160. Can we prevent pathogen adaptation when breeding disease resistant livestock?

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Abstract

Recent research shows that genetic selection has high potential to reduce the prevalence of infectious diseases in livestock. However, as with all interventions targeted at infectious diseases, pathogens might evolve strategies to escape the resistance. Thus, for sustainable breeding, strategies that prevent the invasion of these escape mutants are needed. Here we use a mathematical model of infection transmission that accounts for genetic selection in hosts and pathogens to investigate the conditions under which escape mutants can invade. The results show that genetic selection for resistance typically leads to an 'invasion window', the range in host resistance in which an escape mutant can invade. This window is smallest when resistance is strong. To prevent the invasion of escape mutants, host resistance should be increased fast through the invasion window. This raises questions about the sustainability of the common multi-trait approach when the breeding goal includes infectious disease resistance.

Introduction

Genetic selection has long been considered a potential strategy to combat infectious diseases in livestock (Bishop *et al.,* 2010). Recent theoretical studies show that the response to genetic selection to reduce the prevalence of infectious diseases should be much larger than predicted by common quantitative genetic models (Bijma *et al.,* 2021; Hulst *et al.,* 2021). With each intervention targeted at infectious diseases, however, comes the risk that pathogens evolve strategies to escape the effects of that intervention, with the widespread antibiotic resistance as the most prominent example (Davies and Davies, 2010). Thus, questions arise whether and when pathogens can evolve escape strategies to genetically selected animals, and how this can be prevented.

For some other interventions, strategies exist to prevent the evolution of pathogen escape. An example is the restricted use of antibiotics. antibiotics are preferably used as little as possible, and when used, this should be in sufficiently high dose to kill all bacteria. In this way development of bacterial escape is prevented or at least largely delayed (Walsh, 2003).

For genetic selection of livestock for increased resistance against infectious diseases, however, strategies to prevent pathogen escape have not been investigated as far as we know. In this paper, we use a mathematical model of infection transmission that accounts for artificial genetic selection in the host (i.e. livestock) population and for the evolution of escape by natural selection in the pathogen population, to investigate the conditions under which escape mutants of a pathogen can invade a livestock population. Furthermore, we investigate how such invasion of an escape mutant is influenced by the strength of resistance of the host. Ultimately, we try to find strategies for genetic selection of livestock that limit or prevent the risk of pathogen escape.

Methods & results

In this section we briefly describe and analyse a mathematical model of infection transmission that is tailored to the invasion of escape mutants in a host population under genetic selection for increased resistance (for details see Hulst *et al.,* 2022, in preparation). The starting point of our analysis is a local host population

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endemically infected with the wild type pathogen. We first describe how we model genetic selection for resistance in this host population and show how this affects the prevalence of the wild-type infection for different strength of resistance. Next, we model the invasion of escape mutants in the endemically infected host population and show how the opportunity for invasion depends on the frequency of resistant hosts and the strength of resistance.

Genetic variation in host resistance to wild-type infection. We assume that host resistance is defined by a single locus, which is either fully dominant or fully recessive, such that the host population consists of two types: resistant (with fraction f_R) and non-resistant ($1 - f_R$). Here resistant merely means that animals are less susceptible to the infectious disease, not that they cannot get infected at all.

We model differences in resistance between the two host types through the basic reproduction ratio, which is a key parameter in epidemiology and is defined as the average number of secondary infections caused by a single infected individual in an otherwise fully susceptible population (Diekmann *et al.*, 1990). R_0 has a threshold function; when it is above one an infection may persist in the population, while when R_0 is below one an infection will die out with certainty. Thus, to eradicate an infectious disease, it is essential that genetic selection reduces R_0 below a value of one.

In our case, each of the two host types has its own R_0. For infection with the wild-type (W) pathogen, these are denoted R_{NW} for non-resistant hosts, and R_{RW} for Resistant hosts. Because resistant hosts are less likely to become infected, $R_{RW}<R_{NW}$. The R_0 of the population is a weighted average of these the values, $R_0 = (1 - f_R)R_{NW} + f_R R_{RW}$.

