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Abstract

Genetic selection for production with little emphasis on health can lead to an increase in disease incidence. This trend is observed in many livestock species. A capacity to cope with environmental challenges, especially those leading to disease, is described as resilience. The project explored associations between the resilience traits of immune competence, stress-responsiveness and temperament in 1149 Performance Recorded Angus calves during yard weaning, and production and disease traits during feedlot finishing. Immune competence was moderately heritable and favourably correlated with stress-responsiveness and temperament. Prior vaccination and minimal mixing with unfamiliar animals at feedlot entry provided a low disease risk environment in the study. Nonetheless, animals with superior immune competence had significantly reduced health-associated diseases, significantly fewer mortalities, and incurred substantially lower health related costs during feedlot finishing. We hypothesise that in typical commercial feedlots with higher disease risks, the health benefits of genetic selection or phenotypic classification for immune competence to identify animals suited to feedlot finishing will be greater than described here. Future work will simplify resilience testing, assess genomic associations and validate benefits in typical feedlot finishing systems. MLA's objective of mentoring a Postdoctoral fellow now employed as a cattle research scientist was achieved.

Executive Summary

Bovine respiratory disease (BRD) is the most common disease encountered in Australian feedlots, causing significant economic losses and animal welfare issues. It has been estimated that BRD costs the Australian feedlot sector in excess of $40 million annually, with losses estimated at up to $20 per head (MLA Project AHW.087). BRD is a complex, multi-factorial disease caused by a variety of infectious agents and is most prevalent in cattle during periods of heightened stress such as the initial six weeks spent acclimatising to the feedlot environment. Commercial vaccines have been developed to protect cattle against particular agents contributing to the BRD disease complex, however providing protection against the full complement of potential BRD causing agents and achieving protective responses in all vaccinated animals are difficult to achieve. Therefore, strategies, aimed at reducing the incidence of disease, including BRD, in Australian feedlots, are required to complement existing vaccination programs. Development of such strategies is also expected to play a critical role in maintaining consumer confidence in products of the beef industry. Consumers are increasingly conscious of the health and welfare of the animals producing their food and increasingly concerned with the use of antibiotics to prevent and treat disease in food-producing animals. With consumers demanding the highest possible standards of animal health and welfare through their purchasing choices, maintaining consumer confidence is critical to the future of the beef industry.

Livestock face a variety of challenges from their production environment including exposure to infectious agents, climatic extremes, social stressors as a result of herd hierarchy and mixing with unfamiliar animals and management induced stressors imposed by standard husbandry procedures and practices. Animals respond to these challenges through a variety of host defence reactions involving immunological, behavioural and physiological responses. These responses are highly integrated and in combination determine an animal's resilience or capacity to cope with environmental challenges. Immune competence is an important component of an animal's resilience, reflecting it's ability to cope with disease challenges. The establishment of a protocol to assess immune competence in dairy cattle has enabled genetic selection strategies, aimed at breeding animals with enhanced 'general' disease resistance, to be developed and implemented in industry (Wilkie and Mallard 1999). This approach combines measures of both antibody-mediated immune responses (AMIR) and cell-mediated immune responses (CMIR) to assess 'general' immune competence. Pathogens, like the bacteria and viruses assocated with BRD, differ in the way they infect the host animal. For instance, most bacteria live outside host cells while viruses replicate within host cells. Extra-ceullar pathogens are most effectively controlled by AMIR whereas intracellular pathogens are controlled by CMIR. Therefore individuals identified as having a balanced ability to mount both types of responses are expected to exhibit broad-based disease resistance against a wide range of pathogens. The success of this strategy has already been demonstrated in dairy cattle and pigs.

Genetic selection for production with little emphasis on health can lead to an increase in the incidence of disease. This trend has been observed in many livestock species. Therefore this project aimed to explore the potential for genetic selection, aimed at improving 'general' immune competence to reduce the incidence of disease in Australian beef cattle with particular focus on reducing disease in the feedlot environment.

Specific objectives of the project were to:

1. Mentor and train a postdoctoral fellow to emerge at completion of the project as an early career scientist with strong generalist skills in livestock experimentation and specialist skills in the study of the interactions between, on the one hand, immune competence and on the other hand, stress induced by husbandry practices, temperament and resistance to diseases of the feedlot production environment.
2. Generate new knowledge on the associations described in the objective above that could lead, through subsequent research, to development of new tools and strategies for improving feedlot health that do not rely on vaccines against specific diseases.

To explore associations between the resilience traits of immune competence, stress-responsiveness and temperament and important health and production traits, a total of 1149 performance recorded Angus calves were put through a testing protocol to assess resilience traits at yard weaning. The majority of these animals were steer progeny of the Australian Angus Sire Benchmarking Program (ASBP, n=978) and were subsequently followed through feedlot finishing to monitor health and performance. As part of the ASBP, steer progeny are feedlot finished to allow traits such as feed efficiency, abattoir carcass measurement and meat quality attributes to be measured. A small number of animals (n=171) enrolled in the study were progeny of the CSIRO, Chiswick Angus Performance Recorded (APR) herd. These APR calves are pasture finished (or heifers retained for breeding) and therefore feedlot performance data was not available on these animals.

Specific traits measured on animals during yard weaning included:

1. Immune competence traits
    - AMIR
    - CMIR
2. Stress responsiveness traits
    - weight gain during yard weaning (WtGain)
    - increase in serum haptoglobin (Hapto, a stress response indicator)
3. Temperament traits
    - flight time (FT)
    - crush score (CS)
4. Worm faecal egg count (WEC, an indicator of resistance to internal parasites).

Following testing at yard weaning, calves were pasture backgrounded and then feed efficiency testing at the Tullimba research feedlot (UNE, Armidale, 100 days) and feedlot finished for a minimum of 178 days at a commercial feedlot in Northern NSW. Traits measured by Angus Australia as part of the ASBP included:

1. Growth traits
    - birth weight (BW)
    - yearling weight (YW)
    - feeder weight (FW)

2. Live-scan traits
    - eye muscle area (EMA)
    - intramuscular fat (IMF)
    - fat cover on rump (RUMP)
    - fat cover on rib (RIB)
3. Carcase traits
    - carcase weight (CWT)
    - carcase eye muscle area (CARC_EMA)
    - carcase intramuscular fat (CARC_IMF)
4. Net feed intake (NFI-f).

Analysis was undertaken to estimate genetic parameters for immune competence traits to predict the genetic gains which might be expected when selecting for immune competence. Correlations, both phenotypic and genetic, between immune competence, other resilience traits and important production traits as described above were also determined and detailed feedlot health data was obtained to investigate the influence of immune competence phenotype on disease incidence and disease related mortalities at the feedlot. Key findings from the study include:-

- Heritability estimates for the immune competence traits, AMIR and CMIR are considered moderate, suggesting a reasonable rate of genetic gain can be expected when selecting for immune competence.
- The immune competence traits AMIR and CMIR are strongly positively genetically correlated.
- Immune competence traits are favourably genetically correlated with temperament traits.
- Average daily weight gains during the yard weaning period suggest that immune competence and stress coping ability are favourably correlated.
- Immune competence traits are weak to moderately negatively genetically correlated with growth traits. This negative association is in agreement with the reduced disease resistance seen in other livestock species following selection for production traits. Although differences between immune competence phenotype groups were non-significant, feedlot exit weight (based on “Deads-out” and adjusted for feedlot entry weight and days on feed) was calculated at 817, 815 and 824 kgs for high, average and low immune competence phenotype animals, respectively. However, when the influence of mortalities on productivity were considered feedlot exit weight (based on “Deads-in” and adjusted for feedlot entry weight and days on feed) was calculated at 812, 808 and 811 kgs for high, average and low immune competence phenotype animals, respectively, suggesting that as a group, high immune competence phenotype animals are as equally productive as their average and low responder counterparts in the feedlot environment.
- Immune competence traits are weak to moderately positively genetically correlated with the fat cover traits which may have implications for reproductive performance in females.
- Significant differences in WEC were observed between immune competence phenotype groups with high immune competence phenotype animals having a lower logWEC (2.90 ± 0.17) than their average (3.38 ± 0.06) and low (3.31 ± 0.16) immune competence counterparts.

- Incidence of disease was highest in low immune competence phenotype animals (15.3 cases / 100 animals), followed by average immune competence animals (10.3 cases / 100 animals) and lowest in high immune competence animals (10.2 cases / 100 animals); however, due to low overall disease incidence observed differences between groups were not significant.
- Number of mortalities at the feedlot were highest in low immune competence phenotype animals (6.1%), followed by average immune competence animals (1.2%) and lowest in high immune competence animals where no mortalities observed.
- Health-associated costs due to lost production days at the feedlot as a result of health related mortalities, replacement cost of animals which died due to illness and disease treatment costs were estimated at $3.53, $28.24 and $103.36, (per head) for high, average and low immune competence phenotype animals, respectively.
- Low immune competence phenotype animals represented only 11.7% of all animals entering the feedlot but accounted for 35% of the estimated health associated costs incurred at the feedlot.

Results from the current study demonstrated that the benefits of selecting for immune competence realised through reduced health associated disease and mortalities are significant in a low risk feedlot environment, where animals are vaccinated prior to entry and not mixed with unfamiliar animals at feedlot induction,. We hypothesise that in higher disease risk feedlot environments the health benefits of selecting for immune competence will be even greater than those described here.

Australian biosecurity restrictions prevented the use of the immune competence testing procedure developed by Wilkie and Mallard in the current study. Therefore, a practical method was developed for immune competence testing suited to Australian conditions that employed conventional commercial clostridial vaccines (eg 7 in 1) for immunphenotyping. In addition, by application of the test at the time of yard weaning when calves are experiencing the stress of separation from their mother, a change of diet, close confinement with similar aged cattle, and frequent interaction with humans, the concept of immune competence phenotyping of animals developed by Wilkie and Mallard was extended in the current study to the concept of resilience testing. This represents a substantial conceptual advance on previous approaches to improving functional traits in livestock. We anticipate that immune phenotyping during this period of stress will provide a more rigourous test of the potential of cattle to be resilient and cope with the social and environmental challenges experienced during feedlot finishing than previous methods used for immune competence testing animals.

