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Defining the terms; resistance, tolerance and resilience

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Defining the terms; resistance, tolerance and resilience

Att urskilja termerna; resistens, tolerans och motståndskraft

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Abstract

Farm animals are constantly exposed to different parasite infections. An increased resistance against drugs used against parasites along with a bigger demand for organic food (with restricted use of drugs) and, a need for increased food security and safety makes it necessary to develop alternative methods to combat parasitic diseases. Using knowledge about how to take advantage of the animals own immune system has proved to be beneficial. To apply this to the breeding goals a wider comprehension is needed. Defining resistance (an animal's response to decrease the parasite burden), tolerance (an animal's performance level at an increasing parasite burden) and resilience (an animal's adaptability to different environments) is a crucial step to improve the animal's fitness according to our breeding goals. Considering that increased tolerance may prevent more parasites to harm the host, further studies of how to improve the animal's tolerance level should be encouraged, with consideration of the consequences it may have on the parasite.

Keywords: tolerance, resistance, parasite, resilience, antibiotics

Sammanfattning

Produktionsdjuren exponeras ständigt för olika parasitinfektioner. Parasiternas ökande resistans mot läkemedel, ökad efterfrågan på ekologisk mat samt behov av ökad livsmedelssäkerhet gör det nödvändigt att utveckla alternativa metoder för att bekämpa parasitsjukdomar. Kunskap om hur djurens immunsystem fungerar har visat sig vara fördelaktigt, men innan tillämpning i praktiken krävs det en djupare förståelse för de olika sätten immunsystemet kan agera. Därför krävs en djupare defenition av termerna; resesistens (djurets förmåga att minska parasitbelastningen), tolerans (hur väl djuret kan prestera vid ökad parasitbelastning) och motståndskraft (djurets anpassningsförmåga till nya miljöer). Detta kan i längden förenkla att avelsmålen uppnås. Ökad tolerans kan förhindra flera olika parasiter till att skada värden, därför bör ytterligare studier om hur man förbättrar djurens toleransnivå uppmuntras, där konsekvenserna för fortsatt avel i den inriktningen måste beaktas.

Nyckelord: tolerans, resistans, parasit, motsståndkraft, antibiotika

1 Introduction

Problems with diseases in farm animal production have traditionally been solved with the help of antibiotics and other drugs (Besier & Love, 2003). The usage of drugs without consideration of consequences leads to a high risk that the pathogens evolve a resistance against the drugs, i.e. gastrointestinal parasites resistance to anthelminthic in sheep productions (Periasamy *et al.*, 2014). The development of resistance against drugs in the parasite will prevent the drug to work efficiently and thus cause reduced productivity and health which again will lead to economical loses (Roeber *et al*., 2013; Besier & Love, 2003). An increasing popularity of organic animal farming, in which the use of drugs is more restricted, the animals are required to spend more time outside were the parasite burden may be higher. This are some reasons that demonstrate the requirement of an alternative method to combat parasitic infectious diseases in farm animal production is needed.

In recent years, an increasing interest of using knowledge on the animals own immune system also in animal breeding programs, has developed. Breeding goals are more adapted to improve resistance, tolerance and resilience against diseases. However, the ability to distinguish these three terms apart has been problematic. Resistance has been used as an generic term that included all the aspects (Bishop & Morris, 2007), the misuse of the word may lead to wrong conclusions of the animals ability to protect itself against infectious diseases.

The aim of this review is to point out the importance of breeding against different diseases, define the terms resistance, tolerance and resilience from the perspective of a endoparasite infectious diseases in farm animals and if possible determine which one of resistance, tolerance and resilience would be most favourable to focus on considering future and presence obstacles. My hypothesis is that a selection for tolerance will be more effective as it will have less effect on the parasite, less risk for co-evolution between the host and the parasite, compared to breeding for resistance. Animals which are more disease tolerant will also have a higher likelihood to tolerate new upcoming diseases.

