEP, then in the case of acquiring HIV he will start ART

108   upon positive HIV diagnosis, and pay the cost of being infected and taking ART for the

109   rest of his life; we use the notation $C_{\text{No-PrEP}}$ for the lifetime cost of this strategy. Otherwise,

110   the MSM decides to adopt PrEP prevention, including regular testing for HIV. Thus, he

111   takes and pays the cost of PrEP and, in the case of acquiring HIV despite PrEP uptake,

112   being diagnosed and starting ART, pays the cost of ART for the rest of his life. We use

113   the notation C_{PrEP} for the lifetime cost of the second strategy. The total cost depends

114   explicitly on the yearly costs perceived for ART and PrEP, the PrEP parameters, and,

115   implicitly, the yearly risk of acquiring HIV.

116

117   We introduce r, the cost perceived for the strategy of adopting PrEP versus the cost

118   perceived for the strategy of not adopting PrEP, which we call, for simplicity, the relative

119   cost of PrEP versus ART. Thus the balance of cost, when the probability to adopt PrEP

120   is p, is

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

122   where all functions and parameters, other than p, are given in our mathematical

123   modeling. The value of p that minimizes $C(p, \varepsilon, r)$, denoted $\hat{p}(\varepsilon, r)$, estimates the

124   probability that a typical high-risk individual adopts PrEP, and also represents the

125   voluntary PrEP coverage among high-risk MSM. The solution of the game represents a

126   endemic state where individuals make decisions to adopt PrEP in stationary

127   epidemiological context. We thus assumed that, in the long run, individuals stand by

128   their decisions about adopting PrEP and used our model only for long-term predictions.

129

130   **Application to the HIV epidemic among MSM in the Paris region**

131   We calibrated the epidemic model to represent the epidemiological context before the

132   introduction of PrEP [24,25], and obtained many HIV parameter sets, to reveal

133   uncertainty in the model output (SM section 2 and Tables S1-S4). In our baseline

134   scenario, we assumed that MSM on PrEP get tested for HIV quarterly, according to the

135   French recommendations [26]. The testing frequency on PrEP was thus much higher than

136   that observed off PrEP, as data shows 3.1 years for the median time from HIV infection

137   to diagnosis among MSM before the introduction of PrEP (personal communication with

138   VS). We further assumed that individuals have a fair perception of their infection risk

139   when making decisions about PrEP use; the infection risk was determined by the force of

140   HIV infection of the epidemic model. Furthermore, MSM were assumed to drop condom

141   use from 30% to 20% when adopting PrEP [3], and the condom effectiveness was 58%–

142   80% [27]. Sensitivity scenarios were explored assuming that i) MSM misperceived their

143   risk of acquiring HIV, or ii) MSM adopting PrEP completely dropped condom use [28],

144   (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);

168   • Region II, where some, but not enough, high-risk MSM adopt PrEP, since the

169   relative cost remains high. The epidemic is controlled and incidence decreases,

170   but not enough for elimination (i.e., $R(\hat{p}, \varepsilon) > 1$);

171   • Region I, where PrEP is offered at low relative cost. This allows reaching high

172   levels of PrEP coverage (~54–75%) and the epidemic can be eliminated; for

173   Region I, $R(\hat{p}, \varepsilon) < 1$. HIV elimination for low PrEP effectiveness (bottom part

174   of Figure 1A) occurs as a consequence of the test-and-treat effect of the PrEP

175   rollout; consequently, $\varepsilon_C = \varepsilon_E = 0\%$. In this case, MSM taking PrEP are poorly

176   protected against HIV. However, they are diagnosed and treated very early in the

177   course of infection, because they get tested for HIV every three months. Early

178   diagnosis and treatment prevent further HIV transmission. In contrast, when PrEP

179   effectiveness is high (top part of Figure 1A), most on-PrEP MSM do not acquire

180   HIV, so the test-and-treat benefit of the PrEP rollout is marginal. It is PrEP,

181   particularly its high effectiveness, that contributes decisively to epidemic

182   elimination. If $\varepsilon = 86\%$, as observed in the IPERGAY and PROUD trials, a

183   minimum PrEP coverage of 56% should be reached among high-risk MSM, to

184   eliminate HIV; Figure S4.

