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Abstract

Plant qualitative resistances to viruses are natural exhaustible resources that can be impaired by the emergence of resistance-breaking (RB) virus variants. Mathematical modelling can help determine optimal strategies for resistance durability by a rational deployment of resistance in agroecosystems. Here, we propose an innovative approach, built up from our previous empirical studies, based on plant cultivars combining qualitative resistance with quantitative resistance narrowing population bottlenecks exerted on viruses during host-to-host transmission and/or within-host infection. Narrow bottlenecks are expected to slow down virus adaptation to plant qualitative resistance. To study the effect of bottleneck size on yield, we developed a stochastic epidemic model with mixtures of susceptible and resistant plants, relying on continuous time Markov chain processes. Overall, narrow bottlenecks are beneficial when the fitness cost of RB virus variants in susceptible plants is intermediate. In such cases, they could provide up to 95 additional percentage points of yield compared to deploying a qualitative resistance alone. As we have shown in previous works that virus population bottlenecks are at least partly heritable plant traits, our results suggest that breeding and deploying plant varieties exposing virus populations to narrowed bottlenecks will increase yield and delay the emergence of RB variants.

Keywords: qualitative resistance, quantitative resistance, population bottleneck, yield increase, stochastic epidemic model, resistance durability.

1 Introduction

Plant disease qualitative resistance, i.e. resistance that almost totally prevents any plant infection, does not often provide durable resistance to fungal, bacterial and viral pathogens [1–3]. For viruses, only one or two mutations in their genome may be sufficient to break down the resistance [4]. Once the resistance-breaking (RB) mutant has appeared, it has a disproportionate selective advantage to settle in a hitherto resistant cultivar [3].

In contrast, plant quantitative resistance partially reduces or delays disease development [5]. Combining qualitative and quantitative resistances may help increase the durability of qualitative resistances, as exemplified with the *pvr2*^{3} qualitative resistance gene to *Potato virus Y* (PVY) in pepper plants [6]. This effect can result from a reduction in the fixation probability of beneficial RB mutations [7]. Two main evolutionary forces can modulate fixation probabilities: selection and genetic drift [8,9]. Selection is a deterministic force favoring the fittest variants. Genetic drift generates random fluctuations in variant frequencies, eventually purging variants regardless of their selective value [10]. Genetic drift is stronger in populations with smaller effective population size N_e [11], that can be defined as the size of an ideal population displaying the same fluctuations in allele frequencies as the population under study [12]. For a fixed selective value, the fixation probability of a beneficial mutation decreases with N_e [8].

Small N_e can be observed for viruses during colonization of new plant cells and leaves because population bottlenecks are rather common for those pathogens [12,13]. Depending on the plant – virus pair, N_e estimates vary from 1.15 to 1515 [14–16]. Moreover, during host-to-host transmission, N_e may be as low as 0.5-3.2 virus infectious units on average at inoculation of a plant by one insect vector [17,18]. Importantly, N_e of viruses during plant infection (at inoculation or during systemic movement) has been recently shown to be genetically controlled by pepper genotype for PVY and *Cucumber mosaic virus* [15,16]. Such quantitative resistances reducing pathogen N_e are likely to be widespread at least for plant viruses. Thus, as proposed in medicine to limit the emergence of antibiotic-resistant bacteria [19], plant breeders may take advantage of these quantitative resistance factors to slow down pathogen adaptation and decrease the risks of RB [17,18].

Most epidemiological models of pathogen adaptation to a control method assume infinite pathogen population size [20]. However, intra-host N_e of PVY is negatively correlated to the durability of *pvr2*^{3} [21]. More generally, demographic stochasticity endured by

pathogens within their hosts impacts the effectiveness of control methods, as exemplified for the speed of kill of the gypsy moth by a baculovirus [22]. Also, Lo Iacono *et al.* [23] proposed a stochastic model approximating the pathogen population size by the densities of infected hosts. They showed that stochastic extinctions of infected hosts occurring typically at the start of an epidemic impact resistance durability. Refining how stochasticity affects pathogen populations can be a critical and promising aspect to consider.

Here, we tested whether combining a quantitative resistance narrowing virus population bottlenecks (decreasing N_e) with a qualitative resistance, can increase the durability of the latter. We introduce a stochastic plant epidemic model based on classical healthy - infected deterministic models, coupling epidemiology and population genetics, and featuring mixtures of susceptible and resistant plants. By comparing yield benefits provided by a resistant cultivar combining qualitative and quantitative resistances (named pyramided resistance) with those of a resistant cultivar carrying only the qualitative resistance (named monogenic resistance), we estimated the added value of combining quantitative and qualitative resistances. We investigated the effects of the interactions between agroecosystem features (epidemic intensity, proportion of resistant cultivar) and the characteristics of the qualitative (fitness cost imposed to RB variants in susceptible plants) and quantitative (pathogen N_e) resistances on yield benefits. We found that those characteristics are essential to identify the strategies maximising yield benefits.

2 Model overview

The model is based on [24]. It merges virus epidemic processes at the field scale and virus population genetics processes. It describes, during a cropping season lasting n_d days, the epidemic dynamics in a field composed of susceptible (S) and resistant (R) plants. The field has a constant number of plants, N^p, amongst which a proportion φ are R plants (number of R plants $N^R = \varphi N^p$, and of S plants $N^S = (1-\varphi)N^p$). Two virus variants are considered: the wild-type (WT) and RB variants. Only the RB variant can infect R plants whereas both variants can infect S plants. Bottlenecks undergone by virus populations are considered both for host-to-host transmission and for subsequent within-host infection, from inoculated leaves colonization (cell-to-cell movement) until the onset

of systemic infection (Fig. S1) [12]. During these steps, selection and mutation forces are neglected as we assume that demographic stochasticity is the dominant process. The model summarises the global effect of all bottlenecks in a unique effective population size, denoted N_e^R in R plants and N_e^S in S plants. For R plants with monogenic resistance, i.e. without quantitative resistance narrowing bottlenecks, we set $N_e^R = N_e^S = 10^4$ to represent negligible demographic stochasticity, whereas for R plants with pyramided resistance, i.e. with additional quantitative resistance, we have $N_e^R < N_e^S$. The number of virus particles surviving bottlenecks is drawn from Poisson distributions, and determines the success of infection of a target plant (see Text S1 for details). After the bottlenecks have been crossed, i.e. during systemic infection if it occurs, we assume that virus populations grow quickly to large sizes and thus only selection and mutation are considered. We assume that virus populations reach instantaneously their mutation - selection equilibrium, with 100% of RB variant in R plants and a frequency f_{RB} of RB variant in S plants. The equilibrium frequency f_{RB} results from the balance between the production of RB variants through recurrent mutations and their counter-selection in S plants because of the fitness costs associated with these RB mutations [25]. f_{RB} characterizes the qualitative resistance gene. For a given mutation rate, it depends on the number of mutations required for resistance breakdown and their associated fitness costs in S plants [24]. Main parameters are detailed in Table 1.

Descriptions of deterministic and stochastic forms of the model are available in Text S1. The deterministic form is used to attribute meaningful values to a parameter representative of epidemic intensity in a reference field before deployment of R plants, whereas the stochastic form was used to conduct all simulations of R plants deployment.

3 Results

The analyses are based on ratios of the areas under the disease progress curves (AUDPCs), allowing to assess the benefit of deploying R plants with monogenic or pyramided resistances (see Text S2 for details).

