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► To cite this version:

Pauline Clin, Frédéric Grognard, Ludovic Mailleret, Florence Val, Didier Andrivon, et al.. Taking advantage of pathogen diversity and immune priming to minimize disease prevalence in host mixtures: a model. *Phytopathology*, 2021, 111 (7), pp.1219-1227. 10.1094/PHYTO-09-20-0429-R. hal-03124229

HAL Id: hal-03124229

<https://hal.science/hal-03124229>

Submitted on 28 Jan 2021

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1 Taking advantage of pathogen 2 diversity and immune priming to 3 minimize disease prevalence in 4 host mixtures: a model

5 **Pauline Clin** ^{1,2}, **Frédéric Grogard** ³, **Ludovic Mailleret** ^{2,3}, **Florence Val** ¹, **Didier**
6 **Andrивon** ¹, **Frédéric M. Hamelin** ^{1,*}

7 ¹ IGEPP, INRAE, Institut Agro, Univ Rennes, 35000, Rennes, France; ² Université Côte d'Azur,
8 INRAE, CNRS, ISA, France; ³ Université Côte d'Azur, Inria, INRAE, CNRS, Sorbonne Université,
9 Biocore, France

10 * Corresponding author: frederic.hamelin@agrocampus-ouest.fr

12 **Abstract** Host mixtures are a promising method for agroecological plant disease
13 control. Plant immunity is key to the success of host mixtures against polymorphic
14 pathogen populations. This results from priming-induced cross-protection, whereby
15 plants able to resist infection by specific pathogen genotypes become more
16 resistant to other pathogen genotypes. Strikingly, this phenomenon was thus far
17 absent from mathematical models aiming at designing host mixtures. We
18 developed a model to specifically explore how priming affects the coexistence of
19 two pathogen genotypes in host mixtures composed of two host genotypes, and
20 how it impacts disease prevalence. The main effect of priming is to reduce the
21 coexistence region in the parameter space (due to cross protection), and to
22 generate a singular mixture of resistant/susceptible hosts corresponding to the
23 maximal reduction disease prevalence (in absence of priming, a resistant pure
24 stand is optimal). The epidemiological advantage of host mixtures over a resistant
25 pure stand thus appears as a direct consequence of immune priming. We also
26 showed that there is indirect cross-protection between host genotypes in a mixture.
27 Moreover, the optimal mix prevents the emergence of a resistance-breaking
28 pathogen genotype. Our results highlight the importance of considering immune
29 priming to design optimal and sustainable host mixtures.

31 **Keywords:** cultivar mixtures, gene-for-gene, virulence, avirulent, polymorphism, induced
32 resistance, systemic acquired resistance, priming

33 **1 Introduction**

34 Growing awareness of the negative impacts of pesticides on biodiversity and hu-
35 man health is increasingly driving the development of more sustainable methods to
36 control plant diseases (Matthews, 2015). Until now, the main alternative to using
37 pesticides against plant pathogens has been to breed genetically resistant plant va-
38 rieties or cultivars and deploy them as pure stands (Wolfe and Ceccarelli, 2020). Un-
39 der these conditions, pathogen populations often evolve and break down resistance
40 genes after a few years, while a breeding program may require a least a decade
41 (Brown, 2015; Zhan et al., 2015). More lasting control methods will require manag-
42 ing genetic resistances in time (Bargués-Ribera and Gokhale, 2020; Nilusmas et al.,
43 2020), and/or in space (Fabre et al., 2012, 2015; Djidjou-Demasse et al., 2017; Pa-
44 païx et al., 2018; Rimbaud et al., 2018b,a; Rousseau et al., 2019; Watkinson-Powell
45 et al., 2019; Burdon et al., 2020).

46 Host mixtures are one of the possible methods to achieve host diversification in
47 space. They consist in growing several varieties of the same plant species in the
48 same field and at the same time (Wolfe, 1985; Mundt, 2002). Host mixtures are or
49 have been used against plant pathogens in various regions of the world, including
50 Asia, Europe and North America (Finckh et al., 2000; Zhu et al., 2000; Mundt, 2002;
51 Han et al., 2016; Reiss and Drinkwater, 2018). In the Yunnan province of China, a
52 large-scale experiment on rice blast was carried out over two years with thousands
53 of farmers (Zhu et al., 2000). Disease-susceptible rice varieties were planted in two-
54 component mixtures with resistant varieties. The effectiveness was such that the
55 fungicide treatments could be stopped in the following year. The overall prevalence
56 (more specifically the percentage of rice stems that were showing symptoms) was
57 reduced by 94% compared to pure stands. Although host mixtures have long been
58 studied both theoretically (Kampmeijer and Zadoks, 1977; Jeger et al., 1981a; Oht-
59 suki and Sasaki, 2006) and experimentally (Jeger et al., 1981b; Wolfe, 1985; Zhu
60 et al., 2000; Ben M'Barek et al., 2020), their design remains to be optimized to be
61 more widely and efficiently used (Mikaberidze et al., 2015).

62 Host mixtures are often composed of resistant and susceptible plants in which
63 resistance is qualitative, meaning that infection either succeeds or fails (as opposed
64 to quantitative resistance, which only partially decreases the success of infection).

65 The majority of studies of mixtures of quantitatively resistant host genotypes have
66 shown relatively low levels of disease control (Mundt, 2002). By contrast, the Yunnan
67 large-scale experiment mixed qualitatively resistant and susceptible varieties (Zhu
68 et al., 2000). Qualitative resistance is often conferred by major resistance genes
69 and driven by gene-for-gene interactions (Flor, 1971; Milgroom, 2015). Pathogen
70 genotypes can then be classified into two types: the resistance-breaking (virulent)
71 type, which can successfully infect both resistant and susceptible hosts, and the wild
72 (avirulent) type, which can successfully infect susceptible hosts only. In biotrophic
73 pathogens (those feeding on living host tissues), an interaction between a wild-type
74 pathogen and a resistant genotype generally triggers a hypersensitive response: the
75 plant blocks the infection process by killing its own cells around the point of infection.