185

186 It is important to note that elimination is temporary, as the disease-free state is unstable.

187 Indeed, once the epidemic is eliminated, individuals perceive HIV risk as being low and

188 may reevaluate the pros and cons of PrEP. In turn, this may severely increase the relative

189 cost of PrEP versus ART, since the epidemic is considered to be eliminated and

190 prevention is no longer needed. As fewer individuals consider PrEP use, the PrEP

191   coverage decreases and the HIV epidemic dynamics in Region I can enter Region II,

192   where the epidemic reemerges and becomes again of public health concern.

193

194   We generated the outputs in Figure 1 using each of the ~500 parameter sets obtained

195   through calibration, to estimate uncertainty intervals for our results (SM Section 2).

196   Figure 2A shows the probability that HIV is eliminated, as a function of ε and r. The

197   probability is high on the left, where Region I is found, and declines severely toward

198   Region II. In Figure 2B, we illustrate the boundaries between Regions I and II (continuous

199   line), and between Regions II and III (dashed line); the three-region structure appears

200   robust to parameter uncertainties. Additionally, when $\varepsilon = 86\%$, we found that the 95%

201   confidence interval (CI) of the minimum PrEP coverage needed for elimination (i.e.,

202   55%) is 43%–64%.

203

204   **Sensitivity scenarios**

205   We assumed that individuals could misperceive their HIV risk when deciding to adopt

206   PrEP, and repeated our analyses. Specifically, rather than having a fair sense of HIV risk,

207   based on the force of infection, high-risk MSM could get a sense of HIV risk from, for

208   instance, the proportion of their high-risk MSM peers being diagnosed each year with

209   HIV (SM Section 3.3.1), assuming full disclosure from HIV-diagnosed MSM. The

210   voluntary PrEP coverage computed for this scenario is illustrated in Figure 3 and reveals

211   a qualitatively similar structure to that in Figure 1. However, when high-risk MSM

212   misinterpret and underestimate their HIV risk, Region I is smaller, implying that the

213   relative cost of PrEP versus ART must be lower to achieve epidemic elimination. In

214   particular, when $\varepsilon = 86\%$, the relative cost needed for epidemic elimination decreases

215   by a factor of ~2, making Region I harder to reach in practice of public health.

216

217   We performed another sensitivity analysis, where we analyzed PrEP-driven condom

218   drop. In our baseline scenario, MSM dropped condom use from 30% to 20% when

219   adopting PrEP. Similar results were obtained assuming that PrEP users stopped using

220   condoms completely (SM Section 3.3.2 and Figure S5). We thus concluded that condom

221   drop is not a major factor against HIV elimination when PrEP effectiveness is high.

222   Specifically, epidemic elimination where $\varepsilon = 86\%$ requires a coverage of >57%, rather

223   than >56% in the baseline scenario.

224

225   **Perspectives on the PrEP rollout in the Paris region**

226   In 2016, a PrEP rollout started in the Paris region, offering fully subsidized PrEP to

227   eligible individuals. As mentioned before, under the baseline scenario, for 86% PrEP

228   effectiveness, we found that at least 55% (95%CI: 43%–64%) of the high-risk MSM

229   would need to take PrEP for the HIV epidemic be eliminated. Since, according to our

230   calibration, the estimated number of PrEP-eligible MSM in the Paris region is 14,200

231   (95%CI: 9,200–23,000), this means that 7,700 (95%CI: 5,800–10,100) high-risk MSM

232   should remain on PrEP for the long term. This is an objective to be reached. As of mid-

233   2019, ~6,700 men were on PrEP in the Paris region [31], with a marked growing trend.

234   However, the 30-month dropout rate was ~32% [32]. The PrEP coverage among high-

235   risk MSM was then estimated to be at most 47% (95%CI: 30%–73%), assuming that all

236   men on PrEP were indeed high-risk MSM, which is probably an overestimation. If all

237   these MSM remained on PrEP for the long term, our model predicted epidemic control

238   (i.e., Region II), with a reduction of 90% (95%CI: 81%–100%) in HIV incidence at the

239   new endemic state.