Strategies aimed at reducing the incidence and impact of disease in Australian feedlots such as that described here have the potential to:

- Increase productivity in the feedlot
- Reduce disease treatment costs
- Improve animal health & welfare
- Reduce use of antibiotics in the food-chain

Further development and validation of resilience phenotyping methods will be required to allow the development of a resilience selection index which could be used to rank sires presented for sale by

seed-stock suppliers targeting feeder cattle producers and which would also allow screening of animals for resilience phenotype prior to feedlot entry to identify those animals not expected to perform in the feedlot environment. Results from the current study will allow resilience phenotyping methods to be refined in future studies, improving the practicality of testing large numbers of animals on farm. Central to this refinement is the need for development of field based tests to replace labour intensive laboratory tests, removing the need to transport samples. The current study investigated the benefits of selecting for immune competence in a low disease risk environment, therefore future studies will also be required to validate benefits of selecting for immune competence in higher disease risk environments which are more representative of typical feedlot environments. The potential for additional resilience traits such as heat tolerance to be incorporated into resilience selection indexes also warrants further investigation. Therefore the goal of future projects will be to validate benefits of selecting for immune competence in more typical feedlot environments and to further refine testing procedures to assess resilience for integration into routine Breedplan phenotyping.

More specifically future projects will aim to:-

- Confirm the benefits of selecting for immune competence in higher disease risk environments where animals are not vaccinated prior to feedlot induction and cattle are mixed with unfamiliar animals from a variety of sources including saleyards at feedlot entry.
- Refine testing protocols, minimising the number of farm visits required and time taken to conduct testing.
- Develop field based tests to replace laboratory assays, providing same day results during testing and removing the need to transport serum samples to the laboratory.
- Explore genetic markers for immune responsiveness traits
- Further develop a resilience index for feeder cattle producers looking to improve the resilience of their herds

In summary, the objectives of the current project were successfully achieved as evidenced by the new knowledge gained regarding associations between resilience traits and production traits and the potential benefits of selecting for immune competence to improve the health and welfare of animals in feedlots. The overaching goal of successfully mentoring a post-doctoral scientist, leading to appointment of a research scientist serving the red meat industries was also achieved.

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1 Background

1.1 Project Background

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Brad C. Hine, Bonnie A. Mallard, Aaron B. Ingham, Ian G. Colditz. (2014) Immune competence in livestock. In 'Breeding focus 2014 – Resilience'. (Eds. S. Hermesch and S. Dominik) pp. 49-64. (Animal Genetics and Breeding Unit, University of New England, Armidale, NSW, Australia) ISBN 978-1-921-597-65-7.

Selection for production traits with little or no emphasis on health-related traits has led to an increase in the incidence of disease in many of our livestock species. Currently we are developing testing procedures to assess 'general immune competence' of beef cattle, dairy cattle and sheep on-farm. Immune competence traits will be combined with measures of temperament and ability to cope with management induced stress to estimate an animal's resilience. By exploring associations between resilience and important production traits we aim to develop breeding strategies which will identify animals highly suited to their production environment.

1.1.1 Introduction

The immune system is composed of tissues, cells and molecules which work together to protect the host animal against disease. Effective host defence is reliant on the immune system's ability to detect a wide variety of agents, to distinguish whether such agents are part of the body or foreign (self versus non-self), to determine whether non-self agents are commensals or threats, and to eliminate the potentially infectious agents or pathogens. Livestock, with the exception of those raised in specialised facilities, are exposed to a myriad of pathogens on a regular basis. Such pathogens possess the inherent ability to evolve rapidly, and as a consequence, adapt quickly to changes in the environment, and continually develop new strategies to avoid detection and elimination by the host's immune system. To detect and eliminate pathogens, the immune system has developed a diverse range of defensive responses that work together and which can be broadly categorised as either innate or adaptive responses. When a pathogen is first encountered, the innate immune system is activated. In the initial phases of the innate response, pre-formed anti-microbial substances, present in body fluids and secretions, begin to weaken and kill the pathogen while sending signals to alert the adaptive immune system of impending danger. As these responses advance, innate effector cells recognising common molecule structures described as pathogen-associated signatures become activated, setting in motion a signalling cascade that triggers defence mechanisms aimed at eliminating the pathogen. Should a pathogen breach these initial lines of defence and damage the host, mechanisms are in place to trigger adaptive immune responses. In contrast to innate responses which are largely non-specific, fast acting and not substantially enhanced by repeated exposure to the same pathogen, adaptive responses are highly pathogen-specific, slower to develop and continually refined upon repeated exposure to the same pathogen. Adaptive responses have an important memory component, which enables the effector functions of the adaptive immune system to be deployed more rapidly and with increasing specificity upon re-exposure to a pathogen.

The immune system is the body's main defence against disease, however some commonly used terms describing an individual's response to disease should be considered. Different disciplines and research studies use the related terms of disease resistance, tolerance, resilience and robustness in slightly different ways and therefore the precise relationship between these terms may be context specific. For the purpose of this report the following distinctions will be made between these separate, yet related, terms as they pertain to disease. Disease resistance is considered as the host's ability to limit or eliminate pathogens using a variety of host defence reactions including physiological, behavioural and immunological responses (Colditz, 2008). Morphological traits can also make an important contribution to disease resistance as evidenced by the relationship between breech conformation and resistance to flystrike in Merino sheep (Greeff *et al*., 2014). These various defence mechanisms work in conjunction to block pathogen invasion or to destroy the invader. However, the host can also defend itself by limiting the damage caused by the pathogen using mechanisms that prevent self-harm or modulate escalating immune responses (Schneider and Ayres, 2008). This is termed disease tolerance, or in other words, an ability to minimise the effects of infection at a given level. This terminology can be further refined by identifying individuals that maintain productivity in the face of a disease challenge. This is generally referred to as disease resilience (Bishop and Morris, 2007). A key difference between disease tolerance and disease resilience is that disease tolerance often implies a permanent state of infection where repeated exposure to a particular pathogen reduces sensitivity to its effects, whereas disease resilience is generally considered a more transient state of infection where the host eventually clears the infection with little or no effect on production. Finally, the term robustness is defined as the ability of the individual to maintain its functions in the face of internal and external challenges (Kitano, 2007). Robustness therefore is quantified by performance of various traits, such as growth, fertility, and carcass characteristics, as well as response to disease.

Both the ability to resist infection and the ability to tolerate the effects of disease are likely contributors to an animal's ability to maintain productivity when faced with a disease challenge. Therefore disease resistance and disease tolerance can both be considered to contribute to disease resilience (Bishop, 2012). In considering whether to target, disease resistance or disease tolerance, as the basis for improving animal health in selective breeding programs, there are no simple answers. It is important however to realize that disease resistance and disease tolerance are generally negatively correlated, and are based on different underlying host mechanisms and different genes, and have different impacts on the evolving pathogen (Simm and Triplett, 1994). Because disease resistance and disease tolerance are often negatively genetically correlated, individuals identified as susceptible to disease tend to be more tolerant. Conversely, individuals with resistant genotypes tend to be less tolerant. The implication of these factors is outside the scope of this discussion; however, it highlights the importance of considering the preferred final outcomes for both the host and pathogen when establishing selection strategies to improve animal health. The research described here focuses on general disease resistance because in many cases of infectious disease it is critical to eliminate the causal agent in order to prevent mortality and unintended pathogen transmission to the environment or to other hosts. Furthermore, animals identified using appropriate strategies as having enhanced general disease resistance are likely to be resistant to a wide-range of pathological agents.

When developing strategies aimed at improving animal health, it is important to recognise that disease resilience is just one component of general resilience. Just as disease resilience can be considered as the ability of an animal to maintain productivity in the face of disease challenge, general resilience can be considered as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Livestock are exposed to a variety of environmental challenges in their production environment including abiotic extremes, social and management-induced stressors and disease challenges. The contribution of immune competence to general resilience will be discussed in further detail later in the report.

1.1.2 Immune competence

Immune competence can be considered as 'the ability of the body to produce an appropriate and effective immune response when exposed to a variety of pathogens' (Wilkie and Mallard, 1999). Weak responses may allow pathogens to persist or overcome host defences leading to morbidity and mortality. Inappropriate responses to self antigens (an antigen being any substance that provokes an adaptive immune response can lead to autoimmune diseases, while inappropriate responses to harmless antigens can lead to allergic responses. It is also critical that when faced with a pathogen challenge, the body mounts the most effective type of response to control that pathogen. Some pathogens have devised means by which they enter cells of the body (intracellular pathogens) while others remain in the environment external to cells (extracellular pathogens). Elimination of intracellular pathogens generally requires that infected cells be destroyed. This job is carried out by phagocytes, which are specialised cells with the ability to ingest harmful agents and infected cells, and by cytotoxic cells, which are capable of inducing programmed cell death in infected target cells. Collectively, the actions these host defence cells are described as 'cell-mediated immune responses'. In contrast, extracellular pathogens and soluble antigens are more effectively controlled by 'antibody-mediated immune responses'. Antibodies bind to pathogens and soluble antigens in the extracellular environment, preventing them from damaging or entering cells and tagging them for destruction by immune cells. As the immune system is constantly challenged by both intracellular and extracellular pathogens it is critical that individuals have a balanced ability to mount both cell-mediated and antibody-mediated immune responses. Equally important is the fact that responses must be of a magnitude that effectively eliminates pathogens without causing self harm.

1.1.3 Immune Competence – An Important Selection Trait

Selection for production traits with little or no emphasis on health and fitness traits has led to an increase in the incidence of disease in many livestock species. Antagonistic or unfavourable genetic correlations exist between production traits and the incidence of many common diseases in livestock (Rauw *et al*., 1998). For example, the genetic correlation between milk production and the incidence of mastitis in dairy cows has been estimated at between 0.15 to 0.37 (Lyons *et al*., 1991; Uribe *et al*., 1995; Van Dorp *et al*., 1998). Thus progeny of parents with high genetic potential for milk production have a higher incidence of mastitis than progeny of parents with low genetic potential for milk production. In pigs, selection focussed on high productivity has led to an increase in susceptibility to stress and disease (Prunier *et al*., 2010). In sheep, recent production focussed breeding has been achieved in an environment where chemicals have been available to control the major pathogens, gastrointestinal nematodes. A comparison of progeny sired by contemporary rams or from semen collected over 30 years ago shows advances in many productivity traits during this time however

natural resistance to nematodes has declined significantly (Shaw *et al*., 2012). Such findings suggest that continued selection based on productivity alone will result in further increases in the incidence of disease in livestock species. The animal production sector is becoming increasingly aware of this issue and is actively seeking solutions to the problem.

Changes in community attitudes are also contributing to a renewed focus on breeding production animals that have an enhanced natural ability to resist disease. Consumer awareness of practices that impact the health and welfare of food-producing animals is increasing, as is concern regarding the use of antibiotics to control disease in livestock and the potential food contamination issues that arise from their misuse. However, it must also be acknowledged that selection for increased productivity remains a key profit driver for our livestock industries. Alternative strategies that address these consumer concerns while reducing the incidence of disease, and as a consequence, production losses and treatment costs associated with disease are therefore required. It is therefore proposed that a possible genetic solution is to combine production traits and immune competence traits into a weighted selection index with the aim of breeding high-producing animals with enhanced general immune competence (Mallard *et al*., 1998a; Wilkie and Mallard, 1999).