We first explored the percentage points of additional relative benefit Δ provided by the deployment of a pyramided resistance $\boldsymbol{\delta}_{Rp}$ compared to a monogenic one $\boldsymbol{\delta}_{Rm}$ as a function of RB variant frequency in S plants f_{RB}, for all values of the other parameters (Table

Table 1: **Description of model parameters and values used for numerical simulations.**

Parameter	Designation	Unit	Range or reference value
Ω_{int}	Epidemic intensity before deployment of R plants	Unitless	[0.1, 0.9]
n_d	Duration of the cropping season	Day	120
N^p	Number of plants in the field	Plant	10^3
φ	Proportion of R plants	Unitless	[0.05, 0.95]
f_{RB}	Frequency of RB variant in S plants	Unitless	[10^{-8}, 0.5]
N_e^R	Virus effective population size in R plants	Virus or infectious unit	Small: [1, 100] Large: 10^4
N_e^S	Virus effective population size in S plants	Virus or infectious unit	10^4
n_{iter}	Number of simulation iterations for each set of parameter values	Unitless	500

1). f_{RB} strongly impacts the value of Δ (Fig. 1), intermediate f_{RB} maximising Δ. For f_{RB} in the range [10^{-5}, 0.1], mean Δ remained above 17 percentage points. The highest Δ values are reached for $f_{RB} = 10^{-3}$, with a mean of 54 percentage points and 95% of Δ values falling between 8 and 90 percentage points. Outside this range ($f_{RB} < 10^{-5}$ or > 0.1), the mean Δ remained < 10 percentage points.

We then looked at the combined effects of the four factors Ω_{int} (epidemic intensity before deployment of R plants), f_{RB}, φ and N_e^R on Δ to disentangle their specific impact (Fig. 2). Overall, optimal strategies correspond to large φ and small N_e^R values. Let us first focus on the smallest f_{RB} value tested in Fig. 2 (10^{-4}). When Ω_{int} is small or intermediate (0.2 or 0.5), N_e^R has no visible effect on Δ. Highest Δ values are reached for largest φ, providing up to 50-60 percentage points of additional yield benefit when $\Omega_{int} = 0.2$, and up to 80 percentage points when $\Omega_{int} = 0.5$. When Ω_{int} is higher (0.8), a slight effect of N_e^R appears, with Δ values up to 90-100 percentage points for small N_e^R and large φ.

For the intermediate f_{RB} tested (0.01), N_e^R has an influence for any epidemic intensity, generating J-shaped contour lines when Ω_{int} is small or intermediate.

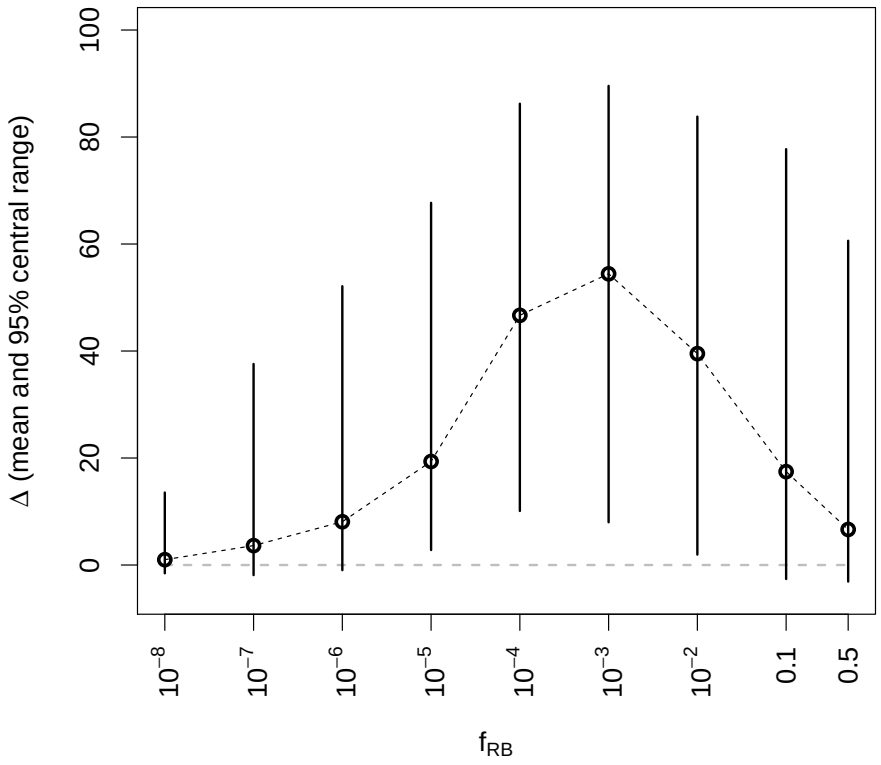

Figure 1: **Additional relative benefit Δ as a function of RB variant frequency in susceptible plants f_{RB}.** All values of the other parameters are combined and Δ corresponds to mean benefits over the 500 stochastic simulations for each combination of parameter values. Dots indicate means of Δ and segments indicate 95% central range for each f_{RB} value (over all combinations of the other parameters). A grey dashed line indicates the limit $\Delta = 0$.

For the largest f_{RB} (0.5), the effect of φ blurs and the area corresponding to significant Δ values (e.g. ≥ 10 percentage points) is reduced to small N_e^R values (< 5). This area shrinks as Ω_{int} increases, moving towards very small N_e^R (< 2) and large φ (> 0.6) values. Values of Δ can reach up to 70 percentage points when $\Omega_{int} = 0.2$ and this maximum decreases to 20 percentage points when $\Omega_{int} = 0.8$.

A description of epidemic dynamics simulated with the model under various scenarios can be found in Text S3 and Fig. S2.