76 Such a strong defense response may result in the plant being primed against fu-
77 ture infections. Immune priming is defined as increased defense to pathogen infec-
78 tions following previous exposure to a pathogen or an elicitor (Tidbury et al., 2012).
79 In the plant disease epidemiology literature, and in particular in host mixtures with
80 gene-for-gene interactions, priming corresponds to the elicitation of specific defense
81 responses which can lead to “induced resistance” (Lannou et al., 1995; Tellier and
82 Brown, 2008). These defense responses include in particular the Systemic Acquired
83 Resistance (SAR) (Vallad and Goodman, 2004; Walters et al., 2005; Conrath, 2011;
84 Pastor et al., 2013). SAR is systematically induced when the aerial tissues of resis-
85 tant plants are tentatively infected by a wild-type biotrophic pathogen (Ross, 1961;
86 Vlot et al., 2008). This defense mechanism involves the activation of signaling path-
87 ways (usually the salicylic acid pathway in the case of biotrophic pathogen infec-
88 tions; Pastor et al. (2013)), allowing SAR to be triggered and active in the entire
89 plant (Cameron et al., 1999; Mishina and Zeier, 2007). SAR effects are long-lasting,
90 and confer partial resistance against subsequent attacks by a broad spectrum of
91 pathogens, including viruses, bacteria, and fungi (Verberne et al., 2000; Durrant and
92 Dong, 2004; Mishina and Zeier, 2007). From now on, for the sake of generality and
93 to avoid confusion with constitutive resistance mechanisms, we will use the term
94 “priming” to denote “induced resistance”.

95 The epidemiological effectiveness of mixtures of resistant and susceptible plants
96 can be explained by three main mechanisms (Wolfe, 1985; Mikaberidze et al., 2015):

97 (i) dilution of susceptible hosts in space, (ii) interception of pathogen transmission
98 forms by resistant hosts (so-called “barrier effect”), and (iii) priming of resistant
99 hosts by wild-type pathogen genotypes. For instance, in the Yunnan large-scale
100 experiment, the prevalence was reduced from 20% to 1% on susceptible varieties in
101 mixtures compared to pure stands. This suggests that resistant varieties indirectly
102 protected susceptible varieties at the population scale, as expected from dilution and
103 barrier effects. More surprisingly, the prevalence on resistant varieties significantly
104 decreased from 2.3% to 1% in mixtures compared to pure stands. This means that
105 susceptible varieties somehow protected resistant varieties, which may be due to a
106 priming effect (Zhu et al., 2000). From a broader perspective, priming is considered
107 as a key to the success of host mixtures. This is because the wild-type pathogen
108 produces little or no symptoms on resistant hosts but triggers a long-lasting immune
109 response protecting against subsequent infections from other pathogen genotypes
110 (Lannou et al., 1995; Calonnec et al., 1996). However, priming was thus far mostly
111 absent from mathematical models aiming at designing host mixtures.

112 This theoretical study aims at exploring the impact of priming on the efficiency of
113 host mixtures against plant diseases. By means of mathematical analyses of a par-
114 simonious model, we analyzed under which conditions the wild-type and resistance-
115 breaking pathogen genotypes can coexist, and whether we can take advantage of
116 pathogen diversity and priming to minimize disease prevalence. In particular, we
117 explored whether susceptible hosts indirectly protect resistant hosts in a mixture,
118 as experimentally observed (Chin and Wolfe, 1984; Zhu et al., 2000), and to what
119 extent this effect is related to immune priming.

120 **2 Modelling**

121 We consider a mixture of susceptible and resistant plant hosts. Note that in plant
122 pathology, the term “susceptible” means the opposite of resistant. We will stick
123 to this terminology and we will refer to “uninfected” plants when it comes to epi-
124 demiology. However, uninfected plants will be denoted as S , in accordance with the
125 reference SIR model in epidemiology. We will consider a continuous-time model with
126 continuous planting and replanting best adapted to perennial crops in tropical re-

127 gions (Madden et al., 2007). More specifically, we consider that the host is present
128 yearlong and we ignore seasonality in climatic conditions for simplicity. This will al-
129 low us to identify the general mechanisms promoting the success (or failure) of host
130 mixtures, which are expected to hold in annual crops as well.

131 We define as $0 \leq p \leq 1$ the proportion of resistant hosts in the mixture; $1-p$ is the
132 proportion of susceptible hosts. As we are interested in epidemiological dynamics in
133 an agricultural context, p is assumed to be a constant. This parameter is a control
134 variable in the hands of the grower.

135 We assume the resistance-breaking (RB) pathogen genotype incurs a cost which
136 reduces its transmission rate by a factor $0 \leq c \leq 1$ relative to the wild-type (WT).
137 The idea of a cost as a counterpart to the ability of breaking a resistance gene
138 originated as a theoretical hypothesis to explain the often observed maintenance
139 of polymorphism in pathogen populations, in both agricultural and wild ecosystems
140 (Vanderplank, 1968; Sasaki, 2000; Gandon et al., 2002; Tellier and Brown, 2007;
141 Brown, 2015). Since then, such a cost has been demonstrated and measured in a
142 number of parasites, including bacteria (Cruz et al., 2000; Wichmann and Bergelson,
143 2004), fungi (Carson, 1998; Thrall and Burdon, 2003; Bahri et al., 2009; Huang et al.,
144 2010; Caffier et al., 2010; Bruns et al., 2014; Bousset et al., 2018), viruses (Jenner
145 et al., 2002; Janzac et al., 2010; Fraile et al., 2010; Poulicard et al., 2010; Ishibashi
146 et al., 2012; Khatabi et al., 2013), nematodes (Castagnone-Sereno et al., 2007) and
147 oomycetes (Montarry et al., 2010).

148 We assume that priming reduces the probability that a resistant host is infected
149 by a RB genotype by a factor $0 \leq \rho \leq 1$ (priming effect). Priming is effective relatively
150 rapidly: a few days after pathogen inoculation in experiments (Ross, 1961; Maleck
151 et al., 2000). Note that priming can be fully effective (Kuć, 1982). In such a case
152 ($\rho = 1$), the RB genotype cannot infect the primed resistant hosts as long as priming
153 is active.

154 The rate at which priming loses its effectiveness is γ . It corresponds to the inverse
155 of the mean time during which priming is effective. Several studies have shown
156 that SAR can last for several weeks. The original one (Ross, 1961) estimates that
157 it persists for 20 days, but more recent reports show that it can last for weeks to
158 months (Kuć, 1982; Fu and Dong, 2013).

159 We assume that infected hosts remain infectious until harvest, as is the case for
 160 most plant viruses and many other parasites. The rate at which a host is replaced
 161 with an uninfected one (due to harvesting and replanting) is α . It corresponds to the
 162 inverse of the length of the growing period.