1.1.4 Selecting for Resistance to Specific Diseases versus Selection for General Disease Resistance

Breeding strategies targeted at increasing resistance to specific diseases in livestock have proven very successful. Such strategies include breeding sheep with enhanced resistance to specific internal parasites (Le Jambre *et al*., 1971), dairy cattle with enhanced resistance to mastitis (Heringstad *et al*., 2000) and beef cattle with increased resistance to brucellosis (Adams and Templeton, 1993) and to cattle ticks (Frisch *et al*., 1998). Based on the knowledge that the host immune system tailors responses to the type of pathogen encountered, it could be expected that selection of animals based on their resistance to a specific disease may inadvertently increase their susceptibility to other diseases. For example, selection of animals based on their resistance to an extracellular pathogen, largely controlled by an antibody-mediated immune response, might inadvertently increase their susceptibility to intracellular pathogens, largely controlled by cell-mediated immune responses. In support of this concept, it has been reported that cell-mediated and antibody mediated immune responses are negatively genetically correlated in dairy cattle even though these immune responses work at the phenotypic level in a coordinated manner to protect the host (Hernandez *et al*., 2006; Thompson-Crispi *et al*., 2012b). More research is required to assess the long term effects of selection for resistance to a specific disease on susceptibility to other diseases in livestock. We hypothesise that long term benefits can be expected from adopting breeding strategies based on enhancing general disease resistance of livestock as an alternative to, or in conjunction with, enhancing resistance to specific diseases of significant economic importance to the livestock industries.

1.1.5 Assessing Immune Competence

Genetic variation in the ability to resist disease is due to a large number of additive genetic effects which together regulate innate and adaptive immune responses (Wilkie and Mallard, 1999). It has been estimated that greater than 7% of all known genes in the mammalian genome are involved in immune function (Kelly *et al*., 2005). Although the underlying genotype involves complex interactions between many genes, by inducing immune responses and objectively measuring such

responses in livestock, general immune responsiveness of individual animals can be assessed (Wilkie and Mallard, 1999) (Fig 1.). This was first demonstrated amongst livestock species in Yorkshire pigs, where measures of innate and adaptive immunity (both antibody and cell-mediated) were combined to generate estimated breeding values (EBVs) for general immune responsiveness and to rank boars and gilts as high, intermediate and low immune responder (IR) phenotypes for use in future breeding programs (Mallard *et al*., 1992). This strategy aimed to simultaneously improve the ability of animals to mount both antibody and cell-mediated responses, and as a consequence, enhance general disease resistance. Following the inbreeding of high, intermediate and low IR phenotype pigs for several generations it was found that high IR pigs had superior antibody responses to test antigens and several commercial vaccines (Wilkie and Mallard, 1999), a lower frequency of non-responders when vaccinated with inactivated influenza vaccine (Wilkie and Mallard, 1998) and higher antibody avidity, a measure of the strength of the antibody-antigen interaction (Appleyard *et al*., 1992), than their intermediate and low IR counterparts. Although such findings provide overwhelming evidence to suggest that selection successfully enhanced general immune responsiveness in high IR pigs, when challenged with *Mycoplasma hyorhinis,* these pigs displayed more severe arthritis than LR pigs, suggesting that high IR phenotype pigs may be more prone to generating inflammatory responses (Magnusson *et al*., 1998). However, in the same study, high IR pigs were found to have less severe peritonitis, less severe pleuritis and produced serum antibody against *M. hyorhinis* both earlier and to a higher level than did their low IR counterparts and therefore survived better. Thus the tradeoff between lameness and survival may be defensible in this case.

More recently, research efforts have been focussed on developing protocols to assess general immune responsiveness in dairy cattle, similar to those used in pigs, and on investigating associations between immune responsiveness phenotypes and the incidence of disease in large-scale commercial dairy farms. This strategy involves immunising animals with antigens that stimulate either strong antibody or cell-mediated immune responses, and then measuring both types of response. The responses are then used in combination to rank animals for general immune responsiveness (Heriazon *et al*., 2009a; Heriazon *et al*. 2009b). Although this ranking strategy does not incorporate measures of innate immunity, in contrast to the strategy used in pigs, it is acknowledged that strong adaptive immune responses are underpinned by strong innate immune responses (Figure 1.). In fact, macrophage function, including both phagocytosis and nitrous oxide production, seems to be stronger in high responder dairy cows (B.A. Mallard, *pers. comm*.) as does TLR2 expression, a receptor involved in the recognition of a wide array of microbial molecules (Wagter-Lesperance *et al*., 2014). Therefore such a strategy can still be expected to identify animals with enhanced general immune responsiveness and, as a consequence, general disease resistance. Researchers have utilised this testing strategy to investigate the influence of hybrid vigour on general immune responsiveness in purebred and crossbreed dairy cattle (Begley *et al*., 2009, Cartwright *et al*., 2012), the influence of age and pregnancy status on general immune responsiveness in dairy heifers (Hine *et al*., 2011), leukocyte (white blood cell) populations in high and low IR dairy heifers (Hine *et al*., 2012) and the influence of geographical location on immune response profiles of Canadian dairy cattle (Thompson-Crispi *et al*., 2012a).

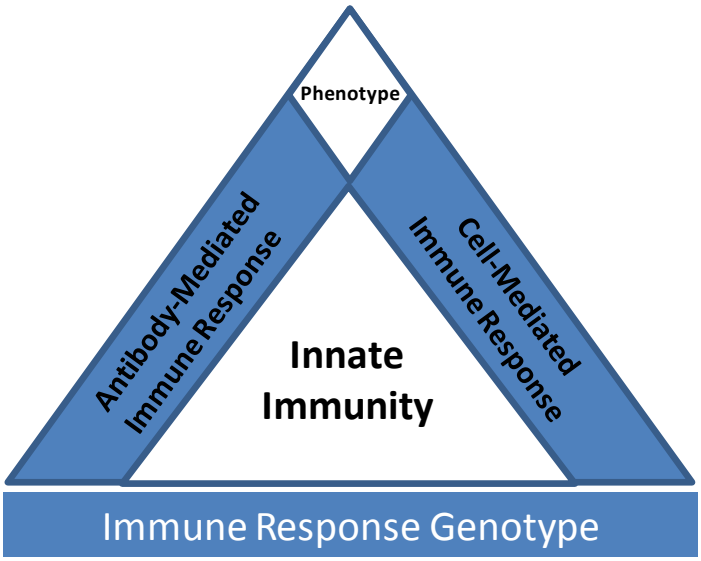

Figure 1. Genetic variation in the ability to resist disease is due to a large number of additive genetic effects which together regulate innate and adaptive immune responses (Source: adapted from Wilkie and Mallard 1999)

2 Project objectives

2.1 Project Purpose (as outlined in original application)

The purpose of this project was to support a postdoctoral fellow to work under the supervision of Dr Ian Colditz at the CSIRO to build and maintain research capacity in the health, welfare and productivity of cattle in Australian feedlots. Dr Colditz was required to guide the postdoctoral fellow's research career as both direct manager and as a mentor in research leadership.

Cattle respond to challenges to their integrity that are created by infectious organisms and husbandry practices through immunological, physiological and behavioural defence reactions. The three modalities of host defence are highly integrated and their activation uses resources that would otherwise be directed towards production. A better understanding of these interactions was expected to improve our ability to manage livestock for optimal welfare outcomes and to identify animals with a reduced risk of being adversely affected by management-induced stress and infectious disease for feedlot finishing and for use in breeding programs.

The Postdoctoral Fellow was to be mentored in two areas of research on immune function during host defence:

- The first was to be the application of immunology to the assessment of the welfare impact of husbandry practices in the sheep and cattle industries. As a member of the animal welfare research team, the post-doc was to participate in ongoing research projects on affective state in sheep and cattle, analgesia for husbandry practices and objective measures of animal welfare.

- The second and larger research activity (Approximately 90% of candidate's time) was to be a project on enhanced immune responsiveness in beef cattle for resistance to feedlot stressors and production diseases such as bovine respiratory disease.

An important aspect of the work was a high degree of "ownership" of the project by the Postdoctoral Fellow with mentored input by the fellow contributing to the detail of the research project undertaken including annual negotiation of project specifics between the post-doctoral fellow, MLA (Des Rinehart) and Ian Colditz.

2.2 Project Objectives (as outlined in original submission)

1. Mentor and train a postdoctoral fellow to emerge at completion of the project as an early career scientist with strong generalist skills in livestock experimentation and specialist skills in the study of the interactions between, on the one hand, immune status and on the other hand, husbandry practices, temperament and resistance to diseases of the feedlot production environment.
2. Generate new knowledge on the associations described in the objective above that could lead, through subsequent research, to development of new tools and strategies for improving feedlot health that do not rely on vaccines against specific diseases.

2.3 Project Plan (as outlined in original submission)

Proposed Methodology

The postdoctoral fellow will be selected from an open competitive application process according to the procedures of CSIRO. A representative of MLA will be one of the members of the selection panel.

Dr Colditz will:

1. Ensure that the postdoctoral fellow has the opportunity to develop leadership skills by acting as a mentor and by enabling the postdoctoral fellow to receive formal leadership training on an annual basis.
2. Develop the research capability of the postdoctoral fellow to a point where he/she will be successful in competitive grant applications.

The experimental research program of the postdoctoral fellow will be developed in discussion with the postdoctoral fellow, his/her CSIRO manager(s) and the MLA manager and will contribute to current RD&E strategic objectives. The research program of the postdoctoral fellow will be approved by the MLA manager prior to implementation.

The project will apply a panel of immune function and host defence assays to beef cattle to examine associations between these tests, genetic markers (SNPs) and production and health phenotypes. The project will be integrated into at least one of 3 beef genetic resources available in New England:

- The 150 Angus cow + follower Beef Information Nucleus (BIN) located at CSIRO Chiswick;
- The Genetic Information Group comprising 350 Angus cows + followers from the 3 leading Angus Seedstock producers in Australia, (also to be hosted at CSIRO Chiswick and used as a resource in collaboration with AGBU for estimation of cross breed EBVs); and

- The Angus BIN located nearest to Armidale.

The salient features of the study populations are high density SNP genotyping plus detailed multi-trait phenotyping (with a strong emphasis on novel traits such as methane production at pasture) with feedlot finishing of male progeny. Access to multiple study populations provides the opportunity for validating findings from the research project in a second population.