The model tends to an equilibrium, where the number infected individuals of both host types do not change. Figure 1 shows the prevalence of the infection in this equilibrium over the frequency of resistant hosts (f_R), for R_{RW} of 1.1, 0.8 and 0.1. For R_{RW} of 0.1 and 0.8, the prevalence decreases to 0 at a certain f_R, meaning that the disease dies out. This point of dying out occurs at lower f_R for stronger resistance (i.e. lower R_{RW}). When R_{RW} is 1.1, the infection can persist in a fully resistant population, reflected in the nonzero prevalence at f_R=1. In the next section we investigate whether an escape mutant can invade a population that is endemically infected with the wild type pathogen, assuming this population is in the equilibrium as shown in Figure 1.

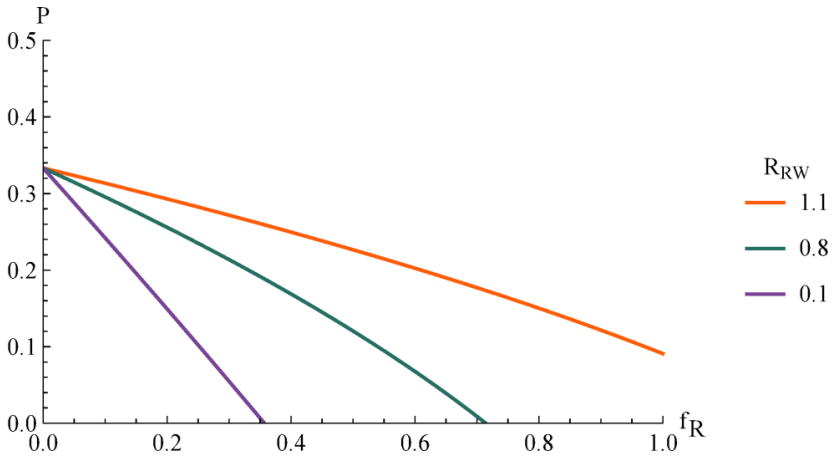

Figure 1. Equilibrium prevalence as a function of the frequency of resistant hosts. R_{NW}=1.5.

Escape mutant invasion. Escape mutants are, by definition, better able to infect resistant hosts than the wild-type pathogen. Furthermore, we assume that the escape mutation comes with a cost in pathogen fitness for infection of non-resistant hosts. We model this again through the reproduction ratios; R_{NE} for infection of non-resistant host with the escape mutant and R_{RE} for infection of resistant hosts with the escape mutant. The conditions above imply that $R_{NE}<R_{NW}$ and $R_{RE}>R_{RW}$.

We assume that escape mutants arise continuously as long as the wild type is present, so we look at their invasion rather than their emergence. Furthermore, we will only look at the invasion of a single type of mutant, with certain R_{NE} and R_{RE}, at a time. Since the mutant arises in a host population that is already infected with the wild type, to determine whether it can invade we need to derive a reproduction ratio for invasion (R_{INV}) in a host population in which the wild type is at endemic equilibrium. This can be done by multiplying the reproduction ratios of the escape mutant with the fraction of non-infected individuals of each type in the equilibrium,

$$R_{INV} = R_{NE}[(1 - f_R) - P_{NW}] + R_{RE}(f_R - P_{RW}) \quad (1)$$

where P_{NW} and P_{RW} denote the endemic prevalence of the wild type in non-resistant and in resistant hosts. If $R_{INV}>1$ the escape mutant can invade, whereas if $R_{INV}<1$, the escape mutant can emerge, but not invade because it is outcompeted by the wild type.