2 Benefits of breeding against diseases in farm animals

In large farm animal productions, the use of antibiotics to prevent disease outbreak is common but may not be a sustainable solution. Studies in recent years have shown that breeding against animal diseases is feasible both economically and practically (Davies *et al.*, 2009; Perry & Grace, 2009; Besier & Love, 2003). According to Davis *et al.* (2009) the most common diseases in different livestock productions could be considered in the breeding goals for a more sustainable production. Some of the most common diseases of economic importance are mastitis in cattle, Porcine Reproductive and Respiratory Syndrome (PRRS) in pigs, Coccidiosis in poultry, as well as gastrointestinal parasites (GI) in cattle and sheep production.

2.1 Diseases in farm animals

Infectious diseases are for many reasons of major importance to farm animal breeders. If the disease indicates to transmit between species it may afflict more than the production were it first was presented. Some infections are zoonotic, i.e. bovine tuberculosis (bTB) (Banos *et al.*, 2017) and toxoplasmosis in sheep (Davies *et al.*, 2009), and become an immediate threat to the human health.

Precise measurement methods are essential to detect different diseases and their impact on animal populations. One additional problem is also lack of knowledge in pathogen burden: fewer diseased animals might indicate that they are less affected, but it could also be that the pathogen burden in the population is low (Carval & Ferriere, 2010). A large amount of data is therefore required to detect successes in achieving breeding goals in traits related to infectious diseases in different animal populations (Hayward *et al.*, 2014), especially when comparing data between different herds and breeds (Bishop, 2012). When using field data and samples, more environmental factors must be considered and if only one diagnostic test is used the probability of errors in the diagnosis may be high.

Discussion on experimental designs to identify breeding strategies related to infectious diseases and decisions on which diseases and strategies should be prioritised are ongoing. Bishop and Woolliams (2014) argue that most research efforts should be placed on costly endemic parasite diseases, because of the huge costs associated with such diseases, both economy losses and intangible losses. Endemic diseases are diseases within the population without need of external input. Even though the study of endemic parasite diseases is less explored than diseases. Two examples of diseases where progress has been made are bTB (Banos *et al.*, 2017) and Infectious Pancreatic Necrosis (IPN) in fish (Moen *et al.*, 2015), encouraging further work for breeding against endemic diseases.

2.2 Parasite infections

Infections caused by parasites mainly occur in extensive systems (Davies *et al.*, 2009), and especially with the increasing popularity of organic food the parasite burden becomes of major concern (Doeschl-Wilson *et al.*, 2012).

If the parasite is settling in another species it is called an endoparasite, while if it is settling on another species it is called an ectoparasite. The other species becomes the parasites host and functions as an environment that provides the parasite with habitat and nutrients.

Parasites normally show preference for a certain host or tissue and will always make damage to the host, the vigor depends on the parasite and sensitivity of the host (Miller *et al.*, 2006). These properties lead to both consequences and specializations for each part of a parasite-host system and may induce co-evolution between them. Co-evolution, meaning that breeding against a parasite encourage the parasite to evolve making the parasite more adaptable to the new environment within the animal.

Endoparasites spread in so-called transmission stages i.e. eggs or cysts, an inactive phase. This makes it possible to quantify the parasite burden by faecal egg count (FEC) (Tarbiat, 2012). The parasite burden represents the amount of parasites within the animal. To further assure the credibility of FEC a *post mortem* counting of the parasites in the host can be done to compare the results and confirm the parasite burden (Smith *et al.*, 1999). Different parasites can damage the animal in various levels, which should encourage to measure a parasite's vigor, resulting in more information about the parasite damage-ratio. Gaining information of the parasite-host interaction is one step in deciding which precaution to take.

2.3 Resistance, tolerance or resilience?

Traditionally the term resistance has been used when speaking of breeding against diseases, this because the lack of knowledge about how to distinguish the different terms; resistance, tolerance and resilience. Defining the different terms gives a more accurate picture of the diverse ways an animal can defend itself against parasite infections. It gives a wider comprehension on the host-parasite system, and possible ways that the parasite and its system may evolve.