Specific indicative tasks will be to:

- Develop an appropriate panel of antigens based on currently used commercial vaccines to measure general immune responsiveness, including measures of innate and adaptive (both antibody and cell-mediated) immune responsiveness.
- Develop an immunisation protocol and timing for assessing general immune function – e.g. during yard weaning in order to replicate some of the stressors that animals experience at feedlot entry
- Collect phenotypic data on immune status in pasture and feedlot environments
- Measure other host defence variables such as response to ACTH challenge and acute phase protein response to social stressors.
- Estimate associations between immune status, host defence variables and performance in pasture and feedlot environments.
- Estimate genetic parameters for immune status, host defence variables and performance in pasture and feedlot environments.
- Explore genetic markers for immune responsiveness traits and for immune responsiveness traits associated with feedlot performance.

3 Methodology

3.1 Study Animals

All animals enrolled in the study were Performance Recorded Angus cattle. The majority of animals (n=978) enrolled in the study were cohort 2 & 3 progeny of the Australian Angus Sire Benchmarking Program (ASBP). As part of the ASBP, steer progeny are feed efficiency tested at a research feedlot and then feedlot finished at a commercial feedlot to allow traits such as feed efficiency, abattoir carcass measurement and meat quality attributes to be measured. A small number of animals (n=171) enrolled in the study were progeny of the CSIRO, Chiswick Angus Performance Recorded (APR) herd. The APR calves are pasture finished (or heifers retained for breeding) and therefore feedlot performance data was not available on these animals. Details of animals enrolled in the study are presented in Table 1. In addition to the 1149 animals immune competence tested at yard weaning (Table 1), weaning weight and crush score (to assess temperament) data were collected on a further 1084 ASBP heifer progeny for Angus Australia recording purposes during yard weaning (data not used in current study).

Table 1. Description of animals enrolled in the study

Location	Drop[#]	Sex[±]	Progeny of Program[†]	Immune Competence Tested At Yard Weaning	Feedlot Performance Data Available
Ardrossan, Holbrook	H	S	ASBP	171	147
	J	S	ASBP	278	227
Glenroy, Bingara	H	S	ASBP	61	58
	J	S	ASBP	78	73
Myola, Black Mountain	H	S	ASBP	122	111
Yaralee, Cassilis	H	S	ASBP	164	149
	J	S	ASBP	104	94
Chiswick, Armidale	H	S	APR	44	0
	K	S	APR	40	0
	H	H	APR	49	0
	K	H	APR	38	0
TOTAL				**1149**	**859**

[#] H=2012 drop, J=2013 drop, K=2014 drop
[±] S=Steer, H=Heifer
[†] ASBP=Angus Sire Benchmarking Program, APR=Angus Performance Recorded

3.2 Angus Sire Benchmarking Program (ASBP)

The ASBP is a major initiative of Angus Australia with support from Meat & Livestock Australia (MLA) and industry partners.

The objectives of the ASBP are:

1. Generate progeny test data on modern Angus bulls, particularly for hard to measure traits such as feed efficiency, abattoir carcass measurement, meat quality attributes & female reproduction.
2. Generate data for the validation & refinement of Angus BREEDPLAN.
3. Build a comprehensive phenotype and genotype database on Australian Angus for genomic technology validation, research and development.

To meet the project objectives Angus Australia aims to join an average of 40 sires a year to approximately 2,000 Angus cows to achieve a minimum of 25 progeny (50:50 steers and heifers) per sire using the fixed time AI program supported by Vetoquinol and using the Cue-Mate devices. The Angus cows are located across several commercial focused co-operator herds spanning Northern to Southern New South Wales and Victoria.

The Angus sires that enter the ASBP are nominated by Angus Australia members. A list of all bulls that have entered the ASBP can be viewed in the catalogues listing page on the Angus Australia website. Their progeny are comprehensively performance recorded for calving ease, growth,

temperament, heifer reproduction, structure, feed efficiency, abattoir carcass and beef quality attributes (source: https://www.angusaustralia.com.au/sire-benchmarking/about/general-information/).

3.3 On-farm Testing at Yard Weaning

The immune competence (while under the stress of yard weaning), stress responsiveness to yard weaning and the temperament of a total of 978 calves were assessed during the yard weaning period using the testing protocol timetable described in Table 2.

Table 2. Timetable for testing procedures conducted on farm during yard weaning

Day	Operation[#]
Day 0	Wean Liveweight recording Crush Score Flight Speed Testing Vaccinate with Ultravac 7 in 1 clostridial vaccine (Zoetis) Collect blood sample Collect faecal Sample
Day 3 or 4 **(standardised within herd cohort)**	Collect blood sample Liveweight recording (where possible)
Day 14 **(dependant on vaccination history,** **standardised within herd cohort)**	Collect blood sample Conduct skin test (DTH) Liveweight recording (where possible)
Day 16 **(dependant on vaccination history,** **standardised within herd cohort)**	Collect blood sample Measure response to skin test (DTH) Liveweight recording

[#]NOTES:

-Timing of blood sample collection (to assess AMIR) and Delayed Type Hypersensitivity (DTH) testing (to assess CMIR) post vaccination were adjusted based on the history of clostridial vaccination in calves from each herd. All animals tested had received a maximum of 2 clostridial vaccinations prior to testing. The following timetable of events was used for calves having received only a primary clostridial vaccination.

-Of calves tested, a total of 61 had received no clostridial vaccinations prior to testing (Glenroy H drop steers), 122 had received both a primary and boost clostridial vaccination (Myola H drop steers) and all other calves a primary clostridial vaccination only (n=966).

-Day 0 of testing coincided with the commencement of yard weaning for all calves with the exception of the Yaralee H drop steers (n=164) in which Day 0 of testing coincided with days 3 (herd cohort 1) or 4 (herd cohort 2) post-weaning.

-When necessary that calves be released from yards before Day 14 & 16, calves were re-mustered from the paddock to the yards for procedures on those days. All calves tested were yard-weaned for a minimum of 7 days.

-All calves tested were weighed a minimum of twice (start and end of testing period) and maximum of four times during the weaning period (depending on facility availability).

3.4 Detailed Methodology for Testing Procedures Conducted at Yard Weaning

Faecal sampling – Faecal samples were collected by taking a grab sample directly from the rectum of animals while restrained in the head bale using standard operating procedures.

Blood sample collection – Blood samples were collected using jugular venipuncture. A total of 2*10ml serum tubes are collected at any single blood collection. Serum was collected from coagulated blood by centrifugation (700 × *g*, 20 min, RT) and stored in multiple aliquots at −20°C (or -80°C for long-term storage) for subsequent laboratory procedures.

Crush score assessment – Calves are placed in the crush (not in head bale) and their behaviour observed for a period of 30 seconds and scored on a scale of 1 to 5 by a trained observer.

Vaccinations – Calves received a 7in1 vaccination (Ultravac 7in1, Pfizer) on day 0 of testing. All vaccinations were administered subcutaneously high on the neck as per manufacturer's instructions.

DTH skin test – To elicit DTH responses, a test or control sample is injected intradermally in the caudal tail fold using an insulin syringe with 30G needle. Prior to injection, injection sites are identified and skin thickness measurements taken with calipers to provide a baseline skin thickness. 48Hrs post-injection, changes in skin thickness at the site of injection are assessed again using calipers. All H drop calves received a total of 2 intradermal injections as part of the testing procedure including 100µL of vaccine (Ultravac 7in1, Zoetis) on one side of the tail (test reaction) and 100µL of saline on the other side of the tail (control reaction). A modified DTH test was conducted on all J & K drop calves with calves receiving a total of 3 intradermal injections as part of the testing procedure including 100µL of vaccine 1 (Ultravac 5in1, Zoetis, test reaction 1) and 100µL of saline (control reaction) on one side of the tail and 100µL of vaccine 2 (Ultravac 7in1, Zoetis, test reaction 2) on the other side of the tail. Where test sites and control sites were located on the same side of the tail (J & K drop calves), injections sites were well separated and the control site located above the test site to avoid interference between reactions.

Flight Speed Testing– Animals are released from the crush following a routine experimental procedure and their flight time recorded using electronic equipment as per standard operating procedures (Burrow et al. 1988). Flight speed testing procedures were standardised for all animals tested in each herd cohort.

3.5 Assessing Antibody-Mediated Immune Responsiveness (AMIR)

Production of antibody, more specifically anti-tetanus toxoid serum IgG1, in response to vaccination was used to assess AMIR. Calves were vaccinated with a commercially available clostridial vaccine (Ultravac 7in1, Zoetis) on day 0 of testing and antibody production to a component of the multi-valent vaccine, tetanus toxoid, was assessed between day 8 and 19 of testing (depending on vaccination history). However, responses for all animals within a herd cohort were always assessed on the same day post-vaccination. For each herd cohort, testing was undertaken to determine which of the two blood samples collected post-vaccination would be analysed for antibody level. The post-vaccination blood sample collected on the day which represented the maximal response observed in that herd cohort of animals was then analysed to determine antibody levels.

It should be noted that of the calves assessed for AMIR, a total of 61 had received no clostridial vaccinations (Glenroy H drop steers), 966 had received a primary clostridial vaccination (majority of animals tested) and 122 had received both a primary and boost clostridial vaccination (Myola H drop steers) at or around the time calf marking prior to testing at weaning. As the majority of animals enrolled in the study had already received a clostridial vaccination prior to testing at yard weaning, serum collected on Day 0 of testing was not assessed for baseline antibody levels. The rationale for this decision was based on the following factors:-

1. Circulating antibody produced in response to previous vaccinations was still detectable in serum at the start of testing and therefore adjusting post-testing antibody level values (assessed on day 14 or 16 of testing) based on pre-testing antibody level values (assessed on day 0 of testing) was expected to disadvantage those animals that had responded strongly to previous vaccinations.
2. To the best of our knowledge, the clostridial vaccination history of calves in each herd cohort was identical and therefore the response assessed during testing at weaning represents cumulative response to the vaccination given at day 0 and any previous vaccinations administered around the time of calf marking.
3. As calves were generally between 5 and 9 months of age at weaning (depending on herd) and the half-life of maternal antibody in the calf being approximately 10-22 days (Cervenak and Kacskovics, 2009), any influence of maternal antibody on responses to vaccination during testing were expected to be minimal.

To assess AMIR, total serum IgG1 antibody against tetanus toxoid antigen (kindly provided by Zoetis, Australia) was determined using an in-house developed indirect ELISA method based on the methodology described by Mallard et al. (1997) with modifications. All test and control samples were assayed in quadruplicate. The co-efficient of variation (CV) of quadruplicate and combinations of triplicate values were calculated and the value for the combination with the lowest CV recorded. Where selected sample values had a CV>10%, samples were repeated. Pooled pre- and post-vaccination serum samples were used as negative and positive controls, respectively. Mean optical density (OD) values for replicates were corrected based on the mean OD value of a positive control serum sample assayed on all plates (Mallard et al., 1997). Antigen-specific total IgG1 was detected using affinity purified sheep anti-bovine IgG1 conjugated to alkaline phosphatase (AbD, Serotec, Product No. AAI21AB). For analysis, adjusted OD values were square root transformed to improve normality (see section 3.11).

