Cheating and imperfect vaccines targetting public goods as drivers of bacterial evolution

Florian Lecorvaisier[1]*, Thomas L. P. Martin[2]

[1] Université Lyon 1, VetAgro Sup, CNRS, LBBE, UMR 5558, Villeurbanne, France

[2] Laboratoire d'Ecologie Alpine, UMR-CNRS 5553 (composante d'affectation : UFR Sciences et Montagne)

* Corresponding author (florian.lecorvaisier@vetagro-sup.fr)

Abstract

Cheating is a ubiquitous evolutionary strategy, appearing everywhere throughout the tree of life. Among bacteria, cheating appears mostly through the consumption of public good without participation in their production. Some vaccines, because they specifically target these public goods, may alter the eco-evolutionary dynamics of cheating in bacterial populations of pathogenic species such as *Corynebacterium diphtheriae*, the etiological agent of diphtheria, which produces a public virulence factor. We expand a series of fitness models to assess how the use of vaccines targeting a public good can impact the selective value of its production, alter the ecological dynamics between producers and non-producers, and select for novel phenotypes. Our results show that producers are counter-selected when a vaccine is used but only when the public good is non-mandatory for the growth and survival of the bacteria (i.e., non-producers can rely on the production of a private good for growth), and that the presence of non-producers facilitates the eradication of the producer phenotype. These results advocate for comprehensive studies of the eco-evolutionary consequences of vaccines and illustrate how the competition between non-producers and producers can be useful in the eradication of public virulence factors producers.

Introduction

In ecology and evolutionary biology, cheating can be defined as "a trait that is beneficial to a cheat[er] and costly to a cooperator in terms of inclusive fitness" (Ghoul et al., 2014). This type of behavior is widespread along the tree of life and can emerge at different ecological scales. For example, it has been described between individuals of the same species and sex, such as lekking male frogs satelliting more competitive males (Castellano et al., 2009) between individuals of the same species but opposite sex, such as male spiders deceiving their mates with worthless nuptial gifts (Beydizada et al., 2025) and between individuals of different species, such as cleaner fishes cheating on their clients by feeding on their tissues (Wilson et al., 2014) or non-rewarding female flowers deceiving pollinators by mimicking rewarding male flowers (Castillo et al., 2012).

Cheating necessarily emerges from cooperative behaviors: in the examples above, lekking frogs gather in a chorus to simplify the mating process for every participating male, male spiders exchange food with a copulation opportunity, cleaner fishes feed on ectoparasites of larger fishes, and pollinators help flowers reproduce while feeding on them. By nature, cheating can thus be differentiated from other interactions such as predation, competition or parasitism (even though intraspecific cheating is sometimes referred to as "intraspecific parasitism"). Cheating has long been questioned in the field of evolutionary biology as an obstacle to the maintenance of cooperative behaviors, while cooperative behaviors themselves have been questioned in the global "selfish-gene" framework (West et al., 2007).

Ghoul et al. (2014) define two families of cheating behavior: interception and manipulation, which we could also refer to as passive and active cheating, respectively. In interception cheating, individuals "hijack" cooperative products or behaviors, while in manipulation cheating cheaters actively exploit cooperative behaviors (for exam-

ple, by mimicking them) to ensure a gain in fitness at the expense of truly cooperative individuals. In the examples given above, the behavior of the satellite male frogs would fit within the definition of interception while other behaviors would be classified as manipulation.

Interception is particularly well represented in the domain of bacteria. Many bacterial species or populations produce public goods, i.e., costly molecules which can be beneficial to other cells in the neighborhood of the producer. By nature, production of a public good is a cooperative behavior: all individuals (should) participate in the production of the good and take a part of the common benefit. One of the most studied example of a bacterial public good might be pyoverdine, a siderophore produced by species of the *Pseudomonas* genus (Ghssein & Ezzeddine, 2022). Pyoverdine is needed for iron acquisition in multiple environments, and its production is modulated by the availability of iron (Ghssein & Ezzeddine, 2022). There are thus high stakes linked with the production of this molecule and, more broadly, with the production of siderophores. Because of the "public good" property of siderophores, it has been both theorized (Bruce et al., 2017; Lecorvaisier et al., 2024) and shown experimentally (Butaitė et al., 2017) that cheaters should and indeed do emerge in siderophore-producing populations of *Pseudomonas*, *Corynebacterium diphtheriae* and other genuses and species.

Cheating bacteria that do not produce siderophores can appear in a variety of contexts. In the pathogenic species *P. aeruginosa*, it has been shown that pyoverdine non-producers emerge during lung infections. These non-producers can be classified as cheaters as they maintain the capacity to exploit the pyoverdine produced by cooperative cells. Moreover, it has been shown that the proportion of non-producers increases with time and that the capacity of cheaters to take up the pyoverdine is maintained only until cooperators disappear from the population (Andersen et al., 2015). In natural communities of pseudomonads, it has been shown that the relationship between producers and non-producers is complex, with non-producers developing strategies to exploit the siderophores produced by cooperators, and producers developing strategies to repress cheating behaviors, much like what the Red Queen hypothesis describes (Bruce et al., 2017; Butaitė et al., 2017).

As any evolutionary strategy, cheating is complex. On one hand, and as exemplified above with pyoverdine cheaters, it may emerge or disappear due to changes in the environment (e.g., change in resources or in population density) and may not always be expected or predictable (Ghoul et al., 2014). On the other hand, we live in an ever-changing world where global warming, globalization, antibiotics and many other factors create new environments and life conditions for millions of species. All these phenomena may have an impact on the evolution of cheating as a behavior and cheaters as a population. In the present study, we focus on one global change: vaccination. Vaccines against many diseases became widespread during the second half of the 20th century and lead to evolutionary consequences such as the emergence of vaccine-escape strains of the hepatitis B virus (Santos et al., 2017; Wang et al., 2017), the emergence of hypervirulent strains of the Marek's disease virus (Gimeno, 2008), and multiple important changes in the genotype and phenotype of circulating strains of *Bordetella pertussis*, the etiological agent of whooping cough (Lefrancq et al., 2022).

We hypothesize that vaccines specifically targeting public goods, such as modern diphtheria vaccines, should alter the dynamics between cooperator (producer) and cheater phenotypes. To investigate this hypothesis, we expand a theoretical model of competition between strains of a bacterium producing a public good. Understanding how vaccination may alter this competition is of great importance as public goods can also be virulence factors or linked to virulence factors, as are the diphtheria toxin of *C. diphtheriae* (Tiwari & Wharton, 2012) or the pyoverdin of *P. aeruginosa* (Buckling et al., 2007).

Model & Results

Bruce et al. (2017) proposed a mathematical model describing the competition dynamics between two types of cells (or phenotypes) in a

population of bacteria. The first type is called "cooperator cell", named like this because it produces a public good necessary for the growth of any cell of the population. The second type is called "cheater cell" because it does not produce the public good but is able to use the good produced by cooperator cells. Their model defines the fitness of the cell as a function of the energetic cost of producing the good, q, among other parameters. If costly, producing the public good is also beneficial to the cell, as it is mandatory for the reproduction and survival of the cell.

This model describes the ecology and evolution of an environmental bacteria, *Pseudomonas fluorescens*, but it can be applied to other biological systems. In the present work, we generalize the phenomenological model developed by Bruce et al. (2017) while simplifying some aspects, and apply its study to the case of pathogenic bacteria with different phenotypes, noted i and considered here through the variability in the production of the public good.