Discussion

241 We addressed the role of individual-level decision-making in the potential impact of PrEP

242 on the HIV epidemic, identified the conditions for epidemic control or elimination, and

243 estimated PrEP coverage levels which may be reached voluntarily. We obtained four

244 major findings for PrEP rollouts. First, HIV epidemics can be eliminated provided that

245 the relative cost of using PrEP versus ART is sufficiently low. Second, frequent HIV

246 testing while taking PrEP can compensate for poor PrEP adherence and act as a test-and-

247 treat intervention. Third, HIV risk perception may play a major role for elimination, while

248 drop in condom use among PrEP users may not. Fourth, epidemic elimination may be

249 only temporary.

250

251 We applied our model to the Paris region. Assuming a PrEP effectiveness of 86%, as

252 reported in two major clinical trials, we found that at least 55% (95%CI: 43%–64%) of

253 the high-risk MSM would need to be on PrEP to achieve HIV elimination. As of mid-

254 2019, at most 47% high-risk MSM were on PrEP in the Paris region, meaning that the

255 PrEP-rollout protocol did not reduce enough the cost of PrEP for epidemic elimination,

256 so far. Still, a recent update on new HIV diagnoses in Paris [33] shows that the numbers

257 among French-born MSM decreased by 28%, between 2015 and 2018, with no significant

258 decrease for other MSM. This decrease could be partly due to the PrEP rollout starting in

259 2016, and, according to our modeling, should continue in the near future. In two other

260 settings, a moderate-high PrEP coverage has been quickly reached. The region of New

261 South Wales witnessed a rapid PrEP rollout (~9,000 MSM on PrEP within 2 years) during

262 an implementation study providing PrEP for free at several sites, including public HIV

263 and sexual health services, and private general practices with expertise in ART

264   prescription [34]. About 41% of the high-risk MSM in Australia were on PrEP in 2017

265   [35]. Since April 2018, PrEP is subsidized by the Australian government and can be

266   prescribed by any practitioner [36]. In San Francisco, a citywide-coordinated PrEP

267   rollout, within the Getting to Zero program, strongly promoted PrEP use and allowed

268   many people to access PrEP for free or at low monetary cost, through insurance benefits

269   or patient assistance programs. Close to 50% of the eligible MSM were on PrEP in 2017

270   in San Francisco [37]. Although these levels of PrEP coverage contributed to decreasing

271   HIV transmission [34,37,38], HIV elimination has not been reported.

272

273   Moving toward epidemic elimination will require further decreasing the cost of PrEP,

274   which may involve reducing monetary and non-monetary barriers to PrEP uptake, such

275   as difficulties in accessing PrEP, pill burden, tolerability of the molecules, social stigma

276   and discrimination, and the acquisition of other sexually transmitted infections in case of

277   dropping condom use [21–23]. Online tools [39], home-based programs [40], long-lasting

278   injectable versions of PrEP [41], rather than daily or on-demand pills, allowing trained

279   general practitioners to prescribe PrEP and interventions that increase awareness,

280   motivations and behavioral skills about risk reduction [42] may also help reduce the

281   perceived cost of PrEP and decrease the drop-out rate. If feasible, estimating the cost of

282   PrEP relative to that of ART would make it possible to predict the resulting PrEP

283   coverage, depending on the PrEP rollout. However, in practice, it may be very complex

284   to estimate this cost, as it depends on many factors. Nevertheless, it is very important to

285   note that estimating the cost is not strictly needed. Indeed, interventions which intuitively

286   increase the accessibility and affordability of PrEP, may be proposed and thus contribute

287   to reducing the cost, placing the PrEP rollout in the right direction. Then, the reduction

288   in cost can be indirectly appreciated by monitoring the increase in PrEP coverage and the

289   decrease in HIV incidence, which can serve as indicators for how far the PrEP rollout is

290   from achieving elimination.