163 We assume that the total host density N is constant. Since the proportion of
 164 resistant hosts is ρ , the total density of resistant host is $N_r = \rho N$, and the total
 165 density of susceptible hosts is $N_s = (1 - \rho)N$. The density of uninfected susceptible
 166 host is S_s . The density of uninfected resistant host is S_r . The density of resistant host
 167 primed by the WT is S_r^* . Priming makes resistant hosts partially immune to the RB
 168 genotype until its effect vanishes (Fig. 1). The density of susceptible hosts infected
 169 by the WT is I_s . The densities of susceptible and resistant hosts infected by the RB
 170 genotype are J_s and J_r , respectively. Although susceptible plants may be co-infected
 171 by the WT and the RB genotype, we do not allow for coinfections for simplicity. We
 172 have $S_s = N_s - I_s - J_s$, and $S_r = N_r - S_r^* - J_r$. The transmission rate of the WT is β . The
 173 forces of infection of the WT and RB genotypes are therefore, respectively: $F = \beta I_s$,
 174 and $G = (1 - c)\beta(J_s + J_r)$. The model is formulated as a system of ordinary differential
 175 equations, in which the dot denotes differentiation with respect to time t :

$$\begin{aligned}
 \dot{I}_s &= F S_s - \alpha I_s, \\
 \dot{S}_r^* &= F S_r - (1 - \rho) G S_r^* - (\gamma + \alpha) S_r^*, \\
 \dot{J}_s &= G S_s - \alpha J_s, \\
 \dot{J}_r &= G S_r + (1 - \rho) G S_r^* - \alpha J_r.
 \end{aligned} \tag{1}$$

176 We re-scale variables and parameters according to

$$x = \frac{I_s}{N}, \quad m = \frac{S_r^*}{N}, \quad y = \frac{J_s}{N}, \quad z = \frac{J_r}{N}, \quad t^* = \alpha t, \quad R = \frac{\beta N}{\alpha}, \quad \nu = \frac{\gamma + \alpha}{\alpha} \geq 1.$$

177 Biologically, the parameter R corresponds to a basic reproduction number (Mad-
 178 den et al., 2007). This is the mean number of secondary infections produced by a
 179 pathogen able to infect N hosts with transmission rate β during an average time $1/\alpha$.
 180 From now on, we assume $R > 1$, otherwise the pathogen would go extinct.

181 We define the total prevalence of the disease as the proportion of infected hosts
 182 in the plant population: $P = (I_s + J_s + J_r)/N = x + y + z$. The prevalences of the WT and

183 RB genotypes are defined as $P_w = I_s/N = x$ and $P_b = (J_s + J_r)/N = y + z$, respectively.
 184 In addition, we define the total prevalences in susceptible and resistant host sub-
 185 populations as $P_s = (I_s + J_s)/N_s = (x + y)/(1 - p)$, and $P_r = J_r/N_r = z/p$, respectively.
 186 Lastly, we define the Area Under Disease Progress Curve (AUDPC) as:

$$A_{UDPC}(t) = \int_0^t P(\tau) d\tau. \quad (2)$$

187 The AUDPC is a standard metric to summarize the epidemic size at time t as it
 188 takes into account the speed at which the epidemic spread from time zero to time t
 189 (Madden et al., 2007).

190 Model (1) can be formulated in dimensionless form, where the prime denotes
 191 differentiation with respect to t^* :

$$\begin{aligned} x' &= Rx[(1-p) - x - y] - x, \\ m' &= Rx(p - m - z) - (1-p)(1-c)R(y+z)m - \nu m, \\ y' &= (1-c)R(y+z)[(1-p) - x - y] - y, \\ z' &= (1-c)R(y+z)(p - m - z) + (1-p)(1-c)R(y+z)m - z. \end{aligned} \quad (3)$$

192 Model (3) has four biologically possible equilibria:

- 193 • $(0, 0, 0, 0)$: the disease (pathogen)-free equilibrium. The prevalence is $P = 0$.
- 194 • $(\hat{x}, \hat{m}, 0, 0)$: the WT-only equilibrium, which is biologically possible if and only if
 195 $R(1-p) > 1$. The associated prevalence is $P_{WE} = (1-p) - 1/R$.
- 196 • $(0, 0, \hat{y}, \hat{z})$: the RB-only equilibrium, which is biologically possible if and only if
 197 $R(1-c) > 1$. The associated prevalence is $P_{RB} = 1 - 1/[R(1-c)]$.
- 198 • The coexistence equilibrium $(\bar{x}, \bar{m}, \bar{y}, \bar{z})$ is biologically possible if and only if

$$\left\{ c > p \text{ and } p(1-c)R - c > 0 \text{ and } \rho < \frac{[p(1-c)R - c][(1-p)R + \nu - 1]}{[R(1-p) - 1](1-c)R\rho} \right\}, \quad (4)$$

199 see Supplementary Information (Section S2).

200 Biologically, $R(1-p)$ and $R(1-c)$ are the basic reproduction numbers of the WT
 201 and RB genotypes, respectively. The above set of conditions implies $R(1-p) > 1$

202 and $R(1-c) > 1$, meaning that for the coexistence equilibrium to be biologically
 203 possible, both the WT and the RB genotypes must be able to invade when alone.

204 The associated prevalence is

$$P_{CE} = \frac{[(1-p)R + \nu - 1][(1-c)R - 1] - \rho(1-c)R[R(1-p) - 1]}{(1-c)R[(1-\rho)(1-p)R + \nu - 1]}. \quad (5)$$

205 3 Results

206 **Conditions for polymorphism persistence in the pathogen population.** Fig. 2
 207 shows the outcome of the competition for susceptible hosts between the WT and the
 208 RB genotype in the parameter space (p, c) , for representative values of R , ρ and ν
 209 (see Fig. S1 for additional parameter sets). The polymorphism region is delimited
 210 by the conditions (4) of biological feasibility of the coexistence equilibrium. In that
 211 region, we proved (Supplementary Section S4) that the coexistence equilibrium is
 212 globally asymptotically stable, meaning that the dynamics converge to this equi-
 213 librium regardless the initial conditions. This implies that complex dynamics such
 214 as cycles or chaos cannot occur in this model. Therefore, polymorphism is stable
 215 in the pathogen population. Both the WT and the RB genotype can persist without
 216 excluding each other, although they compete for susceptible hosts.

217 **Disease prevalence as a function of the proportion of resistant hosts**
 218 **and priming.** In Figure 3B, p^* is a threshold value separating the WT-only region
 219 from the coexistence (middle) region (i.e., the solution of $P_{CE} = P_{WT}$). For $p < p^*$, the
 220 WT competitively excludes the RB genotype (Fig. 2). In this region, the prevalence
 221 ($P_{WT} = 1 - p - 1/R$) decreases linearly with respect to p . For $p > c$, the RB genotype
 222 competitively excludes the WT (Fig. 2). Since susceptible and resistant hosts are
 223 equally susceptible to the RB genotype in the RB-only region, the disease prevalence
 224 in the latter region is a constant ($P_{RB} = 1 - 1/[R(1-c)]$) whenever $c < p < 1$.