The fitness of any i-phenotype cell can be expressed as

$$W_i = C_i\left(B_i + B_j\right)^{\alpha}, \tag{1}$$

where C_i is the cost of producing goods (public or private) for cell i and $\left(B_i + B_j\right)^{\alpha}$ is the benefit for cell i, α being a shape parameter used to decouple the costs and benefits of producing the different types of goods (see below). The benefit is divided in two parts: the benefit linked to the individual production of the i-phenotype cell production (B_i) and the benefit linked to the public good production from other cells, from the same or different phenotypes (B_j). Bruce et al. (2017) assume diminishing returns (i.e., $B_i + B_j > \left(B_i + B_j\right)^{\alpha}$ so $\alpha < 1$). Here, we relax this hypothesis and define $\alpha > 0$.

The cost of the good production is

$$C_i = 1 - q_i - g, \tag{2}$$

where $0 \leq q_i < 1$ is the production of the public good for an i-phenotype cell and $0 \leq g < 1$ is the production of other (private) goods, considered equal among cells. We consider that $q_i + g < 1$ to avoid the cost of producing the different goods to reach one.

The benefit for an i-phenotype cell derived from its own production is

$$B_i = (1 - \lambda)(1 - \eta)q_i + g, \tag{3}$$

where λ is the fraction of the public good production that is shared with other cells in the population and η is the efficacy of an (imperfect) vaccine targeting the public good ($0 \leq \eta \leq 1$). If $\lambda = 0$ then the good is not shared at all and it is in reality a private good. Thus, we posit $0 < \lambda \leq 1$.

The benefit for an i-phenotype cell derived from the production of other cells is

$$B_j = \lambda(1 - \eta)\sum_j x_j q_j \tag{4}$$

where x_j is the fraction of j-type cells in the population and q_j is the good production by j -phenotype cells (including other i-phenotype cells). In the following of this work, we will call B_i the "private benefit" and B_j the "public benefit".

There are three main differences between this model and the one proposed by Bruce et al. (2017). The first one is that their model takes into account a degree of variability in the ability of cells to exploit public goods produced by other cells, which we neglect here. The second one is that their model considers the public good to be essential for the fitness of the cells, while in our model the fitness of an i-phenotype cell can be positive as long as $g > 0$ and $1 - q_i - g > 0$. Finally, the third and most important difference is that our model considers the use of a vaccine targeting the public good.

Homogeneous model

Equation 1 can be modified to illustrate a variety of ecological situations with different degrees of complexity and biological realism. The simplest situation is to consider an homogeneous population where all cells are of the same type h ($i = j = h$) and thus share the same cost of producing the public good ($q_i = q_j = q_h$). In this case, each cell has the same fitness, independent of the fraction of the public good shared with other cells (λ).

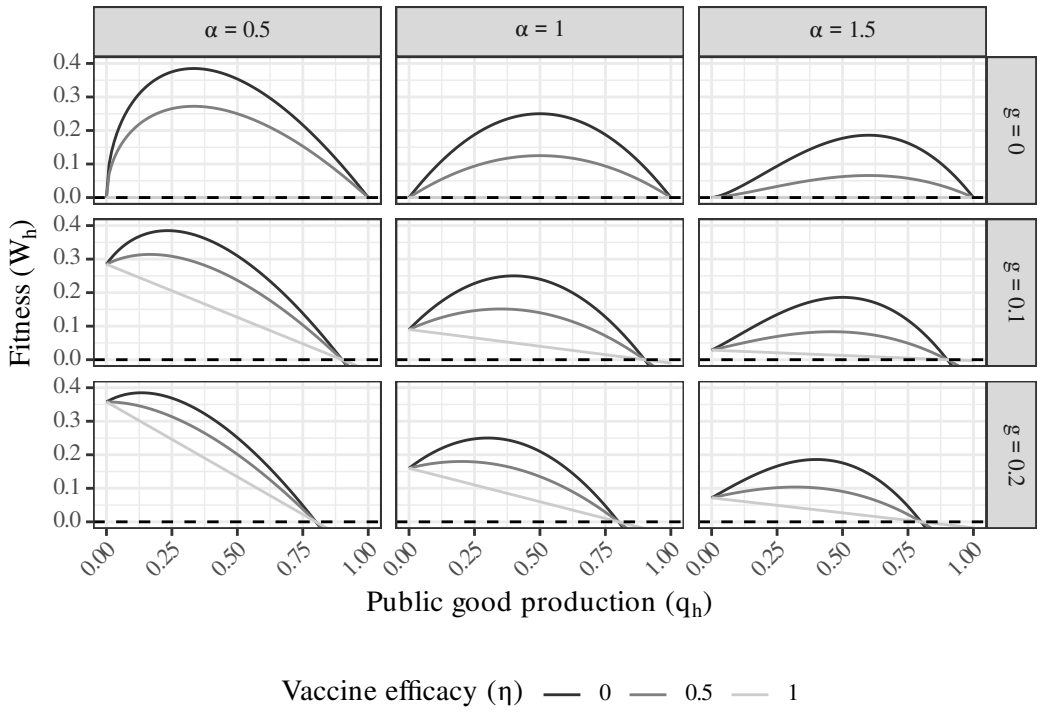


Figure 1: Fitness of the cell type 1 (W_h) as a function of public good production (q_h) for different values of vaccine efficacy (η), private good production (g) and shape parameter (α). The dashed lines indicate the lower natural boundary for W_h.

This fitness is

$$W_h = C_h\big(B_h + B_j\big)^{\alpha}, \tag{5}$$

where $C_h = 1 - q_h - g$ and $B_h + B_j = (1 - \eta)q_h + g$.

We observe that the higher the vaccine efficacy, the lower the fitness of the cells (Figure 1). This is easily explained considering that the vaccine removes the benefit of producing the public good without diminishing the cost of production. Interestingly, we observe that, except when $\eta = 1$ and it is linear, the relation between the fitness, W_h, and the production of the public cost, q_h, follows a concave curve. This means that there exists an intermediate optimal value for the production of the public good that graphically appears to depend on the values of α, g and η.

Let $q_h^\star$ be the optimal production of the public good, i.e., the value of q_h maximizing the fitness of the cells in this scenario. In a first, naive interpretation, this value could be thought as the one eventually reached by the clonal population because of natural selection (but see infra). It can be expressed as

$$q_h^\star = \frac{\alpha}{\alpha + 1} - g\frac{\alpha(1-\eta) + 1}{(1-\eta)(\alpha+1)}. \tag{6}$$

Equation 6 confirms the graphical observation from Figure 1 that the optimal public good production depends on the vaccine efficacy, η, the production of the private good, g, and the shape parameter, α. When $\eta = 1$, the second denominator in Equation 6 goes to zero. This corresponds to a situation in which the vaccine is perfect and the benefit from producing the public good is removed from Equation 5.

