# Breeding tolerant pigs for health and productivity

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## Introduction

The majority of Australian piggeries rely on antibiotics classified as 'low' importance in human medicine (Jordan *et al*., 2009). However, there is evidence of antimicrobial resistance to pathogens sampled in pig carcases that are of significant importance to human health, such as *Escherichia coli* (Smith *et al*., 2010). With increasing consumer awareness of medicine use and pressure for more welfare-friendly approaches in agriculture, pig breeders are faced with finding alternative strategies for production.

The environment of the pig may be a determinant of disease manifestation, and although its control to meet pig requirements improves production and reduces stress (Black *et al*., 2001), it may neither be economically feasible nor necessarily possible in all circumstances. For example, biosecurity practices and controlling environmental factors have their limitations once a disease outbreak has occurred on a farm. Pigs selected in high health environments usually observed in nucleus herds may not perform as well in the more challenging environments possibly observed on commercial farms.

One strategy to maintain health is to improve response to pathogens, through blocking entry and infection, or minimising the effects of infection. That is, selection for the host defence mechanisms of disease resistance or tolerance.

Disease resistance has been well research and characterised in animal breeding, but there has been little focus on disease tolerance. One of the first examples of disease tolerance that the authors are aware of that recognises genetic differences in disease tolerance in animal breeding, although not termed tolerance as such, is by Atkins and Mortimer (1989), who use reaction norms to find differences in the response of sheep flocks for varying incidence of fleece rot and body strike. Råberg *et al*. (2009) discussed the implications of disease tolerance in animals, and although examples were predominantly based on mouse populations in laboratory experiments, the methodology outlined for animal breeding applications is useful.

At present, the open access peer-reviewed journal *Frontiers in Livestock Genomics* is in the progress of publishing a special research topic to discuss genetic improvement in host resistance or tolerance to infectious disease. This research topic is a compilation of papers discussing different aspects of disease resistance and tolerance, one of which is a literature review the authors conducted on disease resistance and tolerance in pig breeding (Guy *et al*., 2012). This workshop paper highlights the main findings of our literature review on the selection of resistance and tolerance, and it's relevance to pig breeding.

## Resistance

Disease resistance can be defined as the active reduction of pathogen burden or prevalence by inhibiting infection and reducing pathogen growth rate (Best *et al*., 2008). Resistance has generally been used when discussing aspects of genetic improvement of the health status of pigs (Rothschild, 1998; Doeschl-Wilson *et al*., 2009). An example of host resistance in pigs is the genetic control of disease susceptibility against the bacteria *E.coli*. The absence of a particular allele for adhesion factor receptors in the host gut avoids binding of various *E. coli* strains, hence inhibiting infection (Gibbons *et al*., 1977). More recently, the genomic regions associated with Porcine Reproductive and Respiratory Syndrome (PRRS) resistance have been identified (Boddicker *et al*., 2012).

It can be argued that mechanisms of host disease resistance exert a selective pressure on the pathogen, resulting in an increase in virulence. This may increase the need for the continual development of new medical products to eliminate the more virulent pathogens. The risk of pathogens evolving to overcome this genetic strategy of the host may be reduced if more than one resistance gene is selected for (Bishop and MacKenzie, 2003).

Selection for resistance can also be seen to have negative feedback on the resistant-allele frequency in a population, as the reduction in pathogen prevalence also reduces the fitness advantage of carrying resistance alleles (Råberg *et al*., 2007). This loss of advantage may limit the success of selection for resistance, and simulations have shown that selection for resistance results in sustained polymorphisms instead of fixation of resistant alleles in the host (Miller *et al*., 2005; Best *et al*., 2008).

## Tolerance

Tolerance can be defined as the ability to limit the detrimental impact caused by a pathogen by counteracting the damage (Råberg *et al*., 2007). A more tolerant pig will therefore be more able to maintain productivity than a non-tolerant pig, despite increasing pathogenic burden. Genetic differences for tolerance in pigs were demonstrated by Potter *et al*. (2012) when average daily gain declined more strongly with increasing viral serum levels for purebred Duroc than synthetic White Pietrain pigs, although it was not termed as 'tolerance'.

Tolerance may be achieved by either ameliorating the damage caused by the pathogen directly (e.g. replacement of damaged red blood cells through induced erythropoiesis for infection of haemolytic pathogen), or the damage caused by the host's immune response (e.g. immunopathology caused by inflammation) (Medzhitov *et al*., 2012).