225 In the absence of priming (specific case $\rho = 0$, dashed line), the prevalence in
 226 the coexistence (middle) region is equal to the prevalence in the RB-only region (i.e.
 227 $P_{CE} = P_{RB}$). If $\rho = 0$, we define $\hat{p} = c/[R(1-c)]$ such that $P_{WT} = P_{CE} = P_{RB}$. The WT
 228 and the RB genotypes actually coexist for all $p \in (\hat{p}, c)$. In the absence of priming,
 229 susceptible and resistant hosts are equally susceptible from the RB genotype per-

230 spective (in the coexistence and RB-only regions). Consequently, the growth rate of
231 the RB genotype only depends on available hosts ($1 - P$), regardless of whether the
232 WT persists or not. This is why the equilibrium prevalence (P) is a constant in the
233 regions where the RB genotype persists.

234 Taking priming into account ($\rho > 0$, solid line), the coexistence interval is reduced
235 as the WT outcompetes the RB genotype for all $p \in (\hat{p}, p^*)$. In the WT-only region, the
236 prevalence decreases down to p^* . In the adjacent coexistence region, the prevalence
237 increases up to that in the RB-only region. The prevalence is then not a constant in
238 the coexistence region, since uninfected and primed hosts are not equally suscep-
239 tible from the RB genotype perspective and their equilibrium ratio depends on the
240 proportion of resistant plants p .

241 As a result, priming (solid line) generates an optimal intermediate proportion of
242 resistant host p^* that minimizes the disease prevalence P . In the absence of priming
243 (dashed line), any $p \in (\hat{p}, 1)$ minimizes the prevalence, meaning that host mixtures
244 will not perform better than a pure stand of resistant hosts. The existence of an
245 optimal host mixture is therefore a direct consequence of priming. Note that for a
246 p just below p^* , the RB genotype cannot invade. Decreasing R and/or increasing ρ
247 increases the optimal proportion p^* , which is a critical threshold to prevent the RB
248 genotype emergence (supplementary Section S1).

249 **Transient dynamics and optimal mixtures in terms of both prevalence**
250 **and AUDPC.** Figure 4 shows the prevalence P and the Area Under Disease Progress
251 Curve (A_{UDPC}) over time as a function of the proportion of resistant hosts p , with
252 and without priming. Initially ($0 \leq t \leq 3$ growing periods in Fig. 4 the prevalence
253 and AUDPC are the same regardless whether priming occurs ($\rho > 0$) or not ($\rho =$
254 0). In both cases, the optimal strategy (minimizing both P and A_{UDPC}) is to use
255 resistant hosts only ($p = 1$). This is because in the initial phase of the epidemic, the
256 probability that a RB genotype enters into contact with a primed host is very small.
257 Mathematically, this translates into the largest eigenvalue of the linearized system
258 evaluated at disease-free equilibrium being independent of parameters associated
259 with priming (ρ and ν), see supplementary section S2.3.1. After this initial phase ($t >$
260 3 growing periods in Fig. 4), the prevalence of the disease becomes sufficiently large
261 for priming to have a significant effect on the epidemiological dynamics. Therefore,

262 the optimal strategy is to mix resistant and susceptible hosts. The optimal mixture
263 is approximately the same in terms of both prevalence and AUDPC. As time goes on,
264 the optimal mix converges towards p^* (the optimal proportion of resistant plants at
265 equilibrium). Overall, these numerical explorations show that our results hold well
266 before reaching equilibrium, provided the epidemiological dynamics have passed an
267 initial phase.

268 **Protection of resistant hosts in the mixture by priming.** Figure 5 shows the
269 cumulated prevalences in susceptible and resistant hosts (P_s and P_r) as a function
270 of the proportion of resistant hosts p , with and without priming.

271 Let us start by considering the case with no priming ($\rho = 0$). Starting from the
272 RB-edge of the coexistence region and decreasing p decreases the prevalence of the
273 RB genotype P_b (Fig. 5A). This is because the RB genotype actually competes with
274 the WT for susceptible hosts but incurs a cost. As a result, the total prevalence in the
275 resistant host (P_r) decreases as well (Fig. 5A). Therefore, there is indirect protection
276 of resistant hosts by susceptible hosts in the coexistence region. Since resistant
277 hosts indirectly protect susceptible hosts by being unavailable for the WT, there is
278 then indirect cross-protection between susceptible and resistant hosts.

279 Taking priming into account ($\rho > 0$) does not change the prevalence in the sus-
280 ceptible host P_s (Fig. 5B). By contrast, the slope of P_r is steeper and occurs on a
281 narrower interval, corresponding to a smaller coexistence region. That happens be-
282 cause presence of the WT leads to a certain proportion of the resistant population
283 to be primed and hence less conducive to the RB genotype. By priming, the WT
284 can decrease host availability of the RB genotype and outcompete it. Therefore,
285 the WT outcompetes the RB genotype faster with the help of priming as p is de-
286 creased, which creates a narrower coexistence region. Likewise, the prevalences of
287 the WT (P_w) and of the RB genotype (P_b) are qualitatively the same as in the case
288 with no priming, even though their slopes are steeper in the smaller coexistence
289 region (Fig. 3B). Overall, priming has no qualitative effect on the prevalences in re-
290 sistant and susceptible hosts. Host mixtures generally decrease the prevalences in
291 susceptible and resistant hosts compared to pure stands ($p = 0$ and $p = 1$, resp.),
292 regardless of whether priming occurs or not. Quantitatively however, priming ex-
293 acerbates the effect of mixtures regarding the prevalence in resistant hosts as the

294 decrease is sharper than in the absence of priming.

295 **4 Discussion**

296 Developing new or preexisting methods based on bio-diversification forms the basics
297 of agroecology (Altieri, 2018); host mixtures are one of these. Indeed, mixtures
298 involving at least one host with gene-for-gene resistance have shown a strong ability
299 to decrease disease prevalence compared to pure stands (Garrett and Mundt, 1999)
300 and are a promising alternative to the unstable dynamics commonly observed in
301 gene for gene systems (the famous “boom and bust” cycles; Wolfe (1985)).