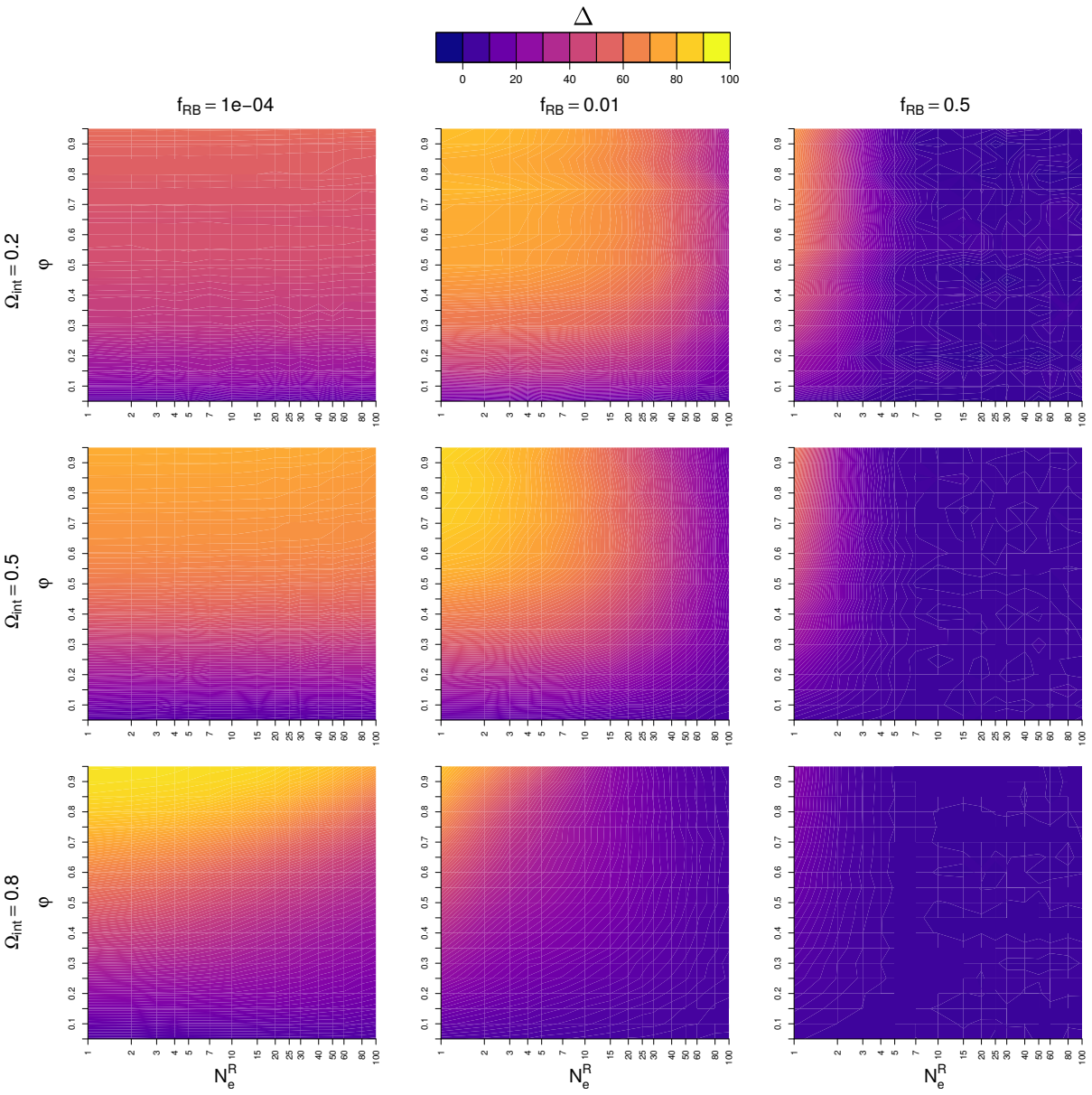

Figure 2: **Effect of four parameters representative of the host, the virus, epidemic intensity and the field on the additional relative benefit Δ.** Contour plots representing Δ as a function of the proportion of resistant plants φ (y-axis) and of virus effective population size in resistant plants N_e^R (x-axis). Panel lines represent contrasted epidemic intensities Ω_{int} and panel columns contrasted RB variant frequencies in S plants f_{RB}.

4 Discussion

The model presented here is to our knowledge the first one to analyze the impact of within-host demographic stochasticity, tuned by pyramiding plant quantitative resistance reducing virus N_e with qualitative resistance, on the durability of the latter. Beyond simulating the impact of demographic stochasticity, the model proposes an original framework for breeders and farmers to decrease pathogen yield losses and increase qualitative resistance durability.

Globally, the additional relative benefit followed a skewed bell-shaped curve as a function of the frequency of the RB variant in S plants, with both ends corresponding to very low Δ values (Fig 1). When f_{RB} is small ($\leq 10^{-6}$), the qualitative resistance is hardly breakable, even without combining it with a quantitative resistance, as it typically requires the virus to accumulate numerous mutations associated with high fitness costs in S plants [24]. Such highly durable qualitative resistances have been reported in agroecosystems, as the *Pvr4* gene in pepper against PVY, requiring only one mutation for breakdown, but with a high fitness cost in S plants [26]. In our model, the probability that at least one RB particle survives the bottlenecks in monogenic R plants when the contact is from an infected S plant is $\leq 10^{-2}$ (see calculation details in Text S1). As a result, epidemics are already well contained with monogenic R plants, especially at large proportions of R plants (Figs. 2, S3 and Text S4).

When f_{RB} is high (≥ 0.1; typically one mutation for virulence associated with low fitness cost in S plants), the qualitative resistance is easily broken down, even when combining it with a quantitative resistance decreasing virus N_e^R. Such cases of poorly durable qualitative resistance have also been reported, as for the *Tm1* gene in tomato against TMV [1]. The probability that at least one RB virus particle survives the bottlenecks in R plants with pyramided resistance when the contact is from an infected S plant is $\geq 10^{-1}$, and increases very fast with N_e^R (see calculation details in Text S1). Thus, even the deployment of R plants with pyramided resistance results in important damage, except when virus N_e^R is very small ($= 1$) and the proportion of R plants is large (Figs. 2, S3 and Text S4). Strong epidemic intensities and large f_{RB} drastically reduce optimal cropping ratios - bottleneck size combinations, due to an increasing number of inoculation events combined with higher probabilities of transmitting the RB variant from an infected S

plant.

Resistance pyramiding provides the largest additional benefits for intermediate f_{RB} because the qualitative resistance is neither highly nor poorly durable. In those common intermediate cases [2, 24], quantitative resistance controlling bottleneck sizes can protect a qualitative resistance by decreasing the success probability of inoculation events from infected S plants to healthy R plants. The best strategy combines a large proportion of R plants and a small virus N_e.

Several conceptual reviews discuss the effect of pathogen N_e on the evolutionary potential of pathogens confronted with a qualitative resistance in plants [2, 10, 27]. Our modelling results are in agreement with their advice of reducing N_e and go further by showing that the interaction between N_e and selection, via f_{RB}, is critical for the added value of reducing N_e in terms of additional yield benefit. Zhan *et al.* [10] highlight agricultural practices that can help reduce N_e, such as seasonal fallows, field hygiene, intercropping or crop rotation. Here, as we recently identified plant loci controlling N_e [15, 16], we propose an alternative and original way of managing pathogen N_e through plant breeding. Our model and proposed breeding method should be directly applicable to plant pathogens that multiply within-host and constitute mixed populations, such as viruses and bacteria. Plant fungi form monoclonal lesions, thus the competition is not direct and the model would need to be adapted for these pathogens.

More generally, our model averages host-to-host and intra-host N_e in a global N_e, but model parameters could be easily refined depending on the pathosystem. In a paper summarising current and future challenges in modelling pathogen dynamics, Gog *et al.* [28] emphasized the importance of transmission bottlenecks, characterised by infection probability and the number and diversity of pathogen particles transferred to a new host, on pathogen evolutionary dynamics. Interestingly, transmission bottleneck sizes are increasingly estimated for both animal and plant pathogens (see [29] and references therein). Decreasing transmission probability by reducing host-to-host N_e is of particular interest for human pathogens, such as preexposure prophylaxis for *Human immunodeficiency virus*. Then, if a host gets infected, an efficient treatment, creating a narrower bottleneck in virus populations, would slow down the appearance of drug resistant strains by creating a hard selective sweep [30]. Overall, bottlenecks are increasingly studied in animal, human and plant pathogens. Depending on the host, the method for narrowing pathogen

bottlenecks can be adapted, but the general concept remains the same.