We observe in Equation 6 that it is possible that $q_h^\star < 0$. Indeed, the left term is always lower than one because $\alpha > 0$ and the right term is always positive because $0 \leq g < 1$ and $0 \leq \eta \leq 1$; and the right term converges toward infinity when η converges toward one. Because the production of the public good has zero as the lower bound, it means that the optimal strategy (i.e., the strategy maximizing the fitness) can be to not produce the

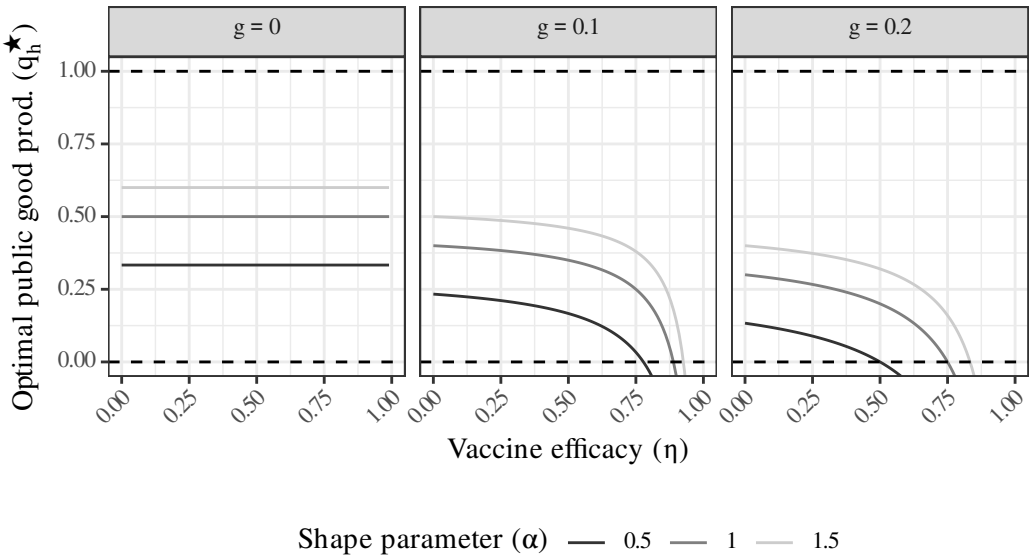


Figure 2: Optimal public good production ($q_h^\star$) as a function of vaccine efficacy (η) for different values of shape parameter (α) and private good production (g). The dashed lines indicate the natural boundaries of $q_h^\star$.

public good. Looking at the partial derivative of Equation 6, we find

$$\frac{\partial q_h^\star}{\partial \eta} = -\frac{g}{(\alpha+1)(1-\eta)^2}, \tag{7}$$

showing that the optimal production of the public good decreases in an accelerating fashion with the vaccine efficacy.

This is graphically confirmed in Figure 2, hinting to the existence of a vaccine efficacy threshold above which counter-selection occurs. Figure 2 (and Equation 7) also show that the vaccine efficacy only impacts the optimal public good production when there is some form of private good production (i.e., $g \neq 0$).

Let η_h' be the vaccine efficacy threshold above which the production of the public good should be counter-selected, i.e., the value such that $q_h^\star(\eta = \eta_h') = 0$. This value is

$$\eta_h' = 1 - \frac{g}{\alpha(1-g)}, \tag{8}$$

and we can show that for all $\eta > \eta_h'$, $q_h^\star < 0$. This finding is particularly interesting because it shows that the private good production plays an important role on the value of this vaccine efficacy threshold. We observe that the higher the private good production, the lower the vaccine efficacy threshold (Figure 3).

Interestingly, we can also observe a certain threshold in the private good production, g_h', beyond which the production of the public good is counter-selected whatever the vaccine efficacy (i.e., $\eta_h'(g = g_h') = 0$). This threshold is

$$g_h' = \frac{\alpha}{\alpha+1}. \tag{9}$$

Competition model

Until now, we considered the simplest possible model where the population was composed of clonal cells. In the following part, we consider a dimorphic population. The first phenotype, which we call "producer" or p-type, produces the public good with a level $q_p > 0$. The second phenotype, which we call "cheater" or c-type, does not produce the public good ($q_c = 0$) but, as hinted in Equation 1, it can profit from public goods produced by producer (cooperator) cells. The fitness of the producer phenotype is

$$W_p = C_p\left(B_p + B_j\right)^\alpha, \tag{10}$$

and the fitness of the cheater phenotype is

$$W_c = C_c\left(B_c + B_j\right)^\alpha. \tag{11}$$

The cost for any producer cell is

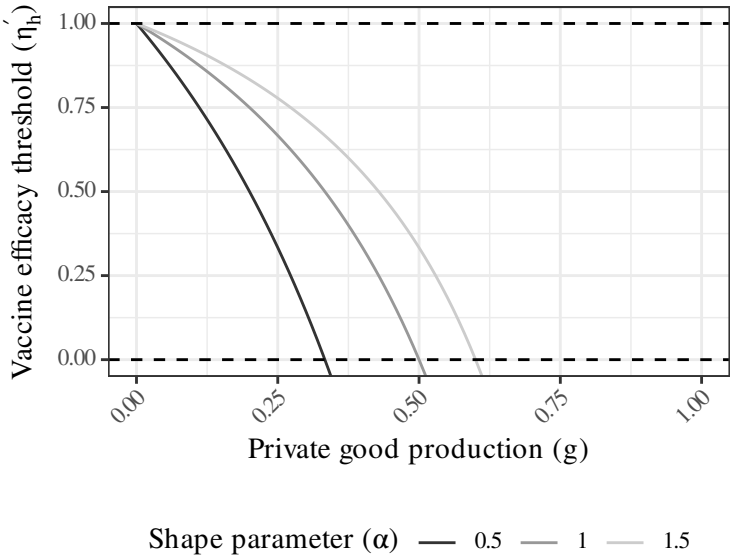


Figure 3: Vaccine efficacy threshold (η_h') as a function of private good production (g) for different values of the shape parameter (α). The dashed lines indicate the natural boundaries of η_h'.

$$C_p = 1 - q_p - g, \tag{12}$$

while the cost for any cheater cell is

$$C_c = 1 - g. \tag{13}$$

Thus, because $q_p > 0$, we know that $C_c < C_p$, meaning that cheater cells have a lower cost than producer cells.

On the other hand, each producer cell has a personal benefit

$$B_p = (1 - \lambda)(1 - \eta)q_p + g, \tag{14}$$

and each cheater cell has a personal benefit

$$B_c = g, \tag{15}$$

while each cell in the population has a public benefit

$$B_j = \lambda(1 - \eta)x_p q_p. \tag{16}$$

where x_p is the proportion of producer cells in the population. We note that, as stated earlier and contrarily to the original model by Bruce et al. (2017), cheater cells can have a positive fitness in the absence of producer cells (i.e., when $x_p = 0$) as long as the production of the private good is not null (i.e., $g > 0$).

Depending on the parameters values, and because the proportion of producer cells is by nature not static, different outcomes may emerge for this scenario. It is possible that the fitness of the producer phenotype exceeds the fitness of the cheater phenotype whatever the proportion of producer cells (e.g., Figure 4, top-left panel). In this case, the proportion of producer cells gradually increases, leading the cheater phenotype to extinction (Figure 5). Another possible outcome is the fitness of the cheater phenotype exceeding the fitness of the producer phenotype whatever the proportion of producer cells (e.g., Figure 4, bottom-left panel). In this case, the proportion of producer cells gradually decreases, leading the producer phenotype to extinction (Figure 5). Finally, in the third possible outcome, the fitness of the producer phenotype may be higher or lower than the fitness of the cheater phenotype depending on the proportion of producer cells (e.g., Figure 4, middle-left panel). In this case, the proportion of producer cells converges toward a value where $W_p = W_c$ and we can show using the replicator equation $\dot{x} = x_p\left(W_p - \bar{W}\right)$ that coexistence of the two strategies becomes the stable strategy (see Figure 5 and the Supplementary information).