2.3.1 Resistance against parasite infections

Resistance is the ability of the host to disturb the parasites lifecycle (Roeber *et al.*, 2013). Immune responses, the possession of a specific gene variant, lack of genes or receptors are examples of how the animal can interact with the parasites lifecycle (Banos *et al.*, 2017; Roeber *et al.*, 2013; Stear *et al.*, 2012; Lillehoj *et al.*, 2007). The parasites replication rate is due to the resistance level in the host (Doeschl-Wilson *et al.*, 2012). Knowing the time point when the host got infected and the level of the parasite burden is crucial when counting the host resistance level (Doeschl-Wilson *et al.*, 2012) and makes resistance a relative rather than an absolute measure (Periasamy *et al.*, 2014). Even though it has been proven that it is possible to breed successfully against a different kinds of diseases (Banos *et al.*, 2017; Moen *et al.*, 2015) there is a risk for co-evolution between the host and parasite that should be considered in the breeding goals (Carval & Ferriere, 2010).

The most common way of measuring progress in resistance is by having a positive correlation in parasite load between parents and offspring (Smith *et al.*, 1999), measuring the parasite burden with methods such as FEC. When progress has been made, Quantitative trait loci (QTL) can be identified on the genome, which allow to measure the variation in specific regions of the genome or in candidate genes involved in the innate or adaptive immune respond. This might allow the identification of DNA-markers that are strongly associated with resistance against parasites possible (Periasamy *et al.*, 2014). And may lead to a better understanding in genotype-phenotype associations, however costs of genotyping animals and the difficulty in designing good experiments for parasite infection trials, may make this approach less feasible. Different measurement methods as FEC, body weight, *post mortem* analyses (Bishop & Morris, 2007) and the environmental parameters considered (Roeber *et al.*, 2013) in different studies are essential to identify useful results. An interesting example related to the difficulty to study the genetic background of parasite infection, is the variation in heritability of resistance against nematode infections in small ruminants. In a study of Smith *et al.* (1999) free-ranging Soay sheep (*Ovies aries)* were used to estimate additive genetic variation of parasite resistance.

Data from individuals were obtained by the catch of 65% of the animals born in the study area for measuring body weight, blood-typing, tissue-typing and sampling for genetic analyses. Parasite data was obtained by FEC-measurement. Combining the parent-offspring rate with results from FEC made it possible to estimate for heritability. The results showed variation in heritability between 0.233 to 0.688 of resistance in a free-range living sheep population (Smith *et al.*, 1999).

Even though no good genetic marker exists for the selection of sheep resistant against parasites, examples in other species have shown that marker based method can be developed. Poultry coccidiosis, is a parasite protozoan infection which requires a high usage of drugs (Lillehoj *et al.*, 2007). The *MLF2*-gene has identified having effects in the chickens' resistance against coccidiosis (Hong *et al.*, 2011; Kim *et al.*, 2010).

But besides the effort and some progress made, an important aspect in the possibility of identifying and measuring the resistance phenotypes, is to take into account that environment, diet among other factors of the environment may be misleading factors that favour or disfavour the health of the host (Smith *et al.*, 1999). Another factor to consider is if the disease is, transmittable between species and if this is the case, to what grade. It is important considering that the infection may spread across many different productions and not only the one where it was induced.

2.3.2 Tolerance against parasite infections

Tolerance describes the host ability to perform while being infected (Bishop, 2012). Breeding for tolerance decrease the host susceptibility to the parasites vigor without interacting with the parasite itself. Immune responses are likely to involve tissues repair and immunological mechanisms that are directed to the toxins or harmful substances that the parasite produce, rather than against the parasite itself (Råberg *et al.*, 2009). Counting on tolerance in animals is conditional upon the animals' resistance to an infection. Meaning that if the resistance-level is high, the lack of parasite-burden would make it hard to measure tolerance-level (Bishop & Woolliams, 2014), the lower the parasite burden the harder to estimate the hosts tolerance level. Considering that the immune responses of the host do not harm the parasite itself, the credibility for a host-parasite co-evolution is less (Raberg *et al.*, 2007). Parameters that should be considered when estimating tolerance are for example the parasite burden and the parasite vigor (Doeschl-Wilson *et al.*, 2012), which give a picture of host susceptibility. Pathogen burden may not always correlate with health which is an argument to increase the tolerance levels in animals (Råberg *et al.*, 2009). Tolerance-levels may be easier to measure in groups (breeds, siblings, wild animals) to get a more credible result and a holistic picture that includes the different environmental factors that affect the animals' performance and health (Bishop, 2012; Råberg *et al.*, 2009).