Coming back to plant resistance deployment, intermediate proportions of R plants were predicted to be optimal for yield benefit in several studies [24, 31] (but [23] predicted that yield benefit increase with the proportion of R plants). Here, we predict a positive correlation between additional relative benefits and the proportion of R plants. This result may be due to our modelling framework that imposes a link between the proportion of R plants and population bottlenecks encountered by viruses, as we only allowed pyramiding qualitative and quantitative resistances. For example, allowing the quantitative resistance to be introduced in the S cultivar would break this link and could slow down the infection spread through S plants and be beneficial for smaller φ values. To this end, the mutation-selection equilibrium assumed in S plants could be replaced by a mutation-selection-drift equilibrium [32]. More generally, N_e at the field scale can be estimated by the product of intra-plant N_e and the total number of newly infected plants [33]. With our pyramiding strategy, φ is also the proportion of plants carrying the quantitative resistance, hence increasing φ should decrease N_e at the field scale, because of the associated conversion of S plants into pyramided R plants, which have lower N_e.

Future developments should include long time and large scale (several seasons within an agricultural landscape) simulations to match the scales at which epidemics spread [34] and should consider diverse deployment strategies (mixture, mosaic, genes pyramiding). They could benefit from models developed to assess resistance durability for plant viruses [35] and fungi [36]. The model ignores the adaptation of the virus to the quantitative resistance controlling N_e. Pathogen adaptation to quantitative resistance has been observed, as for PVY in pepper [37] but, up to now, the mutational pathways leading to such erosion is largely unknown. These evolutionary aspects could be considered in future works, for example based on Rimbaud *et al.*'s (2018) framework [36] that features random mutational processes for the adaptation to qualitative and quantitative resistances.

Deleterious effects of narrow bottlenecks have been reported in nature, as for *Trypanosoma cruzi*, the agent of Chagas disease [38]. The authors argued that seasonal reduction in host population could result in an increased prevalence of *T. cruzi* in the vector population when they feed on a small number of infected hosts, creating a considerable force of infection. A similar effect is likely to occur for vector-borne viruses of annual crops

that are solely hosted by limited wild plant species during the crop-free period. Additionally, narrow bottlenecks during cell-to-cell movement in plants might help isolate variants with adaptive mutations from non-adapted ones, allowing selection to operate more efficiently [39], especially when the fitness of a transitional mutant is lower than those of WT and adapted variants [13]. In our model, narrowing bottlenecks could not be harmful because the probability of infecting a R plant is a strictly increasing function of N_e^R. Future developments could consider more realistic within-host virus dynamics than the instantaneous mutation-selection(-drift) equilibrium hypothesis. In particular, any new viral mutant with selection coefficient s in a drift regime ($N_e s \ll 1$) has a decreasing fixation probability with decreasing N_e, while fixation time increases with N_e [40]. This trade-off could counteract the positive relationship between N_e^R and resistance durability [9, 41].

Our study demonstrates that integrating population genetics principles to minimize the evolutionary potential of plant pathogens, by playing on their effective population size, can guide disease resistance management strategies towards increased resistance durability and epidemic control [10, 27]. Our simple model provides insightful guidelines to optimal strategies for breeders, and shows the benefit of using quantitative resistance reducing virus N_e, particularly when the combined qualitative resistance is neither highly nor poorly durable.

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Data accessibility

R scripts for model simulations and analyses are available in supplementary material.

Authors' contributions

ER MB FF LM and FG conceived the model. ER and MB carried out model simulations. ER MB FF BM LM and FG analysed the data. ER wrote the first draft of manuscript.

All authors made critical revisions and approved the final version.

Competing interests

We have no competing interests.

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Supplementary material

Text S1 Description of the deterministic model

In this supplementary material, we describe our epidemiological model in its deterministic form, for a field composed only of susceptible (S) plants, without quantitative resistance. It is used to attribute meaningful values to a parameter representative of the intensity of epidemics in a reference field before deployment of R plants. In a second part, we describe this deterministic model with the introduction of R plants, and in a third part we describe the stochastic model.

To summarise how we model the infection process, we consider bottlenecks undergone by viruses from host-to-host transmission to subsequent within-host infection (until the onset of systemic infection, see Fig. S1). The global effect of all bottlenecks is summarised in a unique effective population size, denoted N_e^R in R plants and N_e^S in S plants. During these steps, selection and mutation forces are neglected. Then, upon systemic infection, only selection and mutation are considered, and we assume that virus populations reach instantaneously their equilibrium, consisting of a frequency f_{RB} of resistance-breaking (RB) variant in S plants and of 100% of the RB variant in R plants.