302 Our study not only confirmed the theoretical effectiveness of genetic host mix-
303 tures against plant diseases, but allowed us to clearly disentangle the role of priming
304 in this performance. In particular, we showed that the time during which priming
305 is effective is a key parameter for mixture performance (Fig. S1F and Section S1).
306 However, few references document its value. Our study encourages experiments
307 designed to uncover priming duration in a variety of pathosystems. A key feature of
308 our model is that the epidemiological dynamics necessarily converges to an equilib-
309 rium state (Supplementary Section S4). As a corollary, complex dynamics such as
310 cycles or chaos are impossible in our plant epidemic model with immune priming.
311 This observation contrasts with a previous study reporting cycles in an animal epi-
312 demic model with immune priming (Tidbury et al., 2012). From an epidemiological
313 standpoint, immune priming in animals is comparable to immune priming in plants.
314 Tidbury et al. (2012) considered a Susceptible-Primed-Infected model, and showed
315 that cycles can occur if and only if infected hosts bear fecundity costs. Priming does
316 not promote cycles unless host population dynamics are taken into account, which
317 is consistent with our agricultural model, where we observed a globally stable equi-
318 librium in a fixed host population. We showed that disease prevalence at equilibrium
319 was minimized for an intermediate proportion of resistant hosts, which highlights
320 the benefits that can be made by promoting host diversity over growing pure stands
321 of either susceptible or resistant hosts. This proportion depends upon the cost of
322 resistance-breaking, but also on the effectiveness of priming.

323 Moreover, the optimal proportion of resistant plants is also a critical threshold to

324 prevent the emergence of the resistance-breaking pathogen genotype, and hence
325 resistance breakdown. Growing resistant varieties as pure stands increases the se-
326 lection pressure on pathogen populations and thereby promotes the emergence of
327 resistance-breaking pathogen genotypes. Once resistance is broken, the resistance-
328 breaking pathogen genotype may invade and even outcompete the WT, (e.g. Flor,
329 1971; Wolfe, 1985). To control the associated epidemics, breeders then select for
330 new resistance genes and the cycle repeats until the genetic resource is depleted.
331 This “boom and bust” cycle is thus often referred to as an “arms race” co-evolutionary
332 pattern (Tellier and Brown, 2007). By decreasing the disease prevalence on the re-
333 sistant component of the mixture, priming should actually protect resistant hosts
334 during the epidemic, and increase the durability of the resistance gene. Unfortu-
335 nately, there is at the moment little experimental evidence to confirm this theoreti-
336 cal prediction, as few large scale experiments exist (Finckh et al., 2000), and fewer
337 still with pathogen genotypic data. The stability of polymorphism is a central issue in
338 host-parasite coevolution (Hamilton et al., 1990). It has been mainly addressed with
339 population genetics models (Brown and Tellier, 2011), which focus on the frequen-
340 cies of alleles in the host and parasite populations. Stable polymorphism requires
341 negative direct frequency dependent selection (ndFDS), meaning that the frequency
342 of an allele affects its own fitness (Tellier and Brown, 2007). A mechanism pro-
343 moting ndFDS is intraspecific competition, namely negative density-dependence. In
344 population genetics models, density-dependence is not considered explicitly. Mod-
345 els combining epidemiology (i.e. demography) and population genetics checked the
346 stability of polymorphism by numerical simulations (Gandon et al., 2002; Tellier and
347 Brown, 2009; Zivković et al., 2019). Although our model addressed polymorphism in
348 the pathogen population only, its stability was demonstrated mathematically. Con-
349 sistent with a previous study (Tellier and Brown, 2008), priming indeed promotes
350 the fixation of the wild-type and narrows the parameter range for coexistence.

351 We also showed that susceptible hosts indirectly protect resistant hosts, which
352 was less expected than the opposite effect. In the Yunnan province large-scale ex-
353 periment (Zhu et al., 2000), the disease prevalence in resistant varieties significantly
354 and unexpectedly decreased in mixtures compared to pure stands. Disease reduc-
355 tion on resistant hosts was interpreted as a possible effect of priming (Zhu et al.,

2000). Our study confirmed the potential effect of priming but also showed that priming is not necessary to explain this observation. The key point is that competition between the wild-type and the resistance-breaking genotype for susceptible hosts generates apparent cross-protection between resistant and susceptible hosts. This is because increasing the density of susceptible hosts promotes the wild-type, which outcompetes the RB genotype on susceptible hosts and in that way protects resistant hosts. Therefore, although resistant hosts are protected by susceptible hosts even in the absence of priming, priming exacerbates indirect cross-protection.

The multiple effects of priming show that priming (provided it occurs) has the potential to significantly improve mixture performance. The fact that priming is more likely in gene-for-gene systems (implying a hyper-sensitive response) than in quantitatively resistant cultivars may explain why most mixtures and multilines are designed with resistant components possessing major, race-specific resistance. However, priming also occurs in cultivars with quantitative resistance, and may explain in part why mixtures involving this type of resistance also work (Andrivon et al., 2003). As a first step towards understanding the combined effects of genetic resistance and immune priming against plant diseases, we assumed a two-component mixture of a susceptible and a resistant host. Future research may consider a larger number of components in the mixture (Mikaberidze et al., 2015). To begin with, a mixture of two distinct resistance genes with two single-resistance-breaking pathogen genotypes could be considered. This way, priming would occur in two directions (both host genotypes could be primed) and it is likely that the benefits in terms of prevalence would be even greater. Although the presence of an additional pathogen genotype capable of breaking both resistances (a “super-race”) might challenge this optimistic view (Groth, 1976; Lannou and Mundt, 1997; Carson, 2009), both simulation and experimental evidence suggest that this risk might actually be limited (Barrett and Wolfe, 1978; Lannou et al., 2005; Xu, 2012) and strongly depends on resistance-breaking costs, i.e. relative fitness penalties on non-resistant hosts. Since priming actually reduces the fitness advantage of resistance breaking by decreasing the performance of these pathogen genotypes on the resistant host, it is expected to decrease the risk of emergence of such super races in complex mixtures. Exploring the stochastic emergence of resistant-breaking genotypes (Bourget et al., 2013;

388 Chabas et al., 2018) would offer additional insights into the sustainability of host
389 mixtures in agriculture.

390 **Acknowledgments.** PC is supported by a Ph.D. fellowship from the INRAE “Plant
391 Health and the Environment” Division and the Council of Brittany Region. FH ac-
392 knowledges funding from the INRAE “Plant Health and the Environment” Division.
393 The authors thank the reviewers for their helpful suggestions.

394 **Authors’ contributions.** FG, FH, FV, and PC planned and designed the research.
395 FG, FH, LM, and PC built the model and performed its mathematical analysis. DA,
396 FH, and PC wrote the manuscript.