3.6 Assessing Cell-Mediated Immune Responsiveness (CMIR)

DTH responses to clostridial vaccine components were used to assess CMIR. The skin testing methodology used in testing procedures is described in detail in section 3.4. The magnitude of DTH responses were calculated as the log of (double skin fold thickness (DSFT) at test site / DSFT at control site) at 48 hours post-injection (T48). For analysis, the log of (DSFT at test site / DSFT at control site) at T0 was fitted as a covariate in statistical models (see section 3.11). DTH responses to 7in1 (CMIR7) were assessed in all animals tested and DTH responses to 5in1 (CMIR5) were also assessed in a subset of animals.

3.7 AMIR, CMIR and Combined Immune Response (CIR) Groupings

To identify High, Average and Low immune phenotypes for AMIR, CMIR5 and CMIR7, calves were ranked on model residual (observed minus predicted) values for each respective trait. Residuals for ranking were generated from the models described in the statistical analysis section 3.11 and were standardised, by dividing each residual value by the standard deviation of all residual values for that trait. Calves with a standardised residual value which was > 1.0 were considered High responders, calves with a standardised residual value <-1.0 were considered Low responders and calves with a standardised residual value ≤1.0 and ≥-1.0 were considered average for that trait (Table 3).

A combined immune response (CIR) trait was also calculated by combining (with equal weighting) measures of AMIR and CMIR. CIR provides an indicator of an animals overall immune responsiveness and is the trait animals would be selected on if aiming to improve the immune competence and general disease resistance of a herd. Standardisation of residual values was undertaken to ensure equal weighting was given to both AMIR and CMIR traits when summed together. Calves with standardised residuals for both AMIR and CMIR5 which were > 0.5 were considered High for CIR5, calves with standardised residual values for both traits which were <-0.5 were considered Low for CIR5 and all other animals considered average for CIR5. A similar method was used to identify High, Average and Low responder animals for CIR7 using standardised residual values for AMIR and CMIR7 (Table 3).

Table 3. Criteria used to define immune competence groupings. Numbers in table refer to standardised residual values for traits listed. Residual values were standardised by dividing each residual value by the standard deviation of all residual values for that trait. Therefore values in the table represent standard deviations from the mean. For example, for an animal to be classified as a high responder for AMIR their AMIR residual value would need to be >1.0 standard deviation above the mean of all residual values for that trait.

Immune Competence Grouping	Trait Assessed	Low	Average	High
AMIR	AMIR	<-1.0	≥-1.0 to ≤1.0	>1.0
CMIR5	CMIR5	<-1.0	≥-1.0 to ≤1.0	>1.0
CMIR7	CMIR7	<-1.0	≥-1.0 to ≤1.0	>1.0
CIR5	AMIR & CMIR5	<-0.5	≥-0.5 to ≤0.5	>0.5
CIR7	AMIR & CMIR7	<-0.5	≥-0.5 to ≤0.5	>0.5

3.8 Assessing Stress-Responsiveness

Haptoglobin is an acute phase protein whose levels in serum increase in response to stress allowing it to be used as a stress response indicator. In the current study, increases in serum haptoglobin levels in response to yard weaning were used to assess responsiveness to management-induced stress. Serum collected on day 0 of weaning was analysed to provide a baseline haptoglobin concentration for each animal and changes in serum haptoglobin detected on day 3 or 4 of yard weaning (standardised within herd cohort) was used to assess stress responsiveness to yard weaning. Serum haptoglobin was analysed using the method described by Jones and Mould, D.L. (1984) with minor modifications. All standard, control and test samples were run in triplicate. Where triplicate sample values had a CV>15%, samples were repeated. Test sample values were calculated from a standard curve produced using bovine serum with known haptoglobin concentration. Control

samples were run on all assay plates to monitor assay performance. The assay is based on the reaction of Haptoglobin with excess haemoglobin, to form a complex that initiates a peroxidase reaction which releases oxygen from introduced hydrogen peroxide oxidising colourless guaiacol to brown coloured tetraguaiacol. As endogenous peroxidase can affect results, serum blanks for each test sample were run in the assay and values subtracted from test values. For all test samples, a separate haemoglobin assay was performed and serum haptoglobin concentration values adjusted for haemoglobin content as described previously (Slocombe and Colditz, 2012). This adjustment is made as haemolysis of blood samples which occasionally occurs during collection releases haemoglobin which interferes with the haptoglobin assay.

Average daily weight gain during the yard weaning period (WtGain) was also recorded as an indirect measure of responsiveness to management-induced stress. All calves tested were weighed a minimum of twice (start and end of testing period) and maximum of four times during the weaning period (depending on facility availability). Timing of weighing and number of times calves were weighed was consistent within each herd cohort. WtGain was calculated as the mean of average daily gain recorded between each weighing event.

3.9 Assessing Temperament

Crush scores and flight time were measured to assess temperament during testing at yard weaning. Details of methodology used to collect crush score and flight speed data are presented in section 3.4.

3.10 Traits Measured

Traits measured on animals in the current study during yard weaning testing included the immune competence traits, AMIR and CMIR, the stress response trait haptoglobin (Hapto), the temperament traits flight time (FT) and crush score (CS), the growth traits weaning weight (WW) and weight gain during yard weaning (WtGain) and also worm egg count (WEC). Traits measured by Angus Australia as part of the ASBP included the growth traits birth weight (BW), yearling weight (YW) and feeder weight (FW), the live-scan traits, eye muscle area (EMA), intramuscular fat (IMF), fat cover on rump (RUMP) and fat cover on rib (RIB), the carcase traits, carcase weight (CWT), carcase eye muscle area (CARC_EMA), carcase intramuscular fat (CARC_IMF) and also net feed intake (NFI-f). A detailed description of each trait measured on animals in the study is presented in Table 4.

Feedlot entry (WT_IN) and exit weights (WT_OUT), total days on feed (DOF) and detailed health records were obtained from the feedlot operators for all animals feedlot finished. Health records for animals showing signs of illness during feed efficiency testing at Tullimba were not available; however, incidence of disease was reported to be low due to no mixing of animals and small pen size (pers. comm. Christian Duff, Angus Australia). While at the commercial feedlot, animals were monitored daily by experienced pen riders for any signs of illness. For any sick animals, details of days on feed when pulled from feedlot pen, diagnosis of disease, treatments administered and days on feed when recovered were recorded. Diagnosis of disease and appropriate treatment plans were generally determined by experienced feedlot personnel; however, when the cause of disease was unclear the feedlot veterinarian was consulted to confirm disease diagnosis and advise on an appropriate treatment plan.

Mortalities occurring at both Tullimba and the commercial feedlot were recorded. For mortalities observed, details of total days on feed when death occurred and cause of death were recorded. Necropsies were completed on all animals which died at the feedlot (where in a fit state), including collection of appropriate tissue samples for pathology, to determine cause of death. Necropsies were undertaken by either the feedlot veterinarian or, when the feedlot veterinarian was not available, by trained feedlot personnel. Where feedlot personal conducted necroscopies, the procedure was video recorded and the footage subsequently reviewed by the feedlot veterinarian to confirm cause of death.

Table 4. Description of traits measured on animals in the study including details of groups of animals each trait was measured on.

	Description[#]
Immune Competence Traits	
AMIR	Antibody-mediated immune response measured on steer ASBP and steer and heifer APR progeny. Assessed by measuring production of anti-tetanus toxoid serum IgG1 antibody in response to vaccination
CMIR5	Cell-mediated immune response measured on steer ASBP and steer and heifer APR progeny. Assessed by measuring delayed type hypersensitivity (DTH) response to 5in1 vaccine components
CMIR7	Cell-mediated immune response measured on steer ASBP and steer and heifer APR progeny. Assessed by measuring delayed type hypersensitivity (DTH) response to 5in1 vaccine components
CIR5	Combined immune response measured on steer ASBP and steer and heifer APR progeny. Calculated by combining (with equal weighting) measures of AMIR and CMIR5. An indicator of an animals overall immune responsiveness.
CIR7	Combined immune response measured on steer ASBP and steer and heifer APR progeny. Calculated by combining (with equal weighting) measures of AMIR and CMIR7. An indicator of an animals overall immune responsiveness.
Stress Responsiveness Traits	
Hapto	Change in serum haptoglobin concentration in response to yard weaning measured on steer ASBP and steer and heifer APR progeny. Haptoglobin is an acute phase protein produced in response to stress.
Temperament Traits	
CS	Crush score measured on both steer and heifer ASBP and APR progeny.
FT	Flight time measured on steer ASBP and steer and heifer APR progeny.
Growth Traits	
BW	Weight at birth recorded on both steer and heifer ASBP progeny.
WW	Weight at approx. 200 days (i.e. weaning weight) recorded on both steer and heifer ASBP and APR progeny.
YW	Weight at approx. 400 days (i.e. yearling weight) recorded on both steer and heifer ASBP progeny.
FW	Weight at approx. 600 days (i.e. 18 month weight) recorded on both steer and heifer ASBP progeny.
WtGain	Average daily weight gain during the yard weaning period recorded on steer ASBP and steer and heifer APR progeny.
WT_IN	Weight at feedlot entry recorded on steer ASBP progeny
WT_OUT	Weight at feedlot exit recorded on steer ASBP progeny
Live-Scan Traits	
EMA	Eye muscle area from ultrasound scanning both steer and heifer ASBP progeny measured at approx. 500 days of age.
RIB	Rib fat from ultrasound scanning both steer and heifer ASBP progeny measured at approx. 500 days of age.
RUMP	Rump (i.e. P8) fat from ultrasound scanning both steer and heifer ASBP progeny measured at approx. 500 days of age.
IMF	Intramuscular fat from ultrasound scanning both steer and heifer ASBP progeny measured at approx. 500 days of age.
Carcass Traits	
CWT	Weight of hot standard carcase at a standard 750 days of age recorded on steer ASBP progeny.
CARC_EMA	Carcass eye muscle area measured on steer ASBP progeny.
CARC_IMF	Intramuscular fat (ether extracted at the UNE meat science laboratory) in a carcase measured on steer ASBP progeny.
Other Traits	
NFI-f	Feed intake at a standard weight and rate of weight gain recorded on steer ASBP progeny at Tullimba Research Feedlot.
WEC	Worm egg count measured at weaning on steer ASBP and steer and heifer APR progeny.

[#] ASBP = Angus Australia sire benchmarking program, APR = CSIRO Angus performance recorded herd.