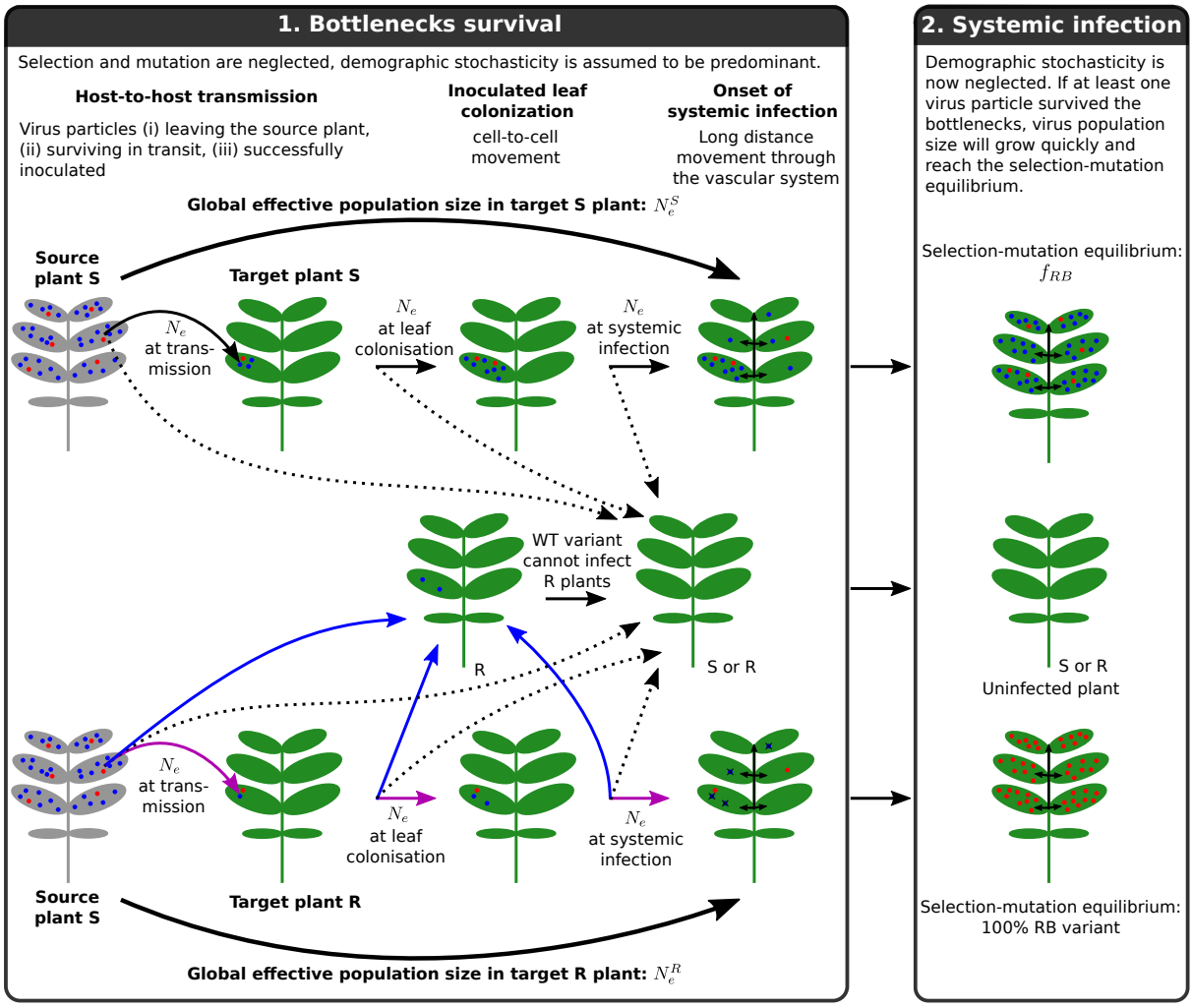

Figure S1: **Modelling of the infection process.** Wild-type (WT), resp. resistance-breaking (RB), virus variants are represented by blue, resp. red, dots. The source plant for infection is in grey and the target plant is in green. In the model, the infection of a new plant is decoupled into two steps: (1) bottleneck survival and (2) systemic infection. In the first step, only demographic stochasticity is considered. The effect of bottlenecks during host-to-host transmission, inoculated leaf colonization until the onset of systemic infection are summarised in the model in a global effective population size, which is N_e^S in susceptible (S) plants and N_e^R in resistant (R) plants (bold arrows). For the purpose of illustration, each bottleneck step is shown here, but the model only simulate a global, average, bottleneck. At each bottleneck step, survival of virus populations is represented by plain arrows whereas extinction is represented by dotted arrows. For a target S plant, plain black arrows indicate cases where either only the WT variant, only the RB variant or both variants pass through the bottleneck. For a target R plant, plain blue arrows indicate cases where only the WT variant passes through the bottleneck, whereas plain

Figure S1 (continued): purple arrows indicate cases where either only the RB variant or both variants pass through the bottleneck.As our model assumes that WT variants cannot infect R plants, these are removed for the second step of systemic infection. After the bottlenecks have been crossed and systemic infection occurs, demographic stochasticity is neglected and virus populations instantaneously reach their selection-mutation equilibrium, at a frequency f_{RB} of RB variant in S plants and 100% of RB variant in R plants. In the case where no virus particles survived the bottlenecks (or only WT variants were transmitted in R plants), the target plant remains healthy. For this illustration, only infections emanating from S plants are shown; infections from R plants are qualitatively identical to the $S \rightarrow S$ case but with only RB variants that go through the bottlenecks, and the selection-mutation equilibrium depends on the target plant, as shown in the figure (systemic infection panel).

1 Fully susceptible field

In this situation, the host carries no resistance at all (qualitative or quantitative) and the virus effective population size N_e^S accounting for bottlenecks from host-to-host transmission to within-host progression is very large (10^4). The dynamics of the number of infected S plants I^S accross the n_d days of the cropping season in the field composed of N^S S plants is assumed to follow a healthy - infected type ordinary differential equation (ODE), as:

$$\frac{dI^S}{dt} = \beta_0 \frac{I^S(N^S - I^S)}{N^S} \left(1 - e^{-N_e^S}\right) . \quad (1)$$

A single S plant is infected initially, i.e. $I^S(0) = 1$. β_0 is the basic contact rate from an infected plant to a healthy one through insect vectors. The last term of eq. 1 accounts for bottlenecks experienced by viruses. We suppose that S plants get infected if and only if at least one virus particle (or infectious unit) passes through all bottlenecks. Assuming that the number of virus particles surviving all bottlenecks results from a Poisson distribution of mean N_e^S, it follows that the probability that at least one virus particle survives all bottlenecks is the opposite of the event leading to zero virus particles surviving, that is $1 - e^{-N_e^S}$. In fact, as the S plant carries no quantitative resistance (i.e. $N_e^S = 10^4$) we have $1 - e^{-N_e^S} \simeq 1$. Hence the impact of bottlenecks on the success of infection in this simple model is negligible.

The analytic integration of the proportion of infected S plants $p_i^S(t) = I^S(t)/N^S$ over n_d days through equation 1 provides the area under the disease progress curve (AUDPC) in the field, $A_0 = \int_0^{n_d} p_i^S(t)dt = \frac{1}{\beta_0} \ln\left(1 + p_i^S(0)\left(e^{\beta_0 n_d} - 1\right)\right)$. Following Fabre *et al.* (2012) [24], we use the AUDPC to attribute meaningful values to the epidemic parameter β_0. For this purpose, we introduce a new parameter, the intensity of epidemics Ω_{int}, giving the average proportion of plants infected along a cropping season in a fully S field. Thereby we have the relationship $\Omega_{int} = A_0/n_d$, from which we can infer values of β_0 for given epidemic intensities.

2 Deployment of resistant plants

Let us now consider the introduction of R plants in the field, with I^R the number of infected R plants and N^R the total number of R plants (the total number of plants is $N^p = N^S + N^R$). The model describing the epidemics then reads as:

$$\begin{cases} \dfrac{dI^S}{dt} = \left(\beta_0 \dfrac{I^S(N^S - I^S)}{N^p} + \beta_0 \dfrac{I^R(N^S - I^S)}{N^p}\right)\left(1 - e^{-N_e^S}\right) & (2) \\ \dfrac{dI^R}{dt} = \beta_0 \dfrac{I^R(N^R - I^R)}{N^p}\left(1 - e^{-N_e^R}\right) + \beta_0 \dfrac{I^S(N^R - I^R)}{N^p}\left(1 - e^{-N_e^R f_{RB}}\right) & (3) \\ I^S(0) = 1\,,\; I^R(0) = 0. & (4) \end{cases}$$

Initially, a single S plant is infected and no R plant is infected. S and R plants can be infected either by S or R plants, at a basic contact rate β_0, as described previously. The mechanism of survival of viruses through bottlenecks is modelled similarly as in eq. 1 for infection of S plants ($1 - e^{-N_e^S}$, eq. 2) and for infection of R plants when the vector comes from a R plant ($1 - e^{-N_e^R}$, left-hand part of eq. 3). Indeed, as we assume that the RB variant is present at a frequency of 1 in R plants, the vector transmitting viruses from an infected R plant to a healthy R plant is necessarily inoculating the RB variant to the target R plant, and we also assume that the survival of at least one RB particle is sufficient to infect the R plant. If a S plant gets infected by a R plant, only the RB variant can be transmitted but we assume that the virus population instantaneously evolves towards an equilibrium frequency f_{RB} of RB variant through mutation and selection. The bottleneck survival term for the infection of a R plant from a S plant is slightly different ($1 - e^{-N_e^R f_{RB}}$, right-hand part of eq. 3). We suppose that the target R plant will be infected if and only if at least one RB particle survives the bottlenecks. We model this condition with the

probability density of a Poisson distribution of mean $N_e^R f_{RB}$. Indeed, if on average N_e^R virus particles survive all bottlenecks, only $N_e^R f_{RB}$ of these virus particles correspond to the RB variant because the infection comes from a S plant. The probability density that at least one RB particle survives all bottlenecks is found by taking the opposite of the event leading to zero RB variant surviving, that is $1-e^{-N_e^R f_{RB}}$. When f_{RB} is low, i.e. when the qualitative resistance is hardly breakable, this probability is at most $1-e^{-10^4\times10^{-6}} \simeq 10^{-2}$ ($N_e^R = 10^4$ and $f_{RB} = 10^{-6}$). On the opposite, when f_{RB} is high, i.e. when the qualitative resistance is easily broken down, this probability is at least $1-e^{-1\times0.1} \simeq 10^{-1}$ ($N_e^R = 1$ and $f_{RB} = 0.1$), and increases very fast with N_e^R.