291

292   Moving toward epidemic elimination will also require reaching MSM who may not

293   perceive themselves at high risk, and thus require a lower cost for adopting PrEP, in order

294   to join the prevention effort. Recent studies found that high-risk individuals can

295   underestimate their HIV risk [43] and there are many missed opportunities for PrEP

296   uptake [44]. Specifically, in France, >90% of the recently infected individuals were

297   eligible for PrEP [44]. Therefore, assessing and communicating individual-level risk for

298   acquiring HIV remains a key objective for achieving elimination. Promoting a fair

299   perception of HIV risk can be achieved through, not only advertising and marketing PrEP

300   [45], but also through using electronic health records to identify high-risk MSM [46].

301

302   Importantly, if HIV is eliminated, interventions will be needed so individuals keep

303   perceiving a low cost for PrEP and fair perception of HIV risk, to maintain a high PrEP

304   coverage. Otherwise, HIV can reemerge and reach again an endemic state of concern for

305   public health. The situation is similar to that of vaccination prevention, which requires

306   continuous vaccine coverage even though the disease is declared to be eliminated [47].

307

308   Our study has some notable limitations. First, some of our modeling assumptions may be

309   applicable only to the Parisian setting and other urban high-income settings. Second, we

310   assumed that individuals act out of self-interest and do not cooperate to avoid getting

311   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, we assumed that MSM are homogeneous regarding risk perception. In reality, the MSM population is certainly heterogenous, fair perception co-existing with misperception. Nevertheless, our baseline and alternative scenarios can be regarded as optimistic and pessimistic scenarios, respectively. 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

331 **Authors' contributions**

332 SJ, VS an RB conceived the model. SJ conducted the numerical simulations. All authors

333 participated to the writing of the manuscript, analysis and interpretation of the results. All

334 authors read and approved the final manuscript.

335

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341

342 **List of abbreviations**

343 ART: Antiretroviral treatment; MSM: Men who have sex with men; PrEP: Pre-exposure

344 prophylaxis; CI: confidence interval.

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502

503 **Figure legends**

504

505 **Figure 1. The voluntary PrEP coverage and its impact on HIV incidence, assuming**

506 **fair risk perception**

507 Color maps of **(A)** the voluntary PrEP coverage among high-risk men who have sex with

508 men (MSM), $\hat{p}$, and **(B)** the corresponding reduction in the overall endemic HIV

509 incidence rate, as functions of ε and r, assuming that individuals have a fair perception

510 of HIV risk. The model outputs were obtained for one typical parameter set calibrating

511 our model. Three regions were identified, depending on $\hat{p}$: Region III, where r is high

512 and no MSM uses PrEP ($\hat{p} = 0\%$), so HIV incidence is not reduced; Region II, where

513 some, but not enough MSM use PrEP, since r remains high, and thus the epidemic is

514 controlled; and Region I (marked by blue stripes), where epidemic elimination is possible.

515

516

517

518 **Figure 2. The probability of HIV elimination and boundary uncertainty for the**

519 **three-region structure**

520 **(A)** The probability of HIV epidemic elimination due to voluntary PrEP coverage,

521 obtained from the ~500 calibrated parameter sets. **(B)** The boundaries (the mean is

522 represented as a line and the 95% confidence interval as grey area) between Regions I

523 and II (continuous line), and between Regions II and III (dashed line).

524

525

526

527 **Figure 3. Sensitivity analyses for the baseline scenario**

528 Decision-making based on misperceived risk of acquiring HIV can significantly reduce

529 the size of Region I, where epidemic elimination is possible (blue stripes), despite high

530 levels of PrEP effectiveness. Note that risk misperception also enlarges region III, where

531 no MSM is willing to adopt PrEP.