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Table 1. Acronyms, model variables and parameters

| Acronym | Definition |
|-----------|--|
| WT | Wild-type |
| RB | Resistance-breaking |
| AUDPC | Area Under Disease Progress Curve |
| Parameter | Definition |
| p | proportion of resistant hosts in the mixture: $p \in [0, 1]$ |
| c | resistance-breaking cost: $c \in [0, 1]$ |
| ρ | priming effect: $\rho \in [0, 1]$ |
| γ | priming loss rate: $\gamma \geq 0$ |
| α | harvest and replanting rate: $\alpha > 0$ |
| β | pathogen transmission rate: $\beta > 0$ |
| N | total host population density: $N > 0$ |
| N_r | resistant host population density: $N_r = pN$ |
| N_s | susceptible host population density: $N_s = (1 - p)N$ |
| R | basic reproduction number: $R = \beta N / \alpha > 1$ |
| ν | dimensionless parameter: $\nu = (\gamma + \alpha) / \alpha \geq 1$ |
| Variable | Definition |
| t | time: $t \geq 0$ |
| I_s | density of WT-infected susceptible hosts |
| S_r^* | density of primed resistant hosts |
| J_s | density of RB-infected susceptible hosts |
| J_r | density of RB-infected resistant hosts |
| S_s | density of uninfected susceptible hosts: $S_s = N_s - I_s - J_s$ |
| S_r | density of uninfected resistant hosts: $S_r = N_r - S_r^* - J_r$ |
| F | force of infection of the WT genotype: $F = \beta I_s$ |
| G | force of infection of the RB genotype: $G = (1 - c)\beta(J_s + J_r)$ |
| x | proportion of WT-infected susceptible hosts: $x = I_s / N$ |
| m | proportion of primed resistant hosts: $m = S_r^* / N$ |
| y | proportion of RB-infected susceptible hosts: $y = J_s / N$ |
| z | proportion of RB-infected resistant hosts: $z = J_r / N$ |
| P | total prevalence of infected hosts: $P = (I_s + J_s + J_r) / N = x + y + z$ |
| P_{WT} | total prevalence at the WT-Only equilibrium: $P_{WT} = (1 - p) - 1/R$ |
| P_{RB} | total prevalence at the RB-Only equilibrium: $P_{RB} = 1 - 1/[R(1 - c)]$ |
| P_{CE} | total prevalence at the Coexistence equilibrium |
| P_s | total prevalence in susceptible hosts: $P_s = (I_s + J_s) / N_s = (x + y) / (1 - p)$ |
| P_r | total prevalence in resistant hosts: $P_r = J_r / N_r = z / p$ |
| P_w | prevalence of the WT genotype: $P_w = I_s / N = x$ |
| P_b | prevalence of the RB genotype: $P_b = (J_s + J_r) / N = y + z$ |
| $AUDPC$ | Area Under Disease Progress Curve: $AUDPC(t) = \int_0^t P(\tau) d\tau$ |

Table 1

630 **Figure 1**

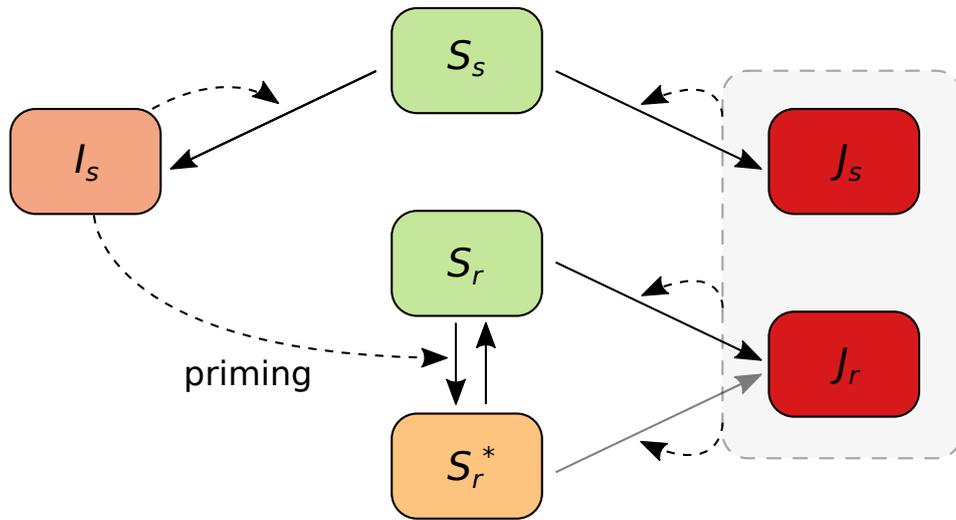


Figure 1: Simplified compartmental diagram for the epidemiological model described by equations (1). The model notations and their definitions are listed in Table 1.

631 **Figure 2**

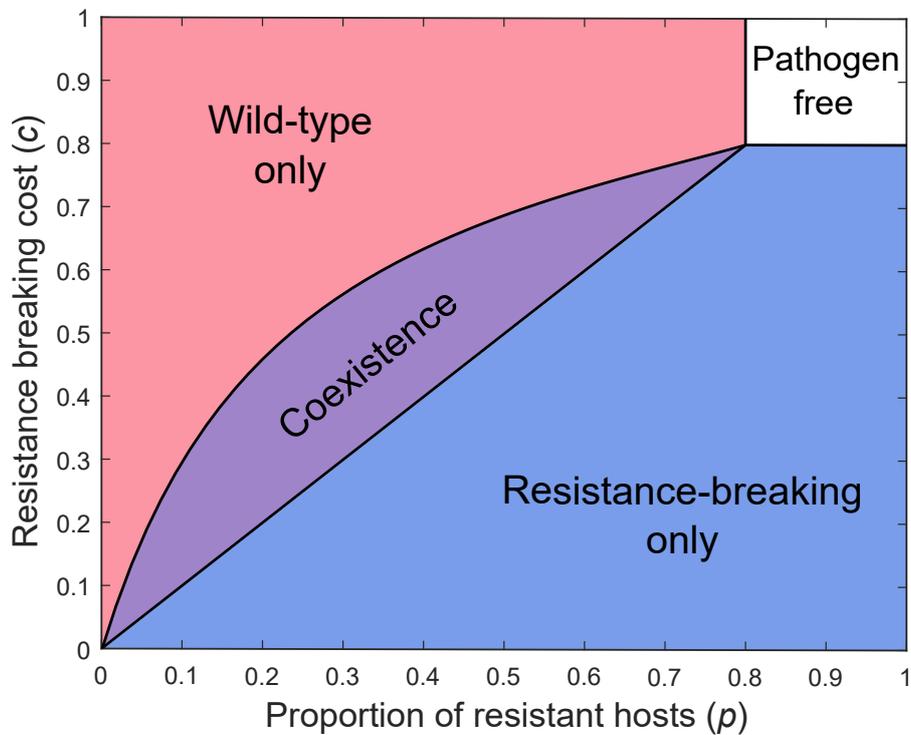


Figure 2: Epidemiological outcomes in the parameter space (p, c) . Other parameter values: $R = 5$, $\rho = 0.5$, and $\nu = 1$. The model notations and their definitions are listed in Table 1.