3 Stochastic model description

Continuous time Markov chains and birth processes were chosen for the stochastic form of the model [?]. We follow the dynamics of the number of S and R infected plants, I^S and I^R respectively, along the cropping season. A single S plant is infected initially, i.e. $I^S(0) = 1$ and $I^R(0) = 0$. Transition rates π^{ij} for the 'birth' of a new infected plant by contact from an infected i (i = S or R) to a healthy j (j = S or R) plant are defined as $\pi^{ij} = \beta_0 \frac{I^i(N^j - I^j)}{N^p}$.

The waiting time until the next infection attempt [?] was modelled with the Gillespie algorithm [?]. Once the waiting time is known, the varieties (S or R) of the actual source and target plants are determined according to the probabilities π^{ij} of each event to occur. Then, the number of virus particles surviving the bottlenecks is drawn from a Poisson distribution, as $X_e^S \sim Pois(N_e^S)$ for a target S plant, and $X_e^R \sim Pois(N_e^R)$ for a target R plant. A target S plant gets infected if and only if $X_e^S \geq 1$ (it otherwise remains healthy). For a target R plant, if $X_e^R \geq 1$, two cases are to be distinguished. If the source plant is R, the plant necessarily gets infected. If the source plant is S, the plant will get infected if and only if at least one RB particle is part of the X_e^R surviving the bottlenecks. We assume that the number of RB particles surviving the bottlenecks follows a Binomial distribution, as $n_{RB} \sim Binom(X_e^R, f_{RB})$. To highlight the match with the deterministic form of the model, let us note that a draw of X_e^R in a Poisson distribution of mean N_e^R followed by a draw in a Binomial distribution of parameters X_e^R and f_{RB} is indeed equivalent a single draw draw in a Poisson distribution of parameter $N_e^R f_{RB}$.

Text S2 Computation of the relative damage and additional relative benefit

In this supplementary material, we describe in details how we compute the relative damage and additional relative benefit. We rely on these two variables to analyse our simulations and assess the impact of deploying qualitative and quantitative resistances on yield benefits.

4 Measuring the yield increase in comparison with the fully susceptible scenario

We analysed the benefit for farmers of deploying resistant (R) plants based on the associated yield increase. This quantity was measured thanks to the area under the disease progress curve (AUDPC), a good proxy of the yield losses caused by a pathogen [**?**, 24]. Calculations were done for each:

- deployment strategy $\boldsymbol{\delta} = (\varphi, f_{RB}, N_e^R)$, involving a proportion φ of R plants, a frequency of the resistance-breaking (RB) variant in S plants f_{RB} and a virus effective population size N_e^R in R plants,
- and epidemiological context before deployment of R plants Ω_{int}, i.e. a value of the intensity of epidemics.

For one simulation over one cropping season, the AUDPC for a particular epidemiological context and deployment strategy is $A(\Omega_{int}, \boldsymbol{\delta}) = \int_0^{n_d} \left[(1-\varphi)p_i^S(t) + \varphi p_i^R(t)\right] dt$, integrating the weighted proportions of susceptible (S) and R infected plants, $p_i^S(t) = I^S(t)/N^p$ and $p_i^R = I^R(t)/N^p$, respectively. This AUDPC is compared to the one obtained in the reference field before deployment of R plants with the same epidemiological context, $A_0(\Omega_{int}) = n_d\Omega_{int}$ (see Text S1). For this purpose, we define the percentage of relative damage for a particular deployment strategy and epidemiological context as:

$$D(\Omega_{int}, \boldsymbol{\delta}) = 100 \times \frac{A(\Omega_{int}, \boldsymbol{\delta})}{A_0(\Omega_{int})} \tag{5}$$

For example, $D = 30\%$ means that, in epidemiological context Ω_{int}, deploying R plants according to strategy $\boldsymbol{\delta}$ reduces the total number of infected plants to 30% of the crop damages before R plants deployment.

5 Evaluating the benefit of narrowing bottlenecks to increase yield

From the relative damage we can assess the additional yield benefit provided by using a pyramided resistance, i.e. combining quantitative resistance reducing virus effective population size with a qualitative resistance, compared to a monogenic resistance, i.e. a R cultivar without such quantitative resistance. Strategies using a monogenic, resp. pyramided, resistance cultivar are denoted $\boldsymbol{\delta}_{Rm}$, resp. $\boldsymbol{\delta}_{Rp}$. The reference value of N_e^R for $\boldsymbol{\delta}_{Rm}$ strategies was set to 10^4 (Tab. 1 in main text). For $\boldsymbol{\delta}_{Rp}$ strategies, N_e^R was varied from 1 to 100, thereby reducing virus effective population size by a factor 100 to 10^4. We evaluated the added value of narrowing bottlenecks for yield benefit by comparing $\boldsymbol{\delta}_{Rm}$ and $\boldsymbol{\delta}_{Rp}$ strategies differing only by parameter N_e^R, i.e. with the same values of φ, f_{RB} and Ω_{int}. Following Fabre *et al.* (2015) [25], we define the additional relative benefit of the pyramided resistance strategies as:

$$\Delta(\Omega_{int}, \boldsymbol{\delta}_{Rp}) = \bar{D}(\Omega_{int}, \boldsymbol{\delta}_{Rm}) - \bar{D}(\Omega_{int}, \boldsymbol{\delta}_{Rp}), \tag{6}$$

with $\bar{D}$ the mean relative damage over the n_{iter} stochastic simulation iterations for one set of parameter values. For example, $\Delta = 20$ percentage points means that using the pyramided resistance reduces the total number of infected plants by 20 percentage points compared to the monogenic resistance, in the same epidemiological context Ω_{int} and with the same proportion of R plants φ and frequency of RB variant in S plants f_{RB}.

Text S3 Epidemic dynamics

Here we present a description of model outputs, which consist of single season epidemic dynamics in a field. The output variables are the proportions of infected susceptible (S) and resistant (R) plants, and the total proportion of infected plants (S and R). In Fig. S2, the reference intensity of epidemics in the fully S field Ω_{int} was set to 0.3. In this reference fully S field, the epidemic took off around 40 days after sowing and 95% of the plants were infected at the end of the season (Fig. S2). Deploying a monogenic resistance cultivar (virus effective population size in R plants $N_e^R = 10^4$) at a proportion $\varphi = 0.8$ with a resistance gene characterized by a frequency of the resistance-breaking (RB) variant in S plants $f_{RB} = 0.01$ slightly reduced the epidemic in S plants, with 86% of S plants infected at the end of the season, on average. In R plants, the epidemic took off approximately at the same period and 85% of R plants were infected at the end of the season on average. Hence, the RB variant quickly invaded the field. Overall, in both S and R plants, adding plants with monogenic resistance only slightly decreased the epidemic intensity, from 0.3 to 0.25, and the mean proportion of infected plants at the end of the cropping season was approximately 10 percentage points less than in the fully S field. Adding quantitative resistance reducing N_e^R to 5 (pyramided resistance) drastically slowed down the epidemic. At the end of the cropping season the proportion of infected plants dropped to 11% in S plants, 7% in R plants, and 8% in the field (S and R plants), on average. With this strategy, the intensity of epidemics was reduced to 0.02. This example shows the potential benefit of pyramiding quantitative resistance reducing virus effective population size in R plants. In that case, the qualitative resistance alone reduces the damage by $(0.3-0.25)/0.3 = 16.7\%$, and pyramiding a quantitative resistance accounts for an additional $\Delta = 100 \times \frac{0.25-0.02}{0.3} = 76.7$ percentage points decrease.