This phenomenon emerges because of the nature of the interaction of the two different phenotypes. Equation 10 and Equation 11 show that the fitness of both phenotypes increases along with the relative prevalence of producer cells,

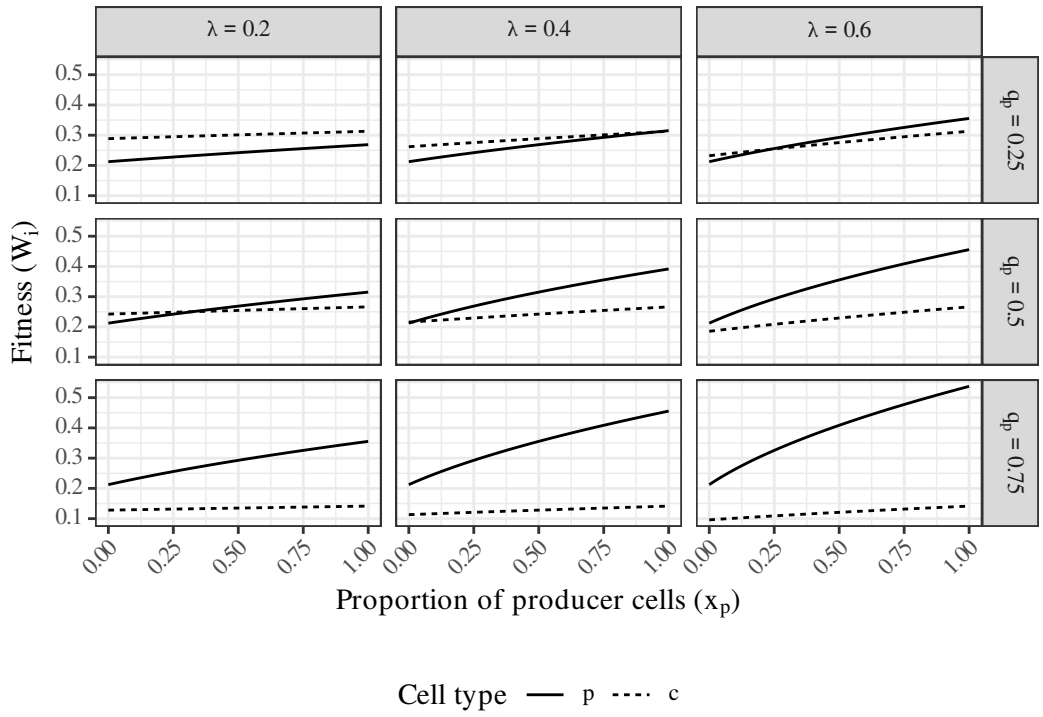


Figure 4: Fitness of the cell types p (W_p) and c (W_c) as a function of the proportion of producer cells (x_p) for different values of the fraction of the public good that is shared (λ) and public good production (q_p). Other parameter values are $\alpha = 0.5$, $\eta = 0.4$ and $g = 0.05$.

x_p. Moreover, because it does not bear any cost of public good production, the fitness of cheater cells, W_c, increases faster than the fitness of producer cells, W_p, when x_p increases (Figure 4,

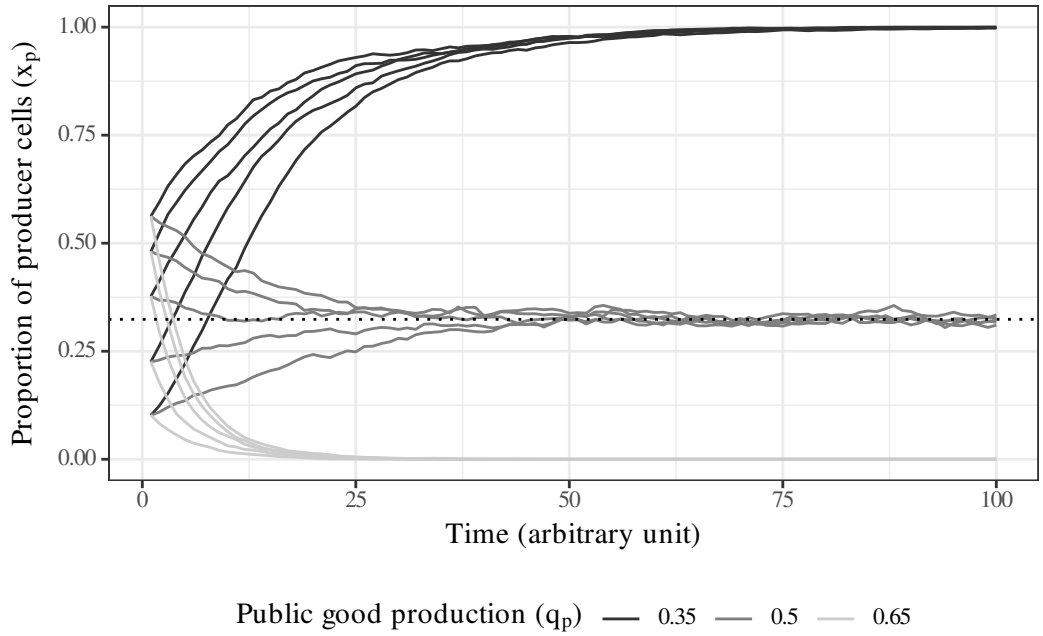


Figure 5: Change in the proportion of producer cells (x_p) with time for different values of public good production (q_p). Other parameters values are $\alpha = 0.5$, $\eta = 0.4$, $g = 0.05$ and $\lambda = 0.2$. The dotted line indicates the converging value of x_p for $q_p = 0.5$ according to Equation 17. For details on the simulator, see the Supplementary information.

all panels). However, if $W_c > W_p$, then the relative prevalence of producer cells should decrease because of the competitive advantage of cheater cells, leading to a decrease in the fitness of the cheater phenotype. Therefore, as stated above, the proportion of producer cells should converge toward an optimal, stable value for which $W_p = W_c$. This value is given in Equation 17.

We observe that the numerator of Equation 17 can fall below zero, which would result in $x_p^\star$ to also fall below zero. This outcome corresponds to the situation exposed earlier where the producer phenotype goes extinct. We observe that the denominator is zero if $\eta = 1$ or $q_p = 0$. In these situations, the production is either null or nullified by the vaccine, leading automatically the producer phenotype to extinction, and $x_p^\star$ does not exist.