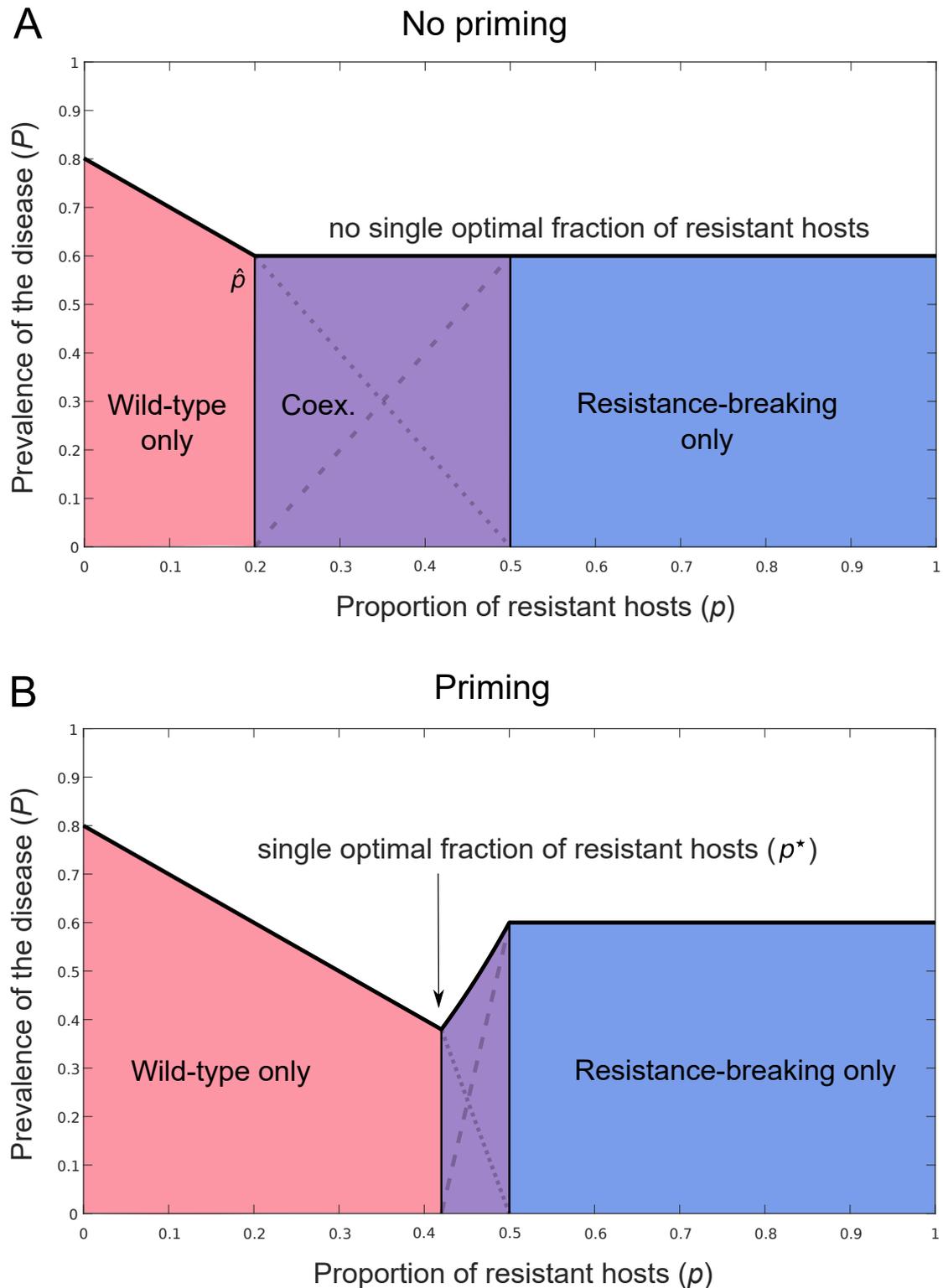


Figure 3: The total prevalence of the disease (P) as a function of the proportion of resistant hosts p . Panel A shows the baseline without priming ($\rho = 0$): all p such that $\hat{p} \leq p \leq 1$ equally minimize the disease prevalence. Panel B shows the effect of priming ($\rho = 0.8$): there is a single optimal fraction of resistant host p^* . Other parameter values: $c = 0.5$, $R = 5$, and $\nu = 1$. The model notations and their definitions are listed in Table 1. The crossing lines in the coexistence region represent the prevalences of the WT (P_w : dotted line) and RB genotype (P_b : dashed line).