3.11 Statistical Analysis

Univariate animal models were run in ASReml (Gilmour et al. 2009) to estimate variance components and heritabilities for immune competence, stress responsiveness, temperament and production traits. Traits were tested for normality using a Shapiro-Wilk test in R (R Core Team 2013) and transformed where required to improve normality. Fixed effects assessed in models included contemporary group (CG, incorporating property of origin, year drop, herd management group and weaning date), sex and dam age. Covariates assessed in models included age at measurement, DSFT at test site / DSFT at control site at T0 (for CMIR traits), baseline haptoglobin measured on day 0 of testing (for Hapto trait), WW (for WtGain trait), CWT (for CARC_EMA and CARC_IMF traits) and WT_IN, DOF (for WT_OUT). Details of fixed effects and covariates assessed in models when analysing each trait are detailed in Table 5. The main effect of CG along with relevant covariates were retained in models regardless of their *P* values. However, models were reduced by removing other fixed effects which were non-significant ($P > 0.05$) terms.

Least square means were generated from the linear model for each of the production traits, fitting relevant fixed effects, and the significance of differences between immune competence grouping (low, average, high) based on AMIR, CMIR7 and CIR7 analysed. Package “LSmeans” was used in R to test group differences (R Core Team 2013). Contrasts were evaluated by Bonferroni *t* statistics for multiple comparisons. For incidence of disease and number of deaths data from the feedlot, differences between immune competence phenotypes were analysed using a Pearson’s chi-square test for independence or a Fisher’s exact test for independence where required due to small sample size (Realstats add-in, Excel).

Table 5. Description of transformations applied to traits for analysis and fixed effects / covariates assessed in models when analysing individual traits. Fixed effects and covariates shown in bold were retained in models when analysing respective trait and those not in bold were tested but removed from final model as they were non-significant ($p > 0.05$).

Trait	Transformation	Fixed effects[#]	Covariates
CMIR5	Log	**CG**, sex, dam age	age at measurement, **(DSFT at test site / DSFT at control site) at T0**
CMIR7	Log	**CG**, sex, dam age	**age at measurement, (DSFT at test site / DSFT at control site) at T0**
AMIR	Square Root	**CG**, sex, dam age	age at measurement
Hapto	None	**CG, sex**, dam age	age at measurement, **baseline hapto measured on day 0 of testing**
BW	None	**CG**, dam age	
YW	None	**CG**, dam age	**age at measurement**
FW	None	**CG**, dam age	**age at measurement**
WW	None	**CG, sex**, dam age,	**age at measurement**
WtGain	None	**CG**, sex, dam age**,**	**age at measurement, WW**
WT_OUT	None	**CG**	**WT_IN, DOF**
RUMP	None	**CG**, dam age,	**age at measurement**
RIB	None	**CG**, dam age	**age at measurement**
EMA	None	**CG**, dam age	**age at measurement**
IMF	None	**CG**, dam age	**age at measurement**
CWT	None	**CG**, dam age	(see footnote)[†]
CARC_EMA	None	**CG,**	**CWT**
CARC_IMF	None	**CG**,	CWT
NFI-f	None	**CG**	(see footnote)[†]
WEC	Log	**CG**, sex, dam age	age at measurement
FT	Log	**CG, sex**, dam age	**age at measurement**
CS	None	**CG**, sex, **dam age**	age at measurement

[#] CG=contemporary group incorporating property of origin, year drop, herd management group and weaning date effects.

[†] CWT values were pre-adjusted prior to analysis to weight of hot standard carcase at a standard 750 days of age.

[†] NFI-f values were pre-adjusted prior to analysis to feed intake at a standard weight and rate of weight gain

4 Results

4.1 Trait Parameters

For traits measured, a description of summary statistics are presented in Table 6. A summary of feedlot finishing information provided by the commercial feedlot operator is presented in Table 7.

Table 6. Description of summary statistics for traits measured

Trait	Units	n[#]	Mean	Min	Max	StdDev
Immune Competence Traits						
CMIR5	Log (increase in skin fold thickness (mm))	510	0.30	0.02	0.64	0.08
CMIR7	Log (increase in skin fold thickness (mm))	1101	0.29	-0.02	0.64	0.10
AMIR	Optical density units	1119	0.70	0.02	2.40	0.41
Stress Responsiveness Traits						
Hapto (baseline)	mg/mL serum	957	-0.09	-1.41	3.75	0.24
Hapto (post-weaning)	mg/mL serum	1119	0.02	-1.87	4.25	0.44
Temperament Traits						
FT	Time (seconds)	1024	0.99	0.33	4.81	0.45
CS	Visual score (1-5)	1147	1.44	1.00	4.00	0.58
Growth Traits						
BW	kg	799	38.27	25.00	61.00	4.82
WW	kg	1127	237.50	88.0	382.00	58.96
YW	kg	302	345.00	206.00	543.00	86.40
FW	kg	875	501.60	308.00	882.00	116.40
WtGain	kg / day	1118	0.25	-6.16	7.77	1.55
Live-Scan Traits						
RUMP	mm	855	12.14	1.00	27.00	5.06
RIB	mm	856	8.93	1.00	16.00	3.43
EMA	Area (cm^2)	861	79.27	48.00	99.00	10.41
IMF	%	862	68.97	15.00	83.00	17.41
Carcass Traits						
CWT	kg	842	453.50	344.40	550.50	35.75
CARC_EMA	Area (cm^2)	840	85.72	62.60	114.00	8.61
CARC_IMF	%	840	9.71	3.00	24.00	3.30
Other Traits						
NFI-f	kg feed intake / day	858	-2.19	-9.30	4.20	1.86
WEC	eggs / gram faeces	1105	77.38	0.00	80.00	127.84

[#] n=Number of observations recorded

Table 7. Description of summary statistics for weight gain data provided by the feedlot operators. Feedlot entry weights were recorded at Tullimba research feedlot where animals were feed efficiency tested (100 days) before being transferred to the commercial feedlot for feedlot finishing (minimum of 178 days) where feedlot exit weights were recorded.

ASBP Cohort	n[#]		Feedlot Entry Weight (kgs)	Feedlot Exit Weight (kgs)	Days on Feed (DOF)[#]	Average Daily Gain (ADG)[#] (kg/day)
2	467	**Mean**	419	838	356	1.24
		Min[†]	256	644	285	0.67
		Max[†]	554	1016	570	1.85
		StdDev[†]	57	65	122	0.27
3	358	**Mean**	389	803	345	1.20
		Min[†]	228	632	278	0.43
		Max[†]	584	976	403	1.60
		StdDev[†]	75	65	62	0.16

[#] n=Number of animals

[#] DOF = Days on feed at Tullimba + days on feed at the commercial feedlot

[#] ADG = Average daily gain between feedlot entry at Tullimba and feedlot exit at commercial feedlot.

[†] Min=Minimum, Max=Maximum, StdDev=Standard deviation

4.2 Genetic parameters for traits measured at yard weaning

Genetic parameters for immune competence and stress responsiveness traits and genetic and phenotypic correlations between traits are presented in Table 8. The heritability of a trait describes the proportion of observed variance of a trait that is attributable to genetics. A correlation describes the relationship between two traits. A phenotypic correlation describes the combined influence of the genetic and environmental components, whereas genetic correlations only describe the inherent genetic component.

Table 8. Genetic parameters for immune competence and stress responsiveness traits. Heritabilities are shown in bold, phenotypic correlations above the diagonal and genetic correlations below the diagonal.

	AMIR	CMIR5	CMIR7	Hapto
AMIR	**0.33 ± 0.09**	0.16 ± 0.05	0.15 ± 0.03	0.03 ± 0.03
CMIR5	0.37 ± 0.38	**0.12 ± 0.10**	0.75 ± 0.02	0.04 ± 0.04
CMIR7	0.51 ± 0.18	1.00 ± 0.07	**0.27 ± 0.08**	0.02 ± 0.03
Hapto	0.07 ± 0.28	0.03 ± 0.51	0.20 ± 0.30	**0.13 ± 0.07**

4.3 Genetic parameters for production traits and correlations with immune competence and stress responsiveness traits

Genetic parameters for production traits and phenotypic and genetic correlations between production, immune competence and stress responsiveness traits are presented in Table 9.

Table 9. Genetic parameters for production traits and phenotypic and genetic correlations between production traits and immune competence/stress responsiveness traits. Values describing phenotypic variance (Vp), heritability (h2), phenotypic and genetic correlations (rp and rg, respectively) are presented with standard errors for each estimate shown in brackets.

			CMIR7		AMIR		HAPTO	
	Vp	**h2**	**rp#**	**rg#**	**rp#**	**rg#**	**rp#**	**rg#**
Growth traits								
BW	18.23	0.38 (0.13)	-0.06 (0.04)	-0.11 (0.24)	-0.06 (0.04)	-0.14 (0.23)	n/a^	0.30 (0.22)
WW	717.82	0.18 (0.08)	-0.03 (0.03)	-0.45 (0.27)	-0.07 (0.03)	-0.38 (0.26)	-0.07 (0.03)	-0.19 (0.34)
YW	1010.5	0.88 (0.26)	0.01 (0.06)	-0.10 (0.24)	-0.15 (0.06)	-0.38 (0.23)	n/a^	0.29 (0.20)
FW	615.34	0.46 (0.11)	0.06 (0.03)	-0.23 (0.22)	-0.11 (0.04)	-0.44 (0.20)	0.02 (0.04)	0.64 (0.28)
WtGain	1.25	0.12 (0.07)	0.11 (0.03)	-0.10 (0.33)	-0.01 (0.04)	0.24 (0.30)	-0.09 (0.03)	0.07 (0.41)
Live-Scan traits								
RUMP	5.73	0.47 (0.12)	0.03 (0.04)	0.24 (0.23)	0.05 (0.04)	0.43 (0.20)	-0.04 (0.04)	-0.47 (0.32)
RIB	2.36	0.51 (0.12)	0.01 (0.04)	0.34 (0.21)	0.01 (0.04)	0.06 (0.21)	-0.02 (0.04)	-0.68 (0.30)
EMA	22.02	0.60 (0.13)	0.05 (0.04)	0.07 (0.21)	-0.13 (0.04)	-0.59 (0.17)	-0.07 (0.04)	0.19 (0.31)
IMF	25.33	0.35 (0.10)	0.02 (0.04)	0.18 (0.23)	-0.02 (0.04)	-0.17 (0.23)	-0.06 (0.04)	-0.31 (0.34)
Carcass traits								
CWT	1218.8	0.52 (0.12)	0.03 (0.04)	0.04 (0.21)	-0.13 (0.04)	-0.40 (0.19)	-0.05 (0.04)	-0.21 (0.21)
CARC_EMA	61.16	0.61 (0.14)	-0.12 (0.04)	-0.20 (0.21)	-0.08 (0.04)	-0.44 (0.18)	-0.04 (0.04)	-0.15 (0.32)
CARC_IMF	9.17	0.67 (0.13)	-0.03 (0.04)	0.21 (0.20)	-0.04 (0.04)	-0.05 (0.18)	0.00 (0.04)	0.36 (0.23)
Other traits								
NFI-f	1.91	0.33 (0.11)	0.00 (0.04)	0.36 (0.23)	0.02 (0.04)	0.17 (0.24)	-0.01 (0.03)	-0.16 (0.37)
WEC*	48.57	0.07 (0.10)	0.04 (0.04)	0.00 (0.49)	0.04 (0.04)	-0.17 (0.51)	n/a^	-0.94 (1.25)
FT	11.22	0.13 (0.07)	0.08 (0.03)	0.59 (0.28)	-0.01 (0.04)	0.63 (0.32)	0.01 (0.04)	0.41 (0.41)
CS	0.32	0.10 (0.07)	-0.05 (0.03)	-0.39 (0.33)	0.04 (0.03)	-0.11 (0.31)	0.04 (0.03)	0.43 (0.42)

*log transformed

^residual covariance constrained to zero.