A study of tolerance against GI on a wild population of Soay sheep *(Ovies aries)*, calculated tolerance by measuring changes in body weight with increasing parasite burden (Hayward *et al.*, 2014). Demographic data and FEC were used, the breeding values were obtained by suing genetic markers together with observations of the lambs. The results of Hayward *et al.* (2014) showed that there was a relatively low additive genetic variance on tolerance.

Measuring how weight and other fitness parameters in the host are relative to the parasite burden are credible ways to estimate the tolerance level in the host (Hayward *et al.*, 2014; Bishop, 2012; Miller *et al.*, 2006). Environmental factors are of immense importance to the performance of the animals and including them when counting on the tolerance is crucial.

Increasing the tolerance levels can have an impact on the infection mortalities that is beneficial (Miller *et al.*, 2006). But there is also a chance that the immune responses triggered by tolerance may alter with a continuing exposure to the toxins (Bishop & Woolliams, 2014). Another theory is that an increasing tolerance level can lead to the vigor to become stronger (Bishop, 2012; Råberg *et al.*, 2009). But the lack of studies makes it hard to rely on just one theory.

2.3.3 Resilience definition

To get a more credible answer to the hypothesis in this review, resilience must be taken in consideration. Resilience has been mentioned in different studies but the definition has not always been the same. The ability of an animal to maintain performance levels while infected irrespective of pathogen burden (Doeschl-Wilson *et al.*, 2012) is one definition that may lead to confusion trying to measure tolerance level. Another confounding explication of the term is: a host ability to tolerate parasites without any clinical signs (Gunia *et al.*, 2013), using this definition makes it hard to understand if the results truly shows the resilience level or alternatively means the tolerance level. A more specific definition is an animals adaptation ability to different environments (Bishop & Morris, 2007).

2.4 Breeding programs and goals

In breeding programs one of the major goals is to select healthy animals, without necessarily exposing them to infections (Bishop & Woolliams, 2014) including parasites. This implements that animals, which have not been infected or even exposed to a parasite should be selected based on their genetic merit for their resistance or tolerance, based on information from relatives which had been exposed to the parasite. Heritability can vary owing to environmental factors and life cycle stages of the host, where the immune responses to infections may differ (Tarbiat, 2012).

Nematode infections are usually quantified by FEC and FEC may therefore be used as an indicator of resistance (Bishop & Morris, 2007). However, the design of such experiments will be relevant and have an impact on the outcome and therefore also on genetic parameter estimates.

In a study of GI-parasites the conclusion was that variation in tolerance is unlikely to be related to the variation in resilience nor variation in resistance, this by observing the immunological response against diseases while controlling the animals productivity and FEC (Hayward *et al.*, 2014). Another study confirmed that there is no correlation between the heritability of resistance contra resilience (Gunia *et al.*, 2013). It was also shown in that study that focusing in one approach gives faster results and breeding for resilience gives a bigger economical profit (Gunia *et al.*, 2013). Gunia *et al.* (2013) further argued that diminishing the usage of anthelmintic may give more economical profits and is a reason to breed for both approaches.

In plant science, it has been acknowledged that defining the terms are essential for how to persecute with treatments and choses of selection. Accepting that the correlations may differ has led to a formula that has inspired both plant- and animal-scientist (Stowe *et al.*, 2000);

$$W_i = a_i + b_i I$$

Equation 1: where $a_{i\ is}$ is fitness when uninfected, I is the infection intensity, W_i the host actual fitness of host type i, b_i is what shows us tolerance, the slope of relationship between W and I

This equation is only applicable if a correlation between resistance, tolerance and resilience is proven.

Another aspect that should be considered is the maternal input. If the mother can maintain her offspring, the parasite may be directly transmittable between them. Those factors may have a direct impact on the original parasite burden of the offspring. Other more complex mother-offspring relationships exist, such as development of immune response, which will not be discussed here.