In the special case where $g = 0$ (i.e., the fitness is completely conditioned by the production of the public good) we can notice that it is not theoretically possible for the producer phenotype to go extinct because of competitive pressure, except if $\lambda = 1$ (the public good is completely shared), or in one of the two situations described above: $\eta = 1$ (the vaccine "perfectly" blocks the fitness) or $q_p = 0$ (no public good is produced). Note that in any of these three possible cases the cheater phenotype should go extinct as well since its fitness relies entirely on the existence of the producer phenotype when $g = 0$. Reciprocally, it is possible that the numerator exceeds the denominator, which would result in $x_p^\star$ to go beyond one. Nevertheless, because x_p is constrained between 0 and 1, it means that the optimal proportion of cheater cells can be zero, i.e., a situation where the cheater is extinct. Looking at the partial derivative of Equation 17, we find

$$\frac{\partial x_p^\star}{\partial \eta} = -\frac{g}{\lambda q_p (1-\eta)^2}, \tag{18}$$

showing that the stable proportion of producer cells decreases in an accelerating fashion with the vaccine efficacy.

Globally, we can observe that the proportion of producer cells decreases when the production of the public good increases, even when there is no production of a private good (Figure 6). It also appears that the larger the fraction of the public good that is shared among the population, the easier it is for the producer phenotype to be maintained (Figure 6, columns); and the higher the vaccine efficacy, the easier it is for the producer phenotype to go extinct (Figure 6, rows). Also, we observe that the higher the private good production, the lower the optimal proportion of producer cells (Figure 6, colors). Interestingly, we also see that the vaccine efficacy has no impact on the proportion of producer cells when no private good is produced, i.e., when $g = 0$ (Figure 6 and Equation 18).

As we did for the first model, it is interesting to investigate the vaccine efficacy threshold, i.e., the value of η such that the producer phenotype should go extinct. We consider that x_p fluctuates way faster than q_p (because, in our model, a change in q_p implies a mutation, while a change in x_p does not). Thus, we will consider the vaccine efficacy threshold, η_p', as the value for which $x_p^\star(\eta = \eta_p') = 0$. This threshold value is given in Equation 19. In this formula, the denumerator goes to zero if $q_p = 0$ or $\lambda = 1$. The first situation implies that no public good is produced, and thus η_p' does not exist. The second situation implies that the good is perfectly public. In this case, the production of the public good is always counter-selected and η_p' does not exist either.

We observe that the vaccine efficacy threshold decreases when the public good production increases, showing how the selective pressure created by the vaccine is stronger when the cell relies heavily on the production of the public

$$x_p^\star = \frac{\left(1-q_p-g\right)^{\frac{1}{\alpha}}\left((1-\lambda)(1-\eta)q_p+g\right) - (1-g)^{\frac{1}{\alpha}} g}{\lambda(1-\eta)\left((1-g)^{\frac{1}{\alpha}} - \left(1-q_p-g\right)^{\frac{1}{\alpha}}\right) q_p} \tag{17}$$

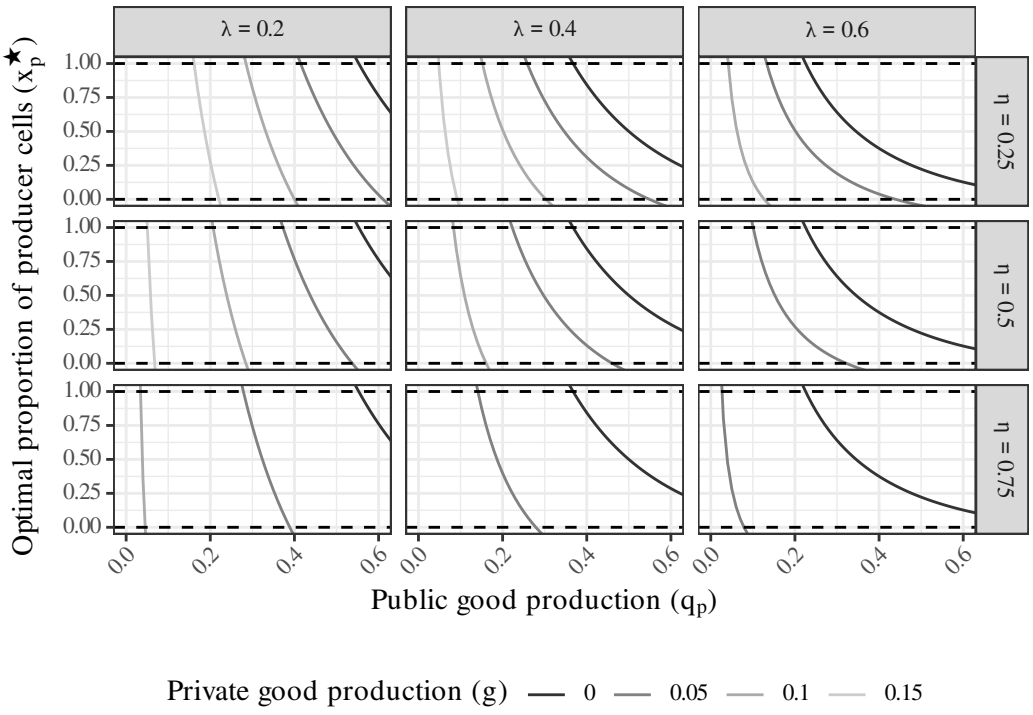


Figure 6: Optimal proportion of producer cells ($x_p^\star$) as a function of the public good production (q_p) for different values of the private good production (g), fraction of the good that is shared (λ) and vaccine efficacy (η). The shape parameter value is $\alpha = 0.5$. The dashed lines indicate the natural boundaries of $x_p^\star$.

good for its fitness (Figure 7). We can also observe that the vaccine efficacy threshold is lower when the proportion of the public good that is shared is high, illustrating how competition between producers and cheaters for access to the public good acts synergically with the vaccine against producers (Figure 7, columns). Similarly, it decreases when the private good production increases, illustrating the selective advantage of producing a private good rather than a public one when the public good is targeted by an highly efficient vaccine (Figure 7, rows).

Adaptive dynamics model

The scenarios presented above, while mentioning mutations and changes in frequency, are really static in nature. They do not take into account the adaptive dynamics of the population. Let's now consider a homogeneous population, much like what was proposed in the first scenario. The fitness of any cell in this scenario is given in Equation 5 but let's name the fitness W_w and the public good production q_w for the sake of clarity. Let's now consider a mutant cell, with a production of the public good q_m. If we consider a very large population such that $x_w = 1$ (where x_w is the proportion of cells with the wild phenotype) when the mutant cell emerges in the population, the fitness of the mutant cell is given in Equation 20.

The mutant cell can multiplicate if its fitness is higher than the fitness of resident cells, i.e., if $W_m > W_w$ or, in other words, if its invasion fitness is positive, i.e., if $\omega_m > 0$ with $\omega_m = W_m - W_w$. We can observe that there are varieties of sit-

$$\eta_p' = 1 - \frac{\left((1-g)^{\frac{1}{\alpha}} - \left(1 - q_p - g\right)^{\frac{1}{\alpha}}\right) g}{(1-\lambda)\left(1 - q_p - g\right)^{\frac{1}{\alpha}} q_p} \tag{19}$$