#correlation values suggesting traits are considered weakly correlated are highlighted in green, moderately correlated are highlighted in blue and strongly correlated highlighted in red. When interpreting results the size of the error associated with the estimate relative to the estimate itself should be considered.

4.4 Influence of immune competence phenotype on production traits

Calves were categorised as low (Lo), average (Avg) or high (Hi) responders for AMIR, CMIR7 and CIR7 as described in section 3.7. Numbers of animals in each immune competence phenotype grouping are shown in Table 10. CIR7 provides an indicator of an animals overall immune responsiveness as it is generated from the combination of antibody and cellular response values, and is the trait animals would be selected on if aiming to improve the immune competence and general disease resistance of a herd. Therefore most emphasis should be placed on the influence of CIR7, rather than AMIR or CMIR7 when interpreting results. We hypothesise that when selecting animals based on immune competence that maximum benefit will be achieved by eliminating low responder CIR phenotype animals rather than selecting high responder CIR phenotype animals.

Table 10. Numbers of animals classified as high (Hi), average (Avg) or low (Lo) responders for AMIR, CMIR7 and CIR7 for analysis of traits WW, WtGain, logFT, CS and logWEC. Numbers in brackets represent number of animals classified as high (Hi), average (Avg) or low (Lo) responders for AMIR, CMIR7 and CIR7 for analysis of all other traits.

	Hi	Avg	Lo	Total
AMIR	170 (124)	768 (579)	180 (133)	1118 (836)
CMIR7	169 (120)	755 (582)	177 (132)	1101 (834)
CIR7	120 (91)	853 (645)	128 (98)	1101 (834)

The influence of immune competence phenotype on production traits was assessed by comparing group least square means for each production trait. Least square means for growth traits are presented in Table 11, for live scan traits in Table 12, for carcass traits in Table 13 and for other traits in Table 14.

Table 11. Least square means for growth traits in calves classified as high, average or low responders for AMIR, CMIR7 and CIR7.

	BW[#]	WW[#]	YW[#]	FW[#]	WtGain[#]
AMIR[±]	ns	P < 0.05	P < 0.05	P < 0.01	P < 0.01
Hi	37.80 (0.42)	225.64 (2.64)[a]	361.20 (6.78)[a]	503.73 (3.56)[a]	0.13 (0.10)[a]
Avg	38.19 (0.22)	229.96 (2.01)[b]	366.77 (4.89)[a]	517.03 (1.88)[b]	0.39 (0.05)[b]
Lo	38.57 (0.42)	232.55 (2.64)[c]	379.61 (6.83)[b]	517.06 (3.42)[b]	0.36 (0.05)[b]
CMIR7[±]	ns	P < 0.001	ns	ns	P < 0.01
Hi	37.86 (0.41)	227.43 (2.66)[a]	363.46 (7.24)	520.60 (3.67)	0.56 (0.09)[a]
Avg	38.13 (0.22)	230.09 (1.98)[b]	367.88 (4.86)	515.39 (1.86)	0.34 (0.05)[b]
Lo	38.76 (0.41)	229.65 (2.71)[a]	363.81 (6.61)	512.05 (3.43)	0.16 (0.09)[c]
CIR7[±]	P < 0.05	ns	ns	ns	ns
Hi	37.48 (0.48)[a]	226.62 (2.98)	364.57 (7.69)	510.29 (4.10)	0.44 (0.11)
Avg	38.16 (0.21)[a]	230.97 (1.97)	366.19 (7.56)	516.26 (1.82)	0.34 (0.04)
Lo	39.17 (0.48)[b]	232.04 (2.95)	367.45 (4.82)	513.61 (3.92)	0.31 (0.10)

[#] Where the group effect was significant least square means with different superscripts are significantly different

[±]Significance of group effect, ns=non-significant

Table 12. Least square means for live-scan traits in animals classified as high, average or low responders for AMIR, CMIR7 and CIR7.

	RUMP[#]	RIB[#]	EMA[#]	IMF[#]
AMIR[±]	ns	ns	P < 0.001	ns
Hi	13.43 (0.27)	9.91 (0.17)	79.38 (0.51)[a]	72.95 (0.57)
Avg	13.48 (0.17)	9.93 (0.11)	81.68 (0.49)[b]	73.95 (0.37)
Lo	13.30 (0.26)	10.01 (0.17)	81.87 (0.49)[b]	73.90 (0.55)
CMIR7[±]	ns	ns	ns	ns
Hi	13.44 (0.27)	9.94 (0.17)	82.29 (0.51)	74.10 (0.57)
Avg	13.45 (0.17)	9.93 (0.11)	81.68 (0.33)	73.72 (0.37)
Lo	13.51 (0.26)	10.07 (0.17)	81.03 (0.50)	74.13 (0.55)
CIR7[±]	ns	ns	ns	ns
Hi	13.75 (0.30)	10.09 (0.19)	81.11 (0.58)	74.25 (0.64)
Avg	13.44 (0.17)	9.93 (0.11)	81.51 (0.33)	73.82 (0.37)
Lo	13.32 (0.29)	9.97 (0.18)	81.27 (0.55)	73.62 (0.60)

[#] Where the group effect was significant least square means with different superscripts are significantly different
[±]Significance of group effect, ns=non-significant

Table 13. Least square means for carcase traits in calves classified as high, average or low responders for AMIR, CMIR7 and CIR7.

	CWT[#]	CARC_EMA[#]	CARC_IMF[#]
AMIR[±]	P < 0.001	P < 0.05	ns
Hi	439.87 (3.24)[a]	84.14 (0.72)[a]	10.12 (0.29)
Avg	455.31 (1.59)[b]	86.33 (0.35)[b]	10.08 (0.14)
Lo	456.66 (3.22)[b]	85.84 (0.71)[b]	10.34 (0.28)
CMIR7[±]	ns	ns	ns
Hi	459.22 (3.36)	86.15 (0.74)	9.90 (0.29)
Avg	452.87 (1.59)	85.89 (0.35)	10.13 (0.14)
Lo	449.59 (3.20)	85.83 (0.71)	10.35 (0.29)
CIR7[±]	ns	ns	ns
Hi	448.08 (3.84)	85.21 (0.85)	9.94 (0.34)
Avg	452.99 (1.53)	86.02 (0.34)	10.09 (0.13)
Lo	460.06 (3.74)	85.84 (0.83)	10.61 (0.33)

[#] Where the group effect was significant least square means with different superscripts are significantly different
[±]Significance of group effect, ns=non-significant

Table 14. Least square means for feed efficiency, temperament and WEC traits in calves classified as high, average or low responders for AMIR, CMIR7 and CIR7.

	NFI-f[#]	logFT[#]	CS[#]	logWEC[#]
AMIR[±]	ns	ns	ns	ns
Hi	-2.29 (0.13)	-0.18 (0.05)	1.50 (0.05)	3.15 (0.14)
Avg	-2.34 (0.06)	-0.17 (0.04)	1.44 (0.04)	3.38 (0.07)
Lo	-2.28 (0.13)	-0.14 (0.05)	1.41 (0.04)	3.23 (0.13)
CMIR7[±]	ns	ns	ns	ns
Hi	-2.43 (0.13)	-0.13 (0.05)	1.39 (0.05)	3.15 (0.14)
Avg	-2.28 (0.06)	-0.17 (0.04)	1.44 (0.03)	3.32 (0.07)
Lo	-2.40 (0.12)	-0.13 (0.05)	1.50 (0.04)	3.51 (0.13)
CIR7[±]	ns	ns	ns	P < 0.05
Hi	-2.34 (0.15)	-0.15 (0.05)	1.46 (0.05)	2.90 (0.17)[a]
Avg	-2.32 (0.06)	-0.17 (0.04)	1.43 (0.02)	3.38 (0.06)[b]
Lo	-2.32 (0.14)	-0.20 (0.05)	1.46 (0.05)	3.31 (0.16)[ab]

[#] Where the group effect was significant least square means with different superscripts are significantly different

[±]Significance of group effect, ns=non-significant

4.5 Feedlot Health

Following feed efficiency testing at the Tullimba research feedlot (UNE, Armidale, 100 days) all steer progeny from the Angus Australia benchmarking project entered a commercial feedlot in Northern NSW for final feedlot finishing (minimum 178 days). All calves received a primary vaccination 4-6 weeks prior to feedlot induction and a boost at feedlot induction of Bovilis MH + IBR (Coopers). Calves entering the feedlot were also vaccinated against clostridial diseases, receiving Ultravac 5in1 (Zoetis) or equivalent at feedlot induction.

Detailed health records for all steers entering the feedlot (n=839) were obtained and analysed to assess the influence of immune competence phenotype on feedlot health. Steers were categorised as low (n=98), average (n=653) or high (n=88) immune responders for CIR7 using the methodology described above. As described previously, CIR provides an indicator of an animal's overall immune responsiveness as it is generated from the combination of antibody and cellular response values. Therefore CIR is an ideal trait to target if aiming to improve the immune competence and general disease resistance of a herd. Cases of disease recorded and days animals were sick (time between recovery date and pull date) within each immune competence phenotype group are summarised in Table 15. The number of health related deaths recorded at the feedlot in each immune competence phenotype group are summarised in Table 16. We hypothesise that when selecting animals based on immune competence that maximum benefit will be achieved by eliminating low responder CIR phenotype animals rather than selecting high responder CIR phenotype animals. Therefore the number of mortalities were compared in high and average CIR7 phenotype animals combined versus low CIR7 animals and results are summarised in Table 17. The significance of group differences in the number of health related deaths recorded at the feedlot are summarised in Table 18. To investigate the influence of mortalities on average daily weight gains achieved at the commercial feedlot a "Deads-in" versus "Deads-out" weight gain comparison was undertaken as described by Galyean and Elam (2009) and results presented in Table 19.