It can be argued that the main way that tolerance differs from resistance is the lack of interaction between host and pathogen. Since there is no impact on pathogen prevalence, selection for tolerance imposes a positive feedback system within the host, which may increase pathogen prevalence and therefore place additional positive selective pressure on tolerance alleles (Miller *et al*., 2005). The fitness advantage of tolerant genes increases with incidence of infection, driving tolerance alleles to fixation (Roy and Kirchner, 2000). Also, since there is no direct effect on the pathogen and therefore no direct selective pressure, a commensalism relationship between host and pathogen may eventuate, where the pathogen benefits but the host is neither harmed nor benefited (Miller *et al*., 2006). This is provided that the host can tolerate the pathogen damage up to a certain level of pathogen load.

Since there is no adverse effect on pathogen prevalence, integrating tolerance into a breeding objective has an element of difficulty due to possible consequences on herd health. Selection for

tolerance allows animals to be a source of infection for susceptible animals and may result in an increase in transmission of infection. A selection program for disease tolerance without resistance may have immunological consequences for the neonatal pig, which are born immunologically naïve (Blecha, 1998). Selection for tolerance, and the possibility of an increase in transmission of infection, may increase piglet mortality.

Breeding for tolerant pigs should therefore be part of an integrated health herd program (Lewis *et al*., 2007) that encompass control of pathogen load and other environmental factors, such as air quality, climatic conditions in sheds, and biosecurity measures. This approach should be employed not only on one farm, but across an entire industry (Lewis *et al*., 2007), with appropriate surveillance programs, such as abattoir health monitoring.

To further understand mechanisms of tolerance, non-pathogenic interactions including non-reactivity to antigens such as intestinal flora, may be examined. Medzhitov *et al*. (2012) argue that general tolerance mechanisms should result in positive preconditioning, and tolerance mechanisms activated against one pathogen would increase tolerance to another unrelated pathogen.

## Resilience

In ecological literature, the outcome of a resistant and/or tolerant individual examined is fitness (reproductive capability) and survival (Baucom and de Roode, 2011), whilst in an animal production context the response can also include productivity and health. It is important to recognise this as the inclusion of breeding for tolerance must also be economically viable, with improved productivity as the aim. This leads us to the term resilience. Resilience is the maintenance of productivity, irrespective of pathogen burden (Albers *et al*., 1987), which makes use of the mechanisms of both resistance and tolerance (Bisset and Morris, 1996). Compared to tolerance, which is considers pathogen burden within the animal, resilience looks at the infection level within the environment. Also, resilience is measured at one specific level of pathogen burden, with tolerance over a varying load of pathogen burden.

Breeding for resilience to nematode infection has been explored in sheep (Albers *et al*., 1987; Bisset and Morris, 1996; Gray, 1997). The inclusion of resilience in a productivity index was trialled with six New Zealand ram breeders, and although progress was slow due to low heritability, it was found to be practical and feasible (Morris *et al*., 2004). Recently, Morris *et al*. (2010) showed that selection for more resilient lines can delay the time until first drench, increase live weight at six months, and decrease breech soiling. These results demonstrate that it may be possible to select for both productivity and improved health status.

## Measuring resistance and tolerance

For optimal benefit to the pork industry, we are focusing on using data that may be routinely collected, instead of relying on measurements taken from laboratory experiments. Modelling is a proven tool to better understand the complex interactions between host response and influencing factors, and to quantify the benefits of selection (Bishop, 2011).

The simplest graphical representation of resistance and tolerance is by a linear regression model, commonly known in animal breeding as a reaction norm. Reaction norms show the regression of phenotype against increasing pathogen burden of a single species, with separate slopes and intercepts for each genotype. A pig genotype can be tolerant and non-resistant, resistant and non-tolerant, or tolerant and resistant. This is shown in Figure 1 as genotypes G1, G2, and G3, respectively. It should be noted that this is an outline of the concept, and the actual levels of

performance or health of resistant versus tolerant pigs for a given pathogen burden will depend on the specifics of each situation.

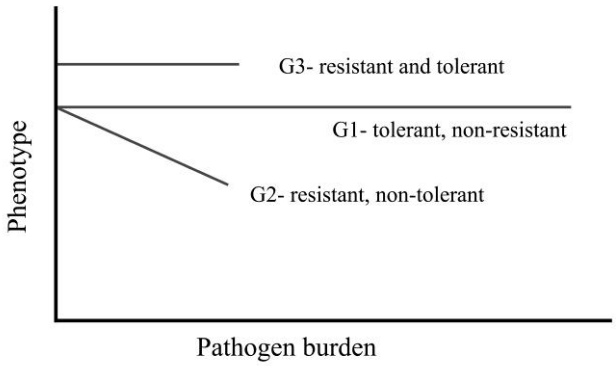


**Figure 1.** The common portrayal of phenotypic responses of genotypes with a single predictor variable of pathogen burden. The three genotypes represented here are tolerant and non- resistant (G1), resistant and non-tolerant (G2), and resistant and tolerant (G3).