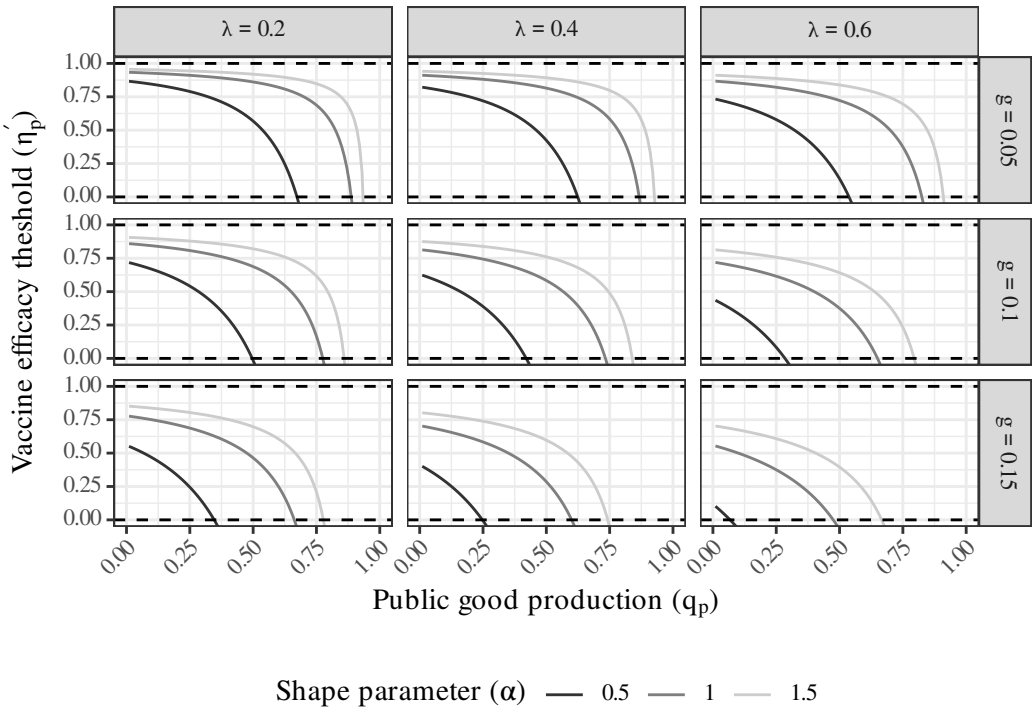


Figure 7: Vaccine efficacy threshold (η_p') as a function of the public good production (q_p) for different values of the shape parameter (α), fraction of the good that is shared (λ) and private good production (g). The dashed lines indicate the natural boundaries of η_p'.

uations where the mutant strain can invade and replace the resident strain population (Figure 8, dark grey areas) and varieties of situations where it can not (Figure 8, light grey areas). In the first situation, the proportion of mutant cells, x_m, increases and eventually reaches one, while the proportion of resident cells, x_w, decreases and eventually reaches zero. In the second situation, x_m stays zero and x_w stays one.

Interestingly, if we reciprocally calculate the invasion fitness of resident strains, ω_w, we discover that there are also q_w and q_m values combinations where both phenotypes can invade each other, leading to coexistence (Figure 8, medium gray areas). This implies that x_w will decrease but not reach zero while x_m will increase but not reach one, contrarily to the situations shown in the dark grey areas. In other words, in light grey areas, we have $\omega_w > 0$ and $\omega_m \leq 0$; in dark grey areas, we have $\omega_w \leq 0$ and $\omega_m > 0$, and in medium gray areas we have $\omega_w > 0$ and $\omega_m > 0$.

Using an extension of Equation 17 for which "cheater" cells have a public good production $q_c > 0$, we observe that the dark, light and medium grey areas on Figure 8 correspond to $x_p^\star < 0$, $x_p^\star > 1$ and $0 < x_p^\star < 1$, respectively (not shown). These represent transient conditions where both the resident and mutant phenotypes can coexist. Interestingly, we observe that the higher the value of η, the smaller the landscape of phenotypes for which coexistence is possible (see the Supplementary information).

We can show that there exists a singular public good production value, $q_w^\star$, that should ultimately be reached when a long enough time has been spent and mutations occur altering the public good production. A phenotype producing such an amount of public good cannot be invaded and is thus a convergence stable strategy (CSS),

$$W_m = (1 - q_m - g)((1 - \lambda)(1 - \eta)q_m + \lambda(1 - \eta)q_w + g)^\alpha \tag{20}$$

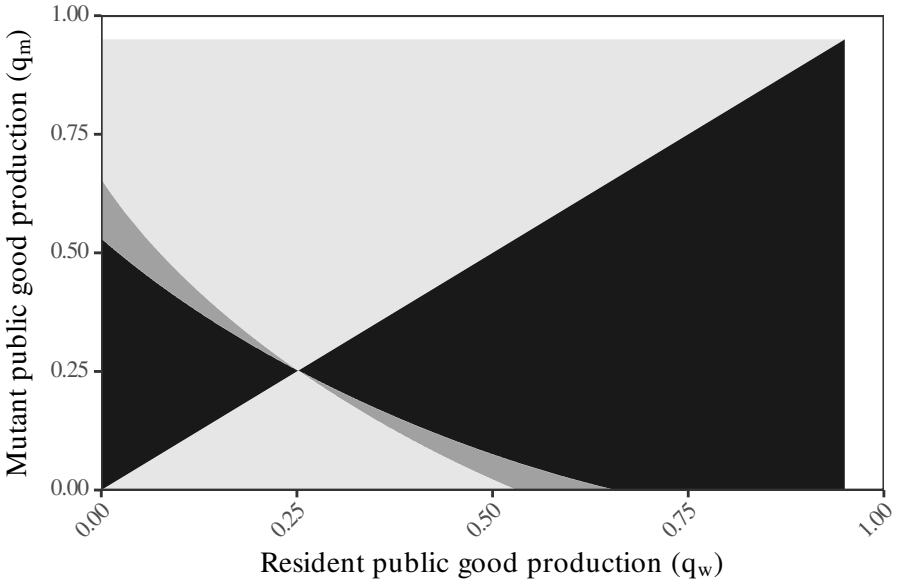


Figure 8: Pairwise invasibility plot. Dark grey areas indicate a positive invasion fitness while light grey areas indicate a negative invasion fitness. Medium gray areas indicate mutual invasion and thus coexistence. White areas indicate undefined space ($q_{(\cdot)} > 1 - g$). Other parameters values are $\alpha = 0.5$, $\eta = 0.2$, $\lambda = 0.1$ and $g = 0.05$.

meaning it is both an evolutionary stable strategy and convergence stable (Diekmann, 2003; Geritz et al., 1998; Taylor & Jonker, 1978). This value is

$$q_w^\star = \frac{\alpha}{\alpha + \frac{1}{1-\lambda}} - g\frac{\alpha(1-\eta) + \frac{1}{1-\lambda}}{(1-\eta)\left(\alpha + \frac{1}{1-\lambda}\right)}. \quad (21)$$

Interestingly, we see that the higher the shared portion of the public good (λ), the lower the value of $q_w^\star$. Reciprocally, the lower the value of λ, the higher the value of $q_w^\star$ and, for $\lambda = 0$ we have $q_w^\star = q_h^\star$, i.e., the CSS matches the optimal strategy. This means that, for $\lambda \neq 0$, the CSS is less than optimal (Figure 9B). In the end, a clonal population should appear with a lower fitness than the maximal one it could theoretically achieve (Figure 9C).

Note that, on Figure 9, new mutants appear even when the population is not clonal (Figure 9A), i.e., the fitness of mutants is not equal to the one formulated by Equation 20 but to the one given by Equation 1. Moreover, the "final" public good production and clonal fitness are different than the theoretical values because of the small population size and high mutation rate, leading to drift (see Supplementary information).