Demographic bottlenecks bring stochasticity to the dynamics of virus populations, and in return also to the epidemics. Hence, it is important to also look at the variability between epidemic simulations. Yet, Fig. S2 shows that the stochastic model intrinsically generates a large variability in the dynamics of the proportion of infected plants, looking at deployment strategies of monogenic resistance, i.e. with negligible bottlenecks. The density of curves at the last day of the cropping season shows that 21% of the curves are concentrated around a peak of density at 96-98% of infected plants (Fig. S2C). The epidemic curves show slightly less variability in simulations of pyramided vs. monogenic

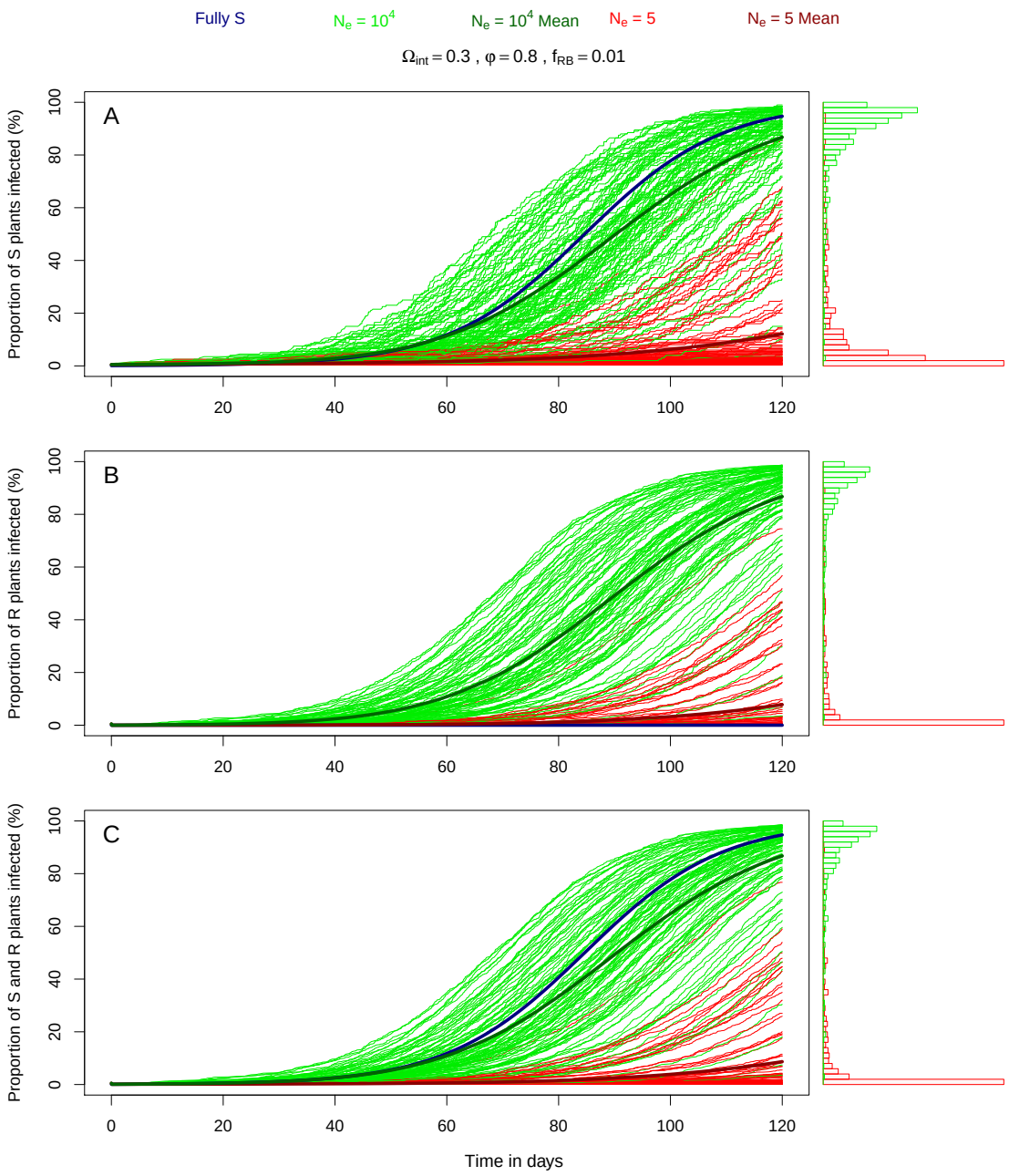

Figure S2: **Epidemic dynamics.** Evolution of the proportion of infected plants along the cropping season for susceptible S plants (A), resistant R plants (B) and both S and R plants (C). Blue thick curves are outputs in a fully S field (deterministic model) with reference epidemic intensity $\Omega_{int} = 0.3$. Green and red curves are outputs for a proportion of R plants $\varphi = 0.8$ and a RB variant frequency in S plants $f_{RB} = 0.01$ (stochastic model). Green is for plants with monogenic resistance ($N_e^R = 10^4$), red for plants with pyramided resistance ($N_e^R = 5$). Thin curves are individual outputs, thick curves are corresponding means. The histograms represent the proportion of infected plants on the last day of the cropping season.

resistance deployment. This is explained by the strong decrease in epidemics spread, leading to flat epidemic curves around 0% of infected plants, generating a so-called saturation effect. The peak of density at the last day of the season is located around 0-2% of infected plants for 61.6% of the simulations (Fig. S2C).

Text S4 Impact of the choice of the resistance gene on the relative damage

In this supplementary material, we describe our results on the relative damage (see Text S2), which allow us to disentangle the effects of deploying a qualitative resistance alone from those of deploying resistant (R) plants pyramiding qualitative and quantitative resistances decreasing virus effective population size in R plants N_e^R. We then briefly discuss those results.

Results

We represented the relative damage D as a function of the choice of the qualitative resistance gene (frequency of resistance-breaking - RB - variant in S plants f_{RB}) for two fixed values of the proportion of resistant plants φ (0.2 and 0.8) and of the intensity of epidemics Ω_{int} (0.2 and 0.8), and four N_e^R values, one corresponding to monogenic resistance strategies ($N_e^R = 10^4$), and the other three to pyramided resistance strategies ($N_e^R = 1$, 10 and 100, Fig. S3). Stronger epidemic intensities (Ω_{int}=0.8) generate larger relative damage on average. When φ is small (0.2), relative damages start on average around 36-37% for the lowest f_{RB} value and low Ω_{int} (0.2), against 73-74% for high Ω_{int} (0.8). The pattern remains the same as f_{RB} increases.

When φ is large (0.8), epidemics can become extinct (i.e. nearly all plants remain healthy over the cropping season), as D approaches 0% for the lowest f_{RB} values. The relative damage curves take off from these epidemic-extinction cases for smaller f_{RB} values when Ω_{int} is stronger. Typically, the departure from epidemic-extinction case is located around $f_{RB} = 10^{-6}$ (resp. 10^{-4} for pyramided resistance strategies) when $\Omega_{int} = 0.2$ against $f_{RB} = 10^{-8}$ (resp. 10^{-6} for pyramided resistance strategies) when $\Omega_{int} = 0.8$.