532

533 **Figures**

534 **Figure 1**
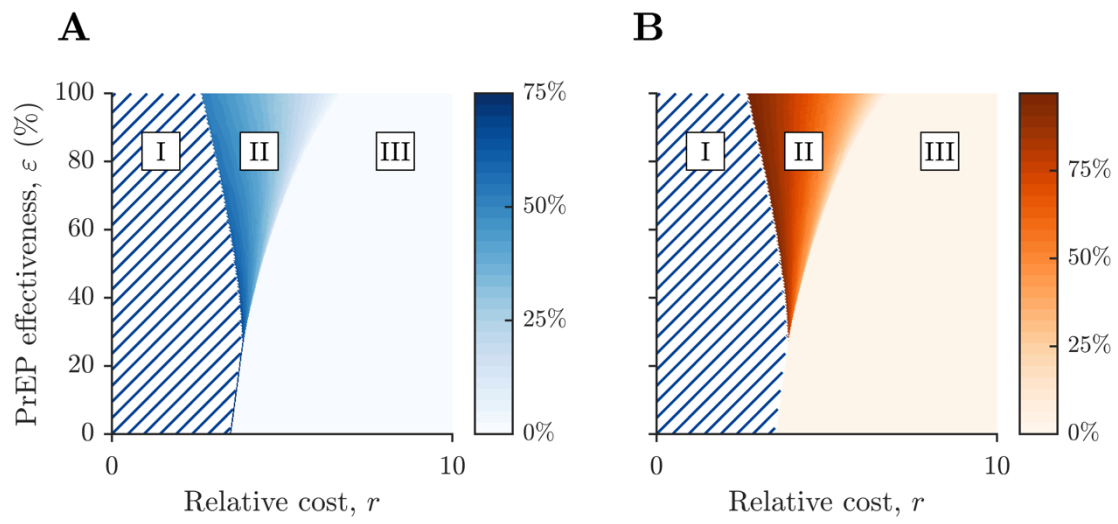
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536

537   **Figure 2**

A

B

538

539

540
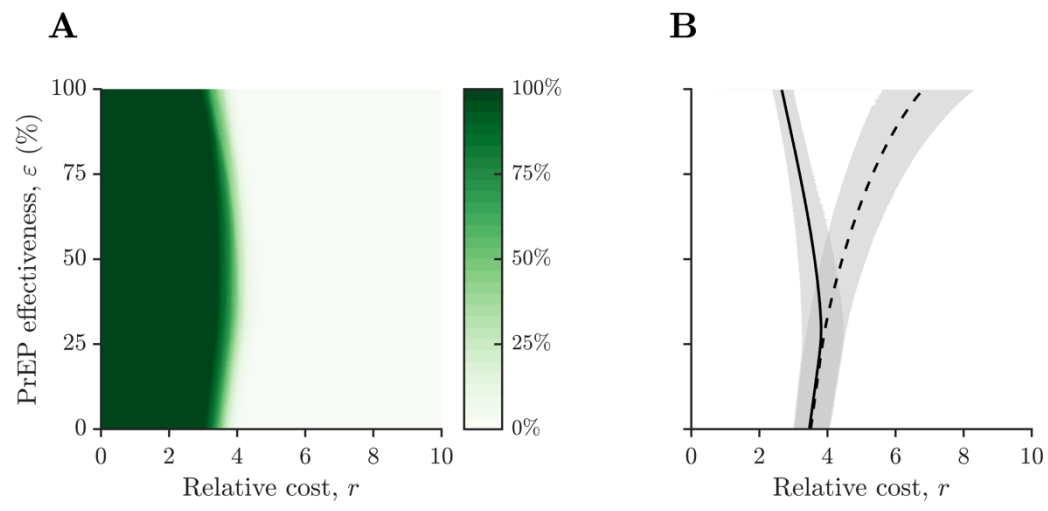
541   **Figure 3**
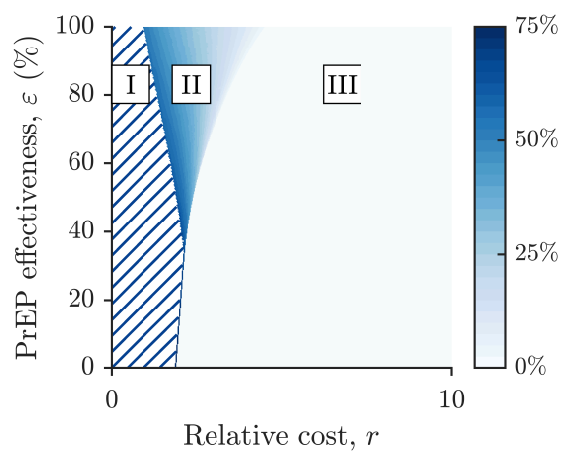
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544 **Supplemental Digital Content**

545 Supplementary Material (pdf document containing the model description, model

546 calibration and supplementary results).

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