Let η'_w be the vaccine efficacy threshold above which the evolutionary stable public good production is equal to zero, i.e., the value such that $q_w^\star(\eta = \eta'_w) = 0$. This value is

$$\eta'_w = 1 - \frac{g}{\alpha(1-\lambda)(1-g)}, \quad (22)$$

and we can show that for all $\eta > \eta'_w$, $q_w^\star < 0$. This formula is simular to Equation 8 with the only difference being the addition of the proportion of the public good that is shared with other cells (λ) in the formula. We observe that the higher this value, the lower the vaccine efficacy threshold (Figure 10). Also, and similarly to what was shown earlier, we observe that the higher the production of the private good, the lower the vaccine threshold. As before, we can show that there is a private good production threshold g'_w above which the public good production is counter-selected whatever the vaccine efficacy (i.e., $\eta'_w(g = g'_w) = 0$). This value is

$$g'_w = \frac{(1-\lambda)\alpha}{(1-\lambda)\alpha + 1}. \quad (23)$$

It implies that the higher the value of λ (i.e., the more the public good is shared among other cells) the lower the private good production needed

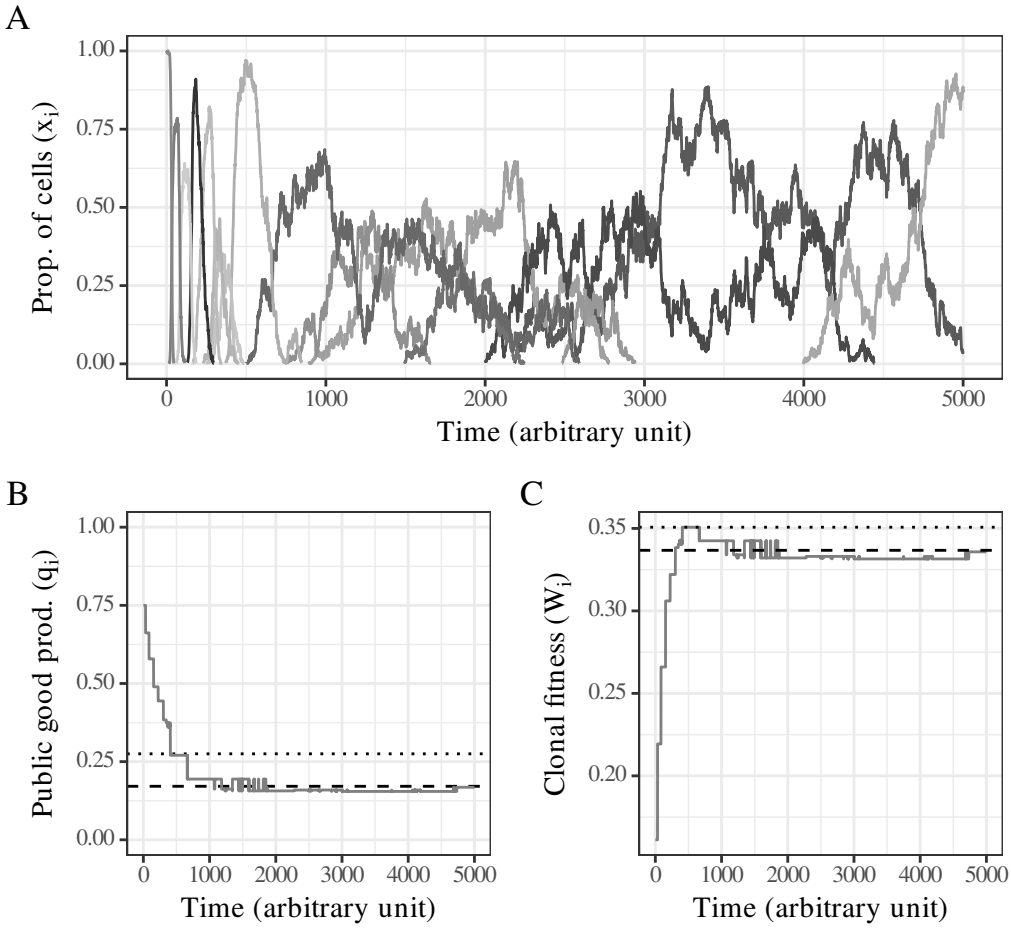


Figure 9: Evolution of the public good production when mutations occur. **(A)** Proportion of cells of different phenotypes (x_i, i as colors) as a function of time. Only phenotypes becoming dominant are shown to increase readability. **(B)** Public good production of the dominant phenotype (q_i) as a function of time. The dotted line represents the optimal public good production according to Equation 6 and the dashed line represents the stable public good production according to Equation 21. **(C)** Fitness of the dominant phenotype (W_i) if it was in a clonal population. The dotted line represents the fitness with the optimal public good production and the dashed line represents the fitness with the stable public good production (Equation 1). Other parameters values are $\alpha = 0.5$, $\eta = 0.2$, $\lambda = 0.4$ and $g = 0.05$. For details on the simulator, see the Supplementary information.

for the public good production to be counter-selected.

Discussion

The first model we presented, which we called the "homogeneous" scenario and that we formulated with Equation 5, may be plausible on a short time scale. At the beginning of an infection, an individual may be infected only by one variant from a bacterial population because of the bottleneck applied when a pathogen jumps from one host to the next (De Ste Croix et al., 2020; Zwart & Elena, 2015) or because the previous host was already carrying a clonal population of bacteria, for example because of the use of an antibiotics therapy (McVicker et al., 2014). We showed with this model that the use of a vaccine targeting the public good should decrease the fitness of the cells, a finding that is of particular interest from a medical point of view. First, because a decrease in the fitness should lead to a decrease in the multiplication rate and thus a decrease in the bacterial load, which is correlated to morbidity and mortality in many pathogenic systems such as *Neisseria meningitidis* (Darton et al., 2009), *Streptococcus pneumoniae* (Rello et al., 2009) or

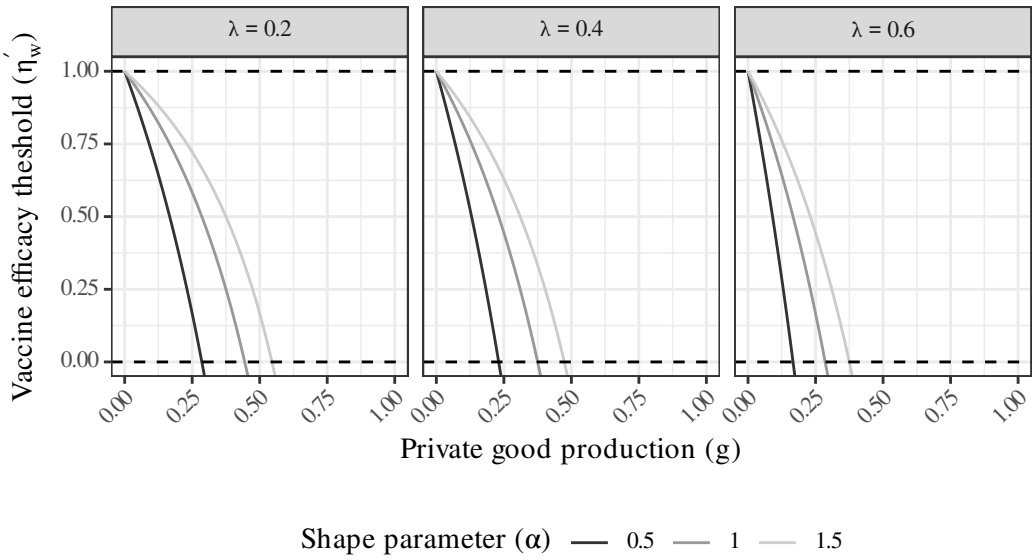


Figure 10: Vaccine efficacy threshold (η'_w) as a function of the private good production (q) for different values of the shape parameter (α) and fraction of the good that is shared (λ). The dashed lines indicate the natural boundaries of η'_w.