Figure 4

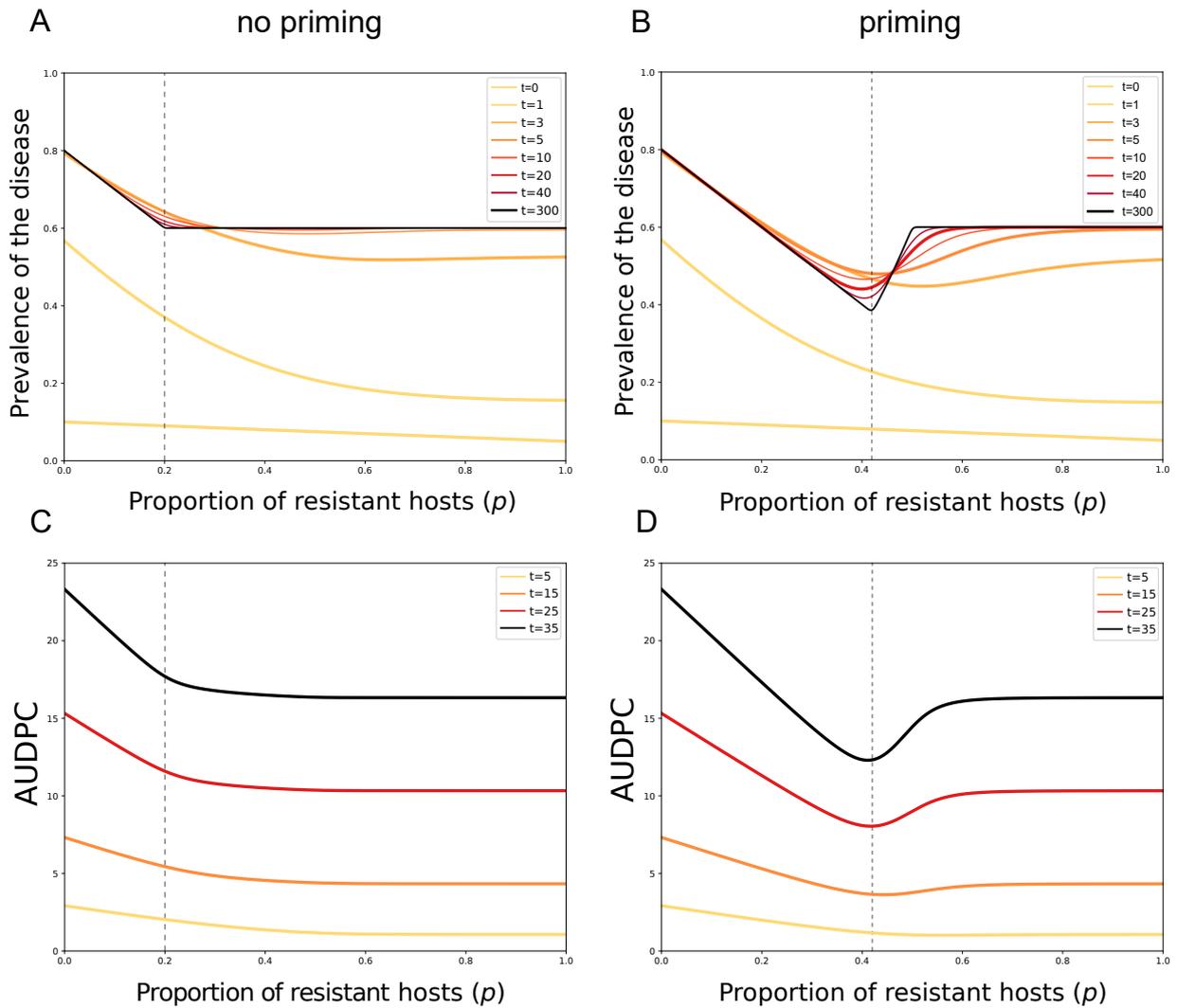


Figure 4: Prevalence of the disease (P) and Area Under the Disease Progress Curve (AUDPC) over time and as a function of ρ , without priming (left column: $\rho = 0$) and with priming (right column: $\rho = 0.8$). Other parameter values: $R = 5$, $c = 0.5$ and $\nu = 1$. The initial conditions are $I_s = 0.01(1 - \rho)/2$, $S_r^* = 0.01\rho/2$, $J_s = 0.01(1 - \rho)/2$ and $J_r = 0.01\rho/2$.

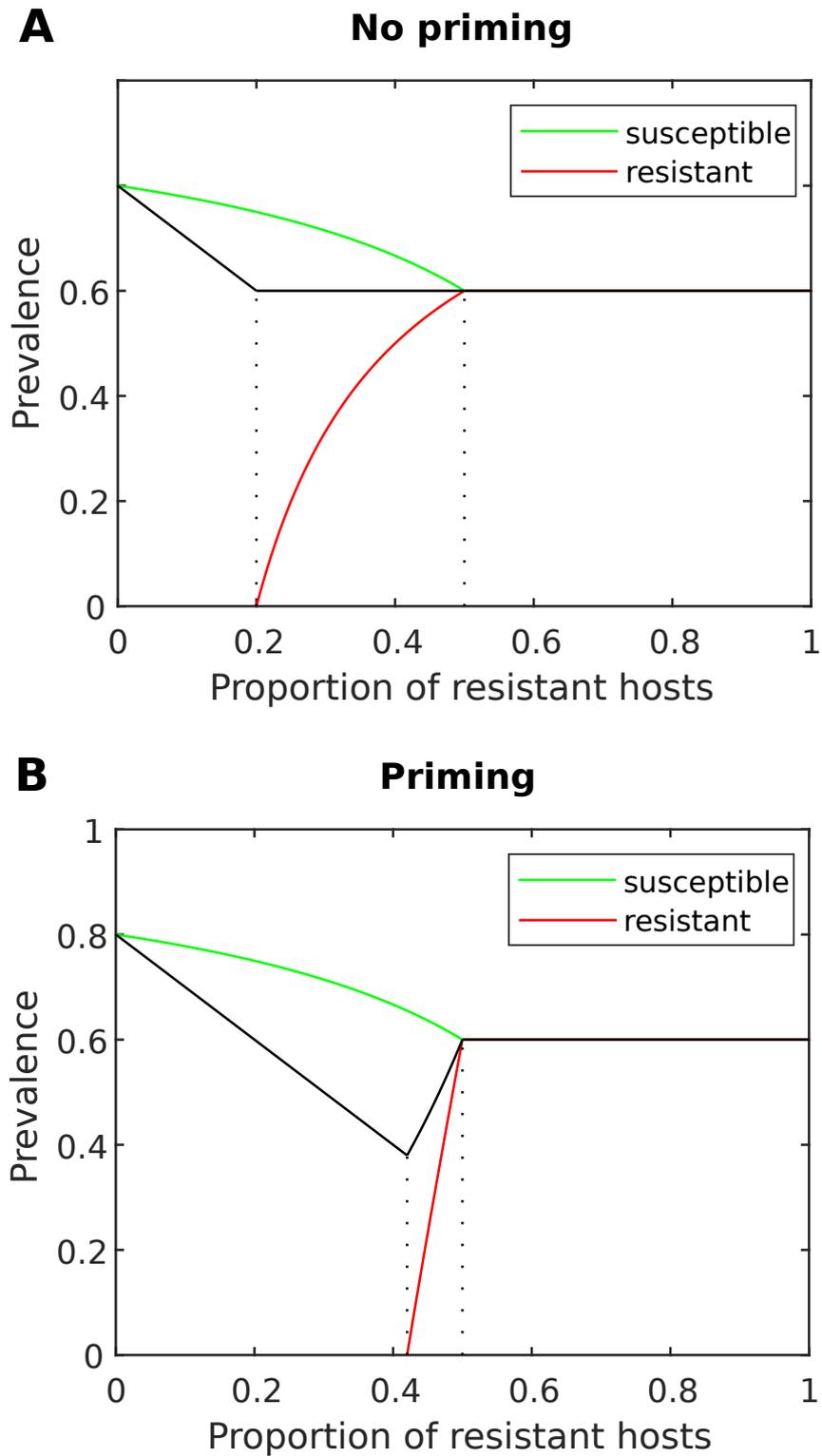
Figure 5

Figure 5: Prevalences in the host population as a function of the proportion of resistant hosts (p). The black lines represent the total prevalence (P). The green and red lines represent the prevalences in susceptible (P_s) and resistant hosts (P_r), respectively. The dotted vertical lines represent transitions from the WT-only, coexistence, and RB-only regions (Fig. 3). Panel A considers no priming ($\rho = 0$), and Panel B takes priming into account ($\rho = 0.8$). Other parameter values: $c = 0.5$, $R = 5$, and $\nu = 1$. The model notations and their definitions are listed in Table 1.