Resistance is typically measured as the inverse of the maximum pathogen burden observed for a genotype.

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A pig with a larger number of pathogens will therefore have lower disease resistance. Measures that indicate level of pathogen burden are often considered as indicators of resistance. This would include, for example, faecal egg count for nematodes in sheep breeding (Albers *et al*., 1987). A fully resistant pig is one that successfully blocks pathogen entry or eliminates the pathogen, and there is no disease beyond an arbitrary threshold. In Figure 1, since genotypes G2 and G3 exhibit a lower pathogen burden than genotype G1, G2 and G3 are said to be more resistant than G1.

Tolerance may be measured as the slope of a regression of a host's response to variation in pathogen burden (Råberg *et al*., 2009), with the response based on performance measures, health status and survival of pigs. A fully tolerant pig is one whose phenotype is not affected by the level of pathogen burden. In Figure 1, genotypes G1 and G3 are fully tolerant. G2 is said to be less tolerant than the other genotypes due to the decline in phenotype with increasing pathogen burden.

The following is an outline of the specific pig measurements for phenotype and pathogen burden, which can be collected on farm in order to assess the resistance or tolerance.

## 1. Outcome/response variable: Phenotype

The outcome variable in the y-axis (also known as the response) is a measure of health or production status. An indirect indicator of animal health is through performance measures routinely collected in piggeries. Healthy phenotype indicators include average daily gain, litter size, post weaning survival and mortality. Growth rate may be an accurate indicator of health status in pig herds as it may decrease when pigs become infected, even when there are no visible signs of disease (i.e. subclinical disease). A simple yes/no or severity scale of disease infection (none, mild, severe) may not be sufficient due to subclinical disease.

Another indirect indicator of animal health is measurement of immune responsiveness. Although immunological traits have been found to be associated with pig performance (Clapperton *et al*., 2009) and have been used as an indicator of disease resistance, higher levels of immune response may not necessarily lead to or indicate improved resistance (Adamo, 2004). Different types of pathogens may elicit a different strength in response varying in time, space and type. The variable immune response of the pig to different pathogenic challenges was highlighted by Salak-Johnson and McGlone (2007). Therefore, the type of immune response should be analysed critically before attempting to measure resistance and/or tolerance.

## 2. Predictor variable: Pathogen Load

The ideal predictor variable is a specific measure of internal pathogen load in the pig, which may involve blood samples to quantify viraemia or bacteria load. However, if routinely collected on-farm data are to be utilised, and not measures collected under experimental conditions, an indirect measure (or proxy) of pathogen load may need to be defined. For example, if a link between pathogen load and, for example, level of medication, performance or survival rate is established, these can be used as a proxy for pathogen load. This approach was used by Lewis *et al*. (2009), who used on-farm records of reproductive performance to identify when a PRRS infection occurred on farm.

### 2.1 The environment

In perfectly designed laboratory experiments of resistance and tolerance, the environment of the pig is assumed to be constant between and within all genotypes. However, if we wanted to incorporate resistance and/or tolerance in breeding objectives using on-farm data, this may not always the case. We therefore also need descriptors of the environment. These may include fluctuations in temperature, humidity, changes in social dynamics, air quality, and stocking density. Just as with pathogen load, on-farm measures of non-disease environmental factors may only be feasible for groups of pigs and not at an individual level. An overall pig farm health index, including health indicators, farm hygiene and reproductive disturbances, can also be utilised to describe the environment, as proposed by Madec *et al*. (1993).

### 2.2 Genetic information

Genetic information can also be taken into account for analysis, including breeds, sires lines, other categories or families, or full pedigree structure. This may be extended to include genomic information as trait predictors. At one level, marker information may be used for QTL mapping, and once these genomic regions are identified, a subset of markers can be used as a panel for marker assisted selection. At the other end of the spectrum, complete genomic SNP information may be used to develop a genomic selection approach. Such strategies have been put forward for host response to PRRS by Boddicker *et al*. (2012).

# In Summary

Whilst most of the research focus in animal breeding has been on resistance, the difference to tolerance needs to be recognised due to consequences on pathogen-host interactions. The ability to quantify resistance and tolerance may be restrained by the lack of knowledge on the specific immunological and physiological response mechanisms of these two host defence strategies. There is a need to extend data collection on farm in order to assess disease resistance and tolerance, which may include not only descriptors of pathogen load, but also descriptors of the environment, as well as any possible interactions.

## Acknowledgements

This project is funded by the CRC for High Integrity Australian Pork (Pork CRC).

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