A striking result is the effect of Ω_{int} on the variability of D. The stronger Ω_{int}, the smaller the variability of D. Also, for the lowest Ω_{int} value, D can reach values larger than 100%. It means that the corresponding simulations generated more crop damage than in the fully S field. Yet, the mean relative damage never gets above 100%, showing that on average deploying R plants is beneficial.

The additional relative benefit Δ is evaluated by the distance between the curves corresponding to the pyramided resistance strategies to the ones of the monogenic resistance strategy ($N_e^R = 10^4$). When f_{RB} is small, all the curves are close to each other at a small

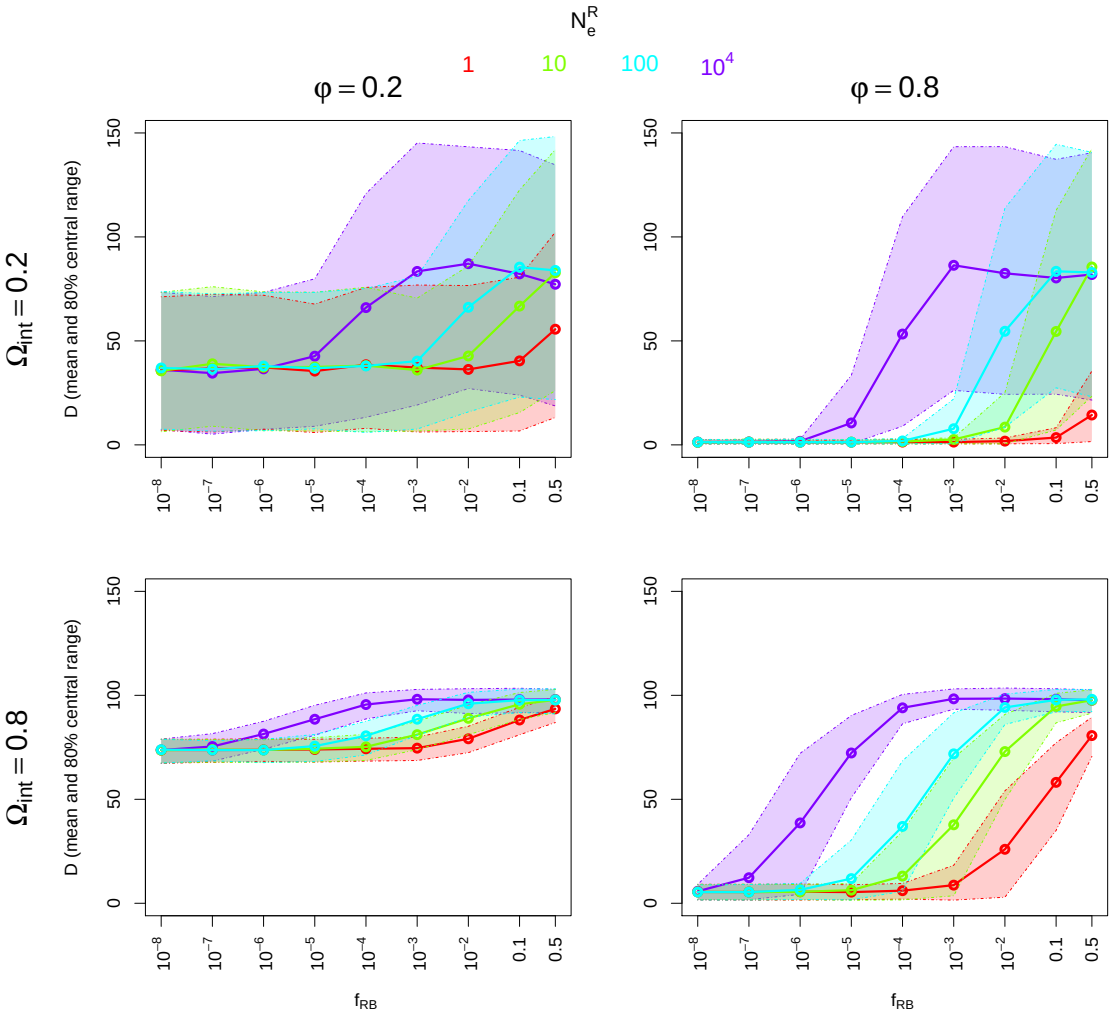

Figure S3: **Relative damage D as a function of RB variant frequency in susceptible plants f_{RB}.** Dots and plain lines are means, dashed lines and semi-transparent areas represent 80% central ranges. Colors represent various viral effective population sizes in R plants ($N_e^R = 10^4$: plants with monogenic resistance, $N_e^R < 10^4$: plants with pyramided resistance). Panel lines represent distinct epidemic intensities Ω_{int} and panel columns distinct proportions of resistant plants φ.

to moderate damage level, hence no additional benefit is provided by adding quantitative resistance. This is especially true when Ω_{int} is low (0.2), as the curves stay close for a larger range of f_{RB} values than when Ω_{int} is high. The result of low Δ when $f_{RB} = 0.5$ in figure 1 is here split in two cases. It is true when $N_e^R = 10$ or 100, but less so when $N_e^R = 1$. In that latter case, it is true only when Ω_{int} is high (0.8) and φ is small (0.2); otherwise the relative damage still gets reduced. As in figure 1, we can see that intermediate values of f_{RB} lead to the largest reduction in relative damage when adding quantitative resistance. We can go further here by noticing that a larger φ (0.8) leads to more additional relative benefit.

Discussion

The model shows an interesting combined effect of the intensity of epidemics Ω_{int} and the proportion of R plants φ on relative damage D (Fig. S3). When the majority of plants is S ($\varphi \leq 0.5$), higher epidemic intensities generate larger relative damage on average. Indeed, high epidemic intensities are associated with high contact rates β_0. As the majority of plants is S, higher epidemic intensities lead to a higher number of successful infections along the season, and hence to larger relative damages.

When the majority of plants is R ($\varphi \geq 0.5$), higher epidemic intensities lead to significantly positive values of additional relative benefits for intermediate RB variant frequencies in S plants f_{RB}. When Ω_{int} and f_{RB} are low, epidemic-extinction cases are observed for both pyramided and monogenic resistance strategies. In those cases, decreasing virus bottleneck size cannot provide more yields. When epidemic intensity is high, the relative damage of the monogenic resistance strategy takes off from the epidemic-extinction cases for lower f_{RB} values. More trials of infection are attempted, leading to overall higher successful infection probabilities. In return, as the epidemic does not become extinct anymore, quantitative resistance can provide additional benefit again.

The variability in relative damages decreased with epidemic intensity. The stronger the intensity of epidemics, the sooner all plants get infected, a point beyond which the dynamics necessarily remain constant.

We reported cases where the relative damage got above 100% when epidemics intensity is small. This does not necessarily imply that deploying R plants was harmful, as one major

change from fully S field simulations was the use of a stochastic model, which can lead to such a result simply because of the intrinsic variability in epidemic dynamics. In any case, the additional relative benefit hardly ever went below 0 percentage points for the set of parameters used in figure 2, showing that on average deploying R plants is beneficial. The few cases of negative additional relative benefit were most probably due to the intrinsic stochasticity of the model and not to a harmful effect of decreasing virus bottleneck size.