3 Discussion

Relevant diseases with high economically losses in farm animals that have been listed (Davies *et al.*, 2009) did show the impact of diseases on farming. Even though that it has been shown that it is feasible to breed against diseases (Davies *et al.*, 2009; Perry & Grace, 2009; Besier & Love, 2003), it is surprising that there are only a few examples of breeding programs including such a selection. The question is if reasons are the lack of studies, the easy access of antibiotics or inaccessibility of breeding stock selected against diseases that did lead to few such examples.

Looking into the topic, is can be seen that one of the first obstacles is the choice of trait for selection in animal breeding, especially how to distinguish the three terms; resistance, tolerance and resilience. In previous studies resistance has been the term used for breeding against diseases (Doeschl-Wilson *et al*., 2012). However, this may lead to confusion considering that resistance, tolerance and resilience have different meanings and a positive correlation between them is not proven.

The three terms need to be distinguished as such, with resistance being the host ability to diminish the number of parasites, for example in such way that the parasite is unable to reproduce (Råberg *et al*., 2009). On the other hand, tolerance is the hosts ability to perform despite an increasing parasite burden without interacting with the parasite itself. Resilience is the host ability to maintain performance while infected (Doeschl-Wilson *et al.*, 2012). With these definitions above, distinguishing the terms tolerance and resilience may be problematic. The definition by Bishop & Morris (2007), resilience is the hosts ability to adapt to different environments, can facilitate to differentiate the terms apart.

If there is a possibility for traits defined by each of the three terms to have an impact on each other, the terms should be separated. Even if they have a positive correlation, such correlation may influence the rate of the progress of the breeding goal negatively. This does not mean that there is no feasibility in breeding for resistance, tolerance and resilience at the same time, but rather that it will take longer time to achieve progress.

Resistance as explained by Råberg *et al.* (2009) should reduce the prevalence of parasites in the host population, which is preferable if the parasite is transmittable between species. Negative effects that should be considered is the passible co-evolution between the host and the parasite. Resistance is likely parasite specific, considering that it is possible to track resistance markers in the hosts genome (Periasamy *et al.*, 2014; Lillehoj *et al.*, 2007). Tolerance on the other hand would not interact with the parasites lifecycle, meaning that it would not affect the prevalence of parasites (Bishop, 2012). Tolerance is thereby not preferable if the disease is transmittable between species. It is important to remember that tolerance is the hosts way of the defending itself from the toxins or other dangerous substrates that the parasite secrete (Doeschl-Wilson *et al.*, 2012). Meaning that if different parasites secrete the same substances the host will automatically be protected from the harm of the substrate and not specifically the parasite, enabling the host to tolerate many different parasites that secrete the same substances. This phenome may be beneficial considering defence against multiple parasites vigor if the substrate they produce is the same. Which would make tolerance of high interest in the breeding goals. Another interesting factor is the natural selection for tolerance in wild populations (Hayward *et al.*, 2014). If a natural selection exists, tolerance should be heritable. Difficulties measuring tolerance according to all the parameters that should be included, may lead to difficulties when estimating the heritability rate for tolerance. These measurements uncertainties may be because of the lack of studies in this territory, but it is important to take into account that both the tolerance and resistance is not necessarily absolute, but may be relative and differ among the same population. It is argued that tolerance can only be measured by the least resistance animals (Bishop & Woolliams, 2014), but this do not exclude tolerance in a resistant animal, i.e. if another parasite with the same damaging substrate would attack the animal, the animal would have a higher tolerance level even though the resistance level would be relatively low. The lack of studies makes it difficult to evaluate potential consequences. More studies about how the tolerance level of the animals react on a longer exposure and how the parasites vigor responses on the tolerance level is essential to further framework this topic.

4 Conclusions

Many studies on how resistance against parasite works have been made, progress in that area has been approached but considering that parasite infection arise in more exposed environments, tolerance may be a more beneficial choice in closed farm systems. It should be prioritized to make more studies on how to improve tolerance and difficulties that can arise when breeding for it. It should also be considered to study how tolerance and resilience co-work. Considering global problems such as global warming and food safety according to the growing population and the popularity of organic food, a need for animals that can perform during different parasite burden (tolerance) as well as adapt to perform in different environmental conditions (resilience) may increase. Making those two terminologies, tolerance and resilience, to co-work may be a greater challenge than deciding which one to breed for.

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