Mycobacterium tuberculosis (Pasipanodya et al., 2015) infections. Second, because the decrease in fitness can be so high that the production of the public good may be counter-selected. This is particularly interesting if the public good targeted by the vaccine is a virulent factor, like the diphtheria toxin is targeted by modern vaccines against *Corynebacterium diphtheriae* (Pappenheimer Jr., 1984).

We also showed with this model that vaccines create novel environmental conditions under which the most efficient phenotype shifts. Interestingly, this finding only holds when there exists an alternative metabolic pathway making the production of the vaccine-targeted public good non-mandatory for the multiplication or survival of the cells. Such alternative pathways are largely documented in the literature, notably regarding iron acquisition methods, and they have been identified as targets for the development of new vaccines (Sheldon & Heinrichs, 2015). Examples include the use of two different siderophores, pyoverdin and pyochelin, by *P. aeruginosa* (Dumas et al., 2013). More broadly, our model illustrates how vaccines alter the selective pressures weighing on (pathogenic) bacteria, something largely described in the literature with species such as *Streptococcus pneumoniae* (Brueggemann et al., 2007) and *Bordetella pertussis* (Lecorvaisier, 2024; Lefrancq et al., 2022).

The second model, which we called the "competition" scenario and that we formulated with Equation 10 and Equation 11, may be more plausible than the first one at an intermediate time scale, when a mutation leading to the appearance of a phenotype not producing the public good had time to emerge and increase in frequency. We showed with this model that, in the absence of a vaccine, the relationship between producers and cheaters is driven by the production of the different types of goods and the accessibility of public goods. Intuitively, one could think that producing a public good in the presence of cheaters while a alternative private metabolic pathway exists should be counter-selected, and that cooperators should ultimately vanish with the capacity of producing said public good (Black Queen hypothesis). This apparent problem finds its solution if we consider that public goods are only partly public and thus that cooperators cells are able to better exploit there own public good production than other cells, improving the global fitness of cells producing both private and (partially) public goods (Bruce et al., 2017; Lerch et al., 2022).

When a vaccine is used, the environmental conditions shift and the advantage given to producers diminishes, increasing the frequency of the cheater phenotype. Nevertheless, for producers to completely vanish, and similarly to what was concluded with the homogeneous model, it is necessary that an alternative metabolic exists to compensate for the loss of the public good production function in the population.

The first and second models have similar conclusions in showing that increasing the vaccine efficacy leads to a decrease in the fitness of cells producing the public good. But the competition model gives us a new insight, as we saw that the decrease in the fitness and thus frequency of producers was amplified by the presence of the competitive, cheater phenotype. In the case where the public good is a virulence factor, this finding implies that designing vaccines specifically targeting such virulence-related public goods could act synergically with the competition by cheater cells to lead to the eradication of pathogenic cells, something already found in a between-hosts model of transmission of diphtheria (Lecorvaisier et al., 2024).

The third model, which we called the "adaptaive dynamics" model and that we formulated with Equation 20, can be plausible on a long time scale, when multiple mutations have time to appear. This model is again interesting when compared to the precedent ones. The homogeneous model gave us the optimal (in term of fitness) public good production. This model shows that, in the long run, natural selection, through competition to the access of public goods, favors a less-than-optimal public good production. This model shows that coexistence between high- and low-producing cells is possible, but the population should ultimately converge toward a clonal phenotype.

When looking at the effect of a vaccine, we discovered that the higher the vaccine efficacy, the lower the CSS of public good production. For really high values of the vaccine efficacy, it is even possible that the CSS is to stop producing the public good. In this case, vaccination appears as a viable strategy to drive the evolution of pathogens toward non-production of a public good. As discussed earlier, this is particularly interesting in the case where the public good is a virulence factor.

Our work shows that cheating may emerge as a medium-term strategy without being evolutionary stable. From a theoretical ecology point of view, this means that cheaters should eventually disappear from the population. Nevertheless, in real-life settings, environmental conditions are so stochastic and perturbations occurs at such high rates that it is unlikely that a population eventually reaches the theoretical CSS. Moreover, in this model, the CSS relies on parameter values that may change over time, such as the vaccine efficacy, which may change one way by the selection of novel bacterial alleles diminishing the efficacy, and the other way by the deployment of new vaccines with a higher efficacy. This implies that the evolution of pathogens following the use of vaccines should be carefully monitored and studied to evaluate the effects of this selective pressure.

As any modeling work, our study has some flaws and limits. One of these is that the public good production is considered as constant, while in real biological settings the production may fluctuate with time and the resource availability. For example, the diphtheria toxin production in *C. diphtheriae* is conditioned by the iron availability in the host (Parveen et al., 2019).

Also, the model focuses on the ecology and evolutionary dynamics of the public good production. However, in a setting where both a public and a private good are produced, both should be under selection. It could thus be interesting to investigate the co-evolution of the production of these two types of goods.

Another important limit is that our analysis focuses on the within-host competitive dynamics between strains, without considering the between-hosts dynamics and the competition for new hosts. It would be interesting to study how selective pressure at the within-host scale could alter the between-hosts spread of novel strains in a vaccination context. For example, we hypothesize that the population heterogeneity in the

vaccine status can strongly alter the competitive dynamics between multiple strains.

Finally, our model relies on the assumption that the fitness is the product of a cost and a benefit, as proposed by other modellers (Bruce et al., 2017; Ross-Gillespie et al., 2007). Nevertheless, this represents a modeling choice and other approaches could have been taken, such as using an additive coupling between costs and benefits.

Despite these limits, our model has strong implications for vaccine development and vaccination strategies. We show that vaccine strategies have complex evolutive outcomes that must be studied before being deployed, and that ecological relationships between organisms can be used in the fight against pathogenic strains or species.

CRediT authorship

Florian Lecorvaisier: Conceptualization, Investigation, Methodology, Software, Visualization, Writing - original draft. **Thomas L. P. Martin:** Investigation, Methodology, Formal analysis, Writing - review & editing.

Data, script and code availability

The code to produce all the figures, including the code for the simulators, is publicly available at https://doi.org/10.5281/zenodo.23469505 (Lecorvaisier & Martin, 2026a).

Supplementary information

Proofs of Equation 6, Equation 8, Equation 17, Equation 21 and Equation 22 are available in the Supplementary information of this article, as well as the protocols used for the simulators illustrated in Figure 5 and Figure 9. The Supplementary material can be accessed at https://doi.org/10.5281/zenodo.23945638 (Lecorvaisier & Martin, 2026b).

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Conflicts of interest discolsure

The authors declare they have no conflict of interest relating to the content of this article.

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