Figure 2 shows R_{INV} as a function of f_R (dashed line) for R_{RW} of 0.8 (green lines) and 0.1 (purple lines). The prevalence of the wild type over f_R is also shown (similar to Figure 1). The threshold value for R_{INV} of 1 is indicated by the dotted line. The invasion possibility of the escape mutant is restricted by two bounds: (1) the lower bound where R_{INV} becomes above 1, the escape mutant can invade from that point; and (2) the upper bound at which the wild type dies out (P=0), from that point the escape mutant cannot emerge anymore because there are no wild-type pathogens to mutate from. We call the range in f_R between these bounds the 'invasion window'. It is clearly visible in Figure 2 that this window is smaller with lower R_{RW} (i.e. stronger resistance). Thus, stronger resistance not only results in faster eradication of the infection, but also corresponds to a lower risk of escape mutant invasion.

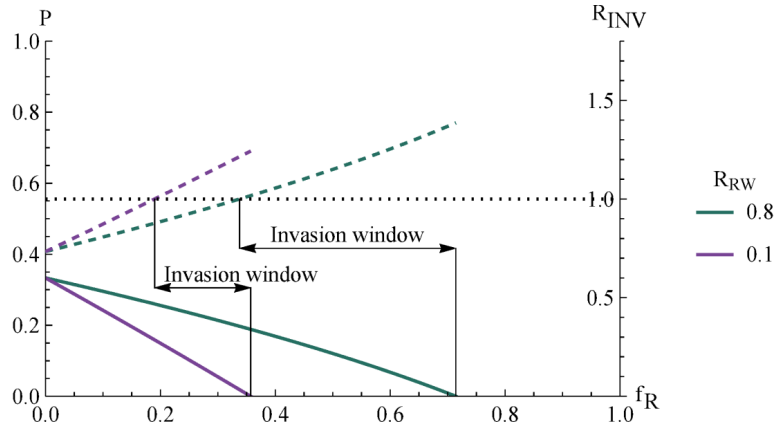

Figure 2. Invasion window for R_{RW} of 0.8 and 0.1. R_{NE}=1.1, R_{RE}=1.5, R_{NW}=1.5.

Discussion

We have demonstrated that an infectious disease can be eradicated from a local population by increasing the frequency of genetically resistant hosts sufficiently. For eradication, it is necessary that the reproduction ratio of the infection in resistant hosts (R_{RW}) is lower than one. Eradication occurs as a consequence of herd immunity, not because resistant individuals cannot become infected. As long as the infection is not eradicated, escape mutants of the pathogen might emerge and invade the host population. The invasion window is bounded by the frequency of resistant hosts from which the escape mutant can outcompete the wild-type pathogen ($R_{INV}>1$) and the frequency of resistance at which the wild type dies out. This window is smaller with lower R_{RW}.

For animal breeding, the above implies that to increase infectious disease resistance sustainably, without escape mutants invading and diminishing the effects of selection, the frequency of resistant hosts in the local population should be increased as fast as possible through the invasion window. A possible strategy to achieve that is by basing herd composition on the resistance status of the animals, such that herds are either on the left (no invasion) or on the right (eradication) side of the invasion window. This is most feasible in species where the animals in production herds are replaced all at once, such as in poultry or fattening pigs.

In genetic improvement of livestock, multi-trait selection has become the standard, because it is superior to other selection strategies for ordinary quantitative traits (Hazel *et al.*, 1994). However, improvement happens typically in small steps for each trait with multi-trait selection, which creates ample opportunity for escape mutants to invade. A relevant question is thus whether the current approach in animal breeding of gradual weak selection for infectious disease resistance is sustainable. On the one hand, it might be more difficult for pathogens to evolve escape strategies when resistance is polygenic, especially if this entails multiple resistance mechanisms. While on the other hand there are clear parallels with the long-term use of low-doses of antibiotics, which has strongly supported the evolution of antibiotic resistant bacteria (Olofsson and Cars, 2007). Further research into this is needed, but if the latter holds, it might be better to use a high dose for a short time, which corresponds to applying a large selection differential for infectious disease resistance within a single or a few generations.

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