A preliminary cost benefit analysis was performed to estimate the influence of immune competence phenotype on health associated costs at the feedlot with results presented in Table 20. It is important to consider when interpreting these results that the direct labour costs associated with administering treatments and monitoring of animals could not be calculated and therefore were not factored into estimates. Similarly, the opportunity cost associated with having a sick animal or an animal which dies taking up pen space which could otherwise have been used to house a healthy animal which was gaining weight and generating income for the feedlot could not be calculated and therefore was also not factored into estimates.

Table 15. Disease incidence and days sick data for the Angus Australia cohort 2 and cohort 3 benchmarking steers (n=839) recorded during feedlot finishing at a commercial feedlot. For each illness, data is presented as the number of incidences of that disease observed in steers in each of the immune competence phenotype groups, low (n=98), average (n=653) and high (n=88). Numbers in red and black square brackets indicate the number of animals which died from that illness in that immune competence phenotype group at Tullimba and the commercial feedlot, respectively.

Illness	Low		Average		High		TOTAL	
	n	/100 head	n	/100 head	n	/100 head	n	/100 head
Foot abscess	1	1.02	8	1.23	1	1.14	10	1.19
Bloat	6	6.12	31	4.75	2	2.27	39	4.65
Caste	1 [1]	1.02	3	0.46	0	0	4 [1]	0.48
Lame	0	0	3	0.46	1	1.14	4	0.48
Respiratory / Pneumonia	1	1.02	7 [1]	1.07	3	3.41	11 [1]	1.31
Digestive	1	1.02	0	0	1	1.14	2	0.24
Cellulitis	0	0	1	0.15	0	0	1	0.12
Ascites	1 [1]	1.02	0	0	0	0	1 [1]	0.12
Heart Failure	0	0	1[1]	0.15	0	0	1 [1]	0.12
Unknown (disease state too advanced when identified)	4 [1][3]	4.08	13 [1][5]	1.99	1	1.14	18 [10]	2.15
TOTAL[#]	**15 [2][4]**	**15.31[a]**	**67 [1][7]**	**10.26[a]**	**9 [0]**	**10.23[a]**	**91 [14]**	**10.85**
Sick Days[†]	**78**	**80**	**602**	**92**	**101**	**115**	**781**	**93**

[#] Values that differ significantly are depicted using different superscripts.

[†] Sum of days between pull date and recovery date for all sick animals within group.

Table 16. Number of deaths recorded in Angus Australia cohort 2 and cohort 3 benchmarking steers (n=839) during feedlot finishing at a commercial feedlot. Data is presented as the number of deaths observed in steers in each of the immune competence phenotype groups, low, average and high.

	Low	Average	High	TOTAL
Total Deaths	6	8	0	14
Total Animals	98	653	88	839
Deaths[#]	**6.12%[a,A]**	**1.23%[b,B]**	**0%[b,B]**	**1.67%**

[#] Values that differ significantly are depicted using different superscripts. Lower case superscripts describe results obtained using a Pearson's chi-square test for independence and upper case superscripts describe results obtained using a Fisher's exact for independence.

Table 17. Number of deaths recorded in Angus Australia cohort 2 and cohort 3 benchmarking steers (n=839) during feedlot finishing at commercial feedlot. Data is presented as the number of deaths observed in steers in the immune competence phenotype groups, low and average/high combined.

	Low	Average/High Combined	TOTAL
Total Deaths	6	8	14
Total Animals	98	741	839
Deaths[#]	**6.12%[a,A]**	**1.08%[b,B]**	**1.67%**

[#] Values that differ significantly are depicted using different superscripts. Lower case superscripts describe results obtained using a Pearson's chi-square test for independence and upper case superscripts describe results obtained using a Fisher's exact for independence.

Table 18. Probability values associated with differences in the number of deaths recorded in Angus Australia cohort 2 and cohort 3 benchmarking steers (n=839) categorised as low (n=98), average (n=653), high (n=88) or average/high combined (n=741) immune competence phenotype groups, during feedlot finishing at a commercial feedlot. Probability values obtained using a Pearson's chi-square test for independence are shown below the diagonal and probability values obtained using a Fisher's exact test for independence are shown above the diagonal. Deaths (% of animals) in each immune competence phenotype group are shown on the diagonal.

	Low[#]	Average[#]	High[#]	Average/High Combined[#]
Low	**6.12%**	** (0.005)	* (0.030)	** (0.003)
Average	** (0.001)	**1.23%**	NS (0.606)	NA
High	* (0.018)	NS (0.297)	**0%**	NA
Average/High Combined	** (0.001)	NA	NA	**1.08%**

[#] NS=non-significant, *=significant (p<0.05), **=highly significant (p<0.01).

Table 19. "Deads-in" versus "Deads-out" weight gain comparison for Angus Australia cohort 2 and cohort 3 benchmarking steers (n=839) categorised as low (n=98), average (n=653) or high (n=88) immune competence phenotype groups during feedlot finishing.

	n[#]	Mean Feedlot Entry Weight (kgs)	Mean Feedlot Exit Weight (kgs)	Mean Feedlot Weight Gain (kgs)[#]	Mean Days on Feed (DOF) (days)	Average Daily Gain (ADG) (kgs/day)[#]	Adjusted Mean Feedlot Exit Weight[‡] (kgs)
"Deads-in" [†]							
Low	98	406	782	376	337	1.116	810[a]
Average	653	409	812	402	347	1.159	808[a]
High	88	389	822	433	372	1.164	812[a]
"Deads-out" [†]							
Low	92	404	833	429	350	1.224	824[a]
Average	645	409	822	413	349	1.183	815[a]
High	88	389	822	433	372	1.164	817[a]

[#] n=Number of animals.

[#] Total Feedlot Weight Gain = Total Feedlot Exit Weight – Total Feedlot Entry Weight.

[#] Average Daily Gain = Total Feedlot Weight Gain / Total Days on Feed.

[‡] Least square means for feedlot exit weight adjusted for contemporary group (CG), feedlot entry weight (WT_IN) and days on feed (DOF). Values that differ significantly are depicted using different superscripts.

[†] For "Deads-in" calculations feedlot entry weight and days on feed data for animals which died during feedlot finishing included in calculations (see Gaylean and Elam, 2009).

[†] For "Deads-out" calculations feedlot entry weight and days on feed data for animals which died during feedlot finishing was not included in calculations (see Gaylean and Elam, 2009).

Table 20. Estimated health associated costs incurred for Angus Australia cohort 2 and cohort 3 benchmarking steers (n=839) categorised as low (n=98), average (n=653) or high (n=88) immune competence phenotype groups during feedlot finishing.

	Estimated Health Associated Costs					
	Lost Production Costs (/100 head)		Lost Capital Investment (/100 head)		Disease Treatment Costs (/100 head)	Total Cost (/100 head)
	Days on Feed (DOF) at Time of Death (A)[#]	Cost (B)[#]	Deaths (C)	Cost (D)[#]	Cost (E)[#]	Total Cost (F)[#]
Low	790	$3855	6.12	$6336 ($2.37)	$145	$10336
Average	255	$1244	1.23	$1434 ($2.56)	$146	$2824
High	0	$0	0	$0	$353	$353

[#] A = Sum of days on feed at time of death for all animals within group which died (includes days between pull date and death).
B = Total lost production costs for all animals within the group (A*$4.88). Costs were estimated by the feedlot operator and is based on an average dry matter intake of 13.5 kg/head/day at a cost of $280 / tonne + GST ($4.16) + daily direct costs per head of $0.65+GST ($0.72).
C = Deaths observed per 100 animals within each group.
D = Total cost associated with lost capital investment for all animals within the group. Cost represents the sum of purchase costs (inclusive of GST) obtained from the feedlot for individual animals which died within each group. Figure in brackets represents average cents / kilogram liveweight (inclusive of GST) paid at purchase.
E = Total cost associated with the purchase of therapeutic agents used to treat disease. Figures represent estimated retail cost of therapeutic agents calculated at cost price (inclusive of GST) + 70%.
F = Total cost associated with lost production days, lost capital investment and disease treatment costs for all animals within the group (B+D+E).

5 Discussion

5.1 Genetic parameters for immune competence traits

The heritability of the immune competence traits AMIR and CMIR7 were estimated at 0.33 (± 0.09) and 0.27 (± 0.08). These heritability estimates are considered moderate, suggesting a reasonable rate of genetic gain can be expected when selecting for immune competence. As described above, CMIR was assessed by measuring DTH responses to 7in1 clostridial vaccine in all calves tested (CMIR7, n=1149). In a subset of these animals DTH responses to 5in1 clostridial vaccine (CMIR5, H drop calves, n=611) was also assessed to allow comparison of responses to the two vaccines to be investigated. Results indicated that DTH responses to both vaccines were strongly correlated with phenotypic and genetic correlations between the two traits estimated to be 0.75 (± 0.02) and 1.00 (±0.07), respectively (Figure 3). Based on these results which suggested that CMIR5 and CMIR7 were essentially the same trait, it was decided to only explore associations between CMIR7, AMIR and production traits when analysing data from the study and to only combine measures of CMIR7 and AMIR, rather than incorporating CMIR5, when calculating the immune response phenotype of individual animals.

In the current study, a weak positive phenotypic correlation (0.15 ± 0.03) and a strong positive genetic correlation (0.51 ± 0.18) was observed between AMIR and CMIR7. This is in contrast to findings in North American dairy cattle where Thompson et al. (2012) reported weak to moderate negative genetic correlations between AMIR and CMIR (-0.13 ± 0.37 and -0.45 ± 0.32, depending on timing of measuring AMIR). However in another study in North American dairy cattle, Hernandez et al. (2006) reported a weak positive genetic correlation between AMIR and CMIR when using one antigen to induce CMIR (0.309) and a weak negative genetic correlation when inducing CMIR with a different antigen (-0.295). Regardless, results from the current study suggest that based on their strong positive genetic correlation, selecting for AMIR in beef cattle will simultaneously improve the ability of animals to mount CMIR and vice versa. On this basis it is tempting to suggest that measuring just CMIR7 or AMIR (but not both) is all that is required to improve the general disease resistance of your herd. However, it is important to consider that even when AMIR and CMIR7 are strongly positively genetically correlated, when selection is based on only AMIR or CMIR7 that a proportion of animals will be low responders for the other trait. As the immune system is constantly challenged by both intracellular and extracellular pathogens it is critical that selection strategies aimed at improving general disease resistance are based on selecting individuals which have a balanced ability to mount both cell-mediated and antibody-mediated immune responses. Therefore we propose that selection based on direct measures of an animal's ability to mount both AMIR and CMIR remains the most efficient and sustainable means of improving general disease resistance in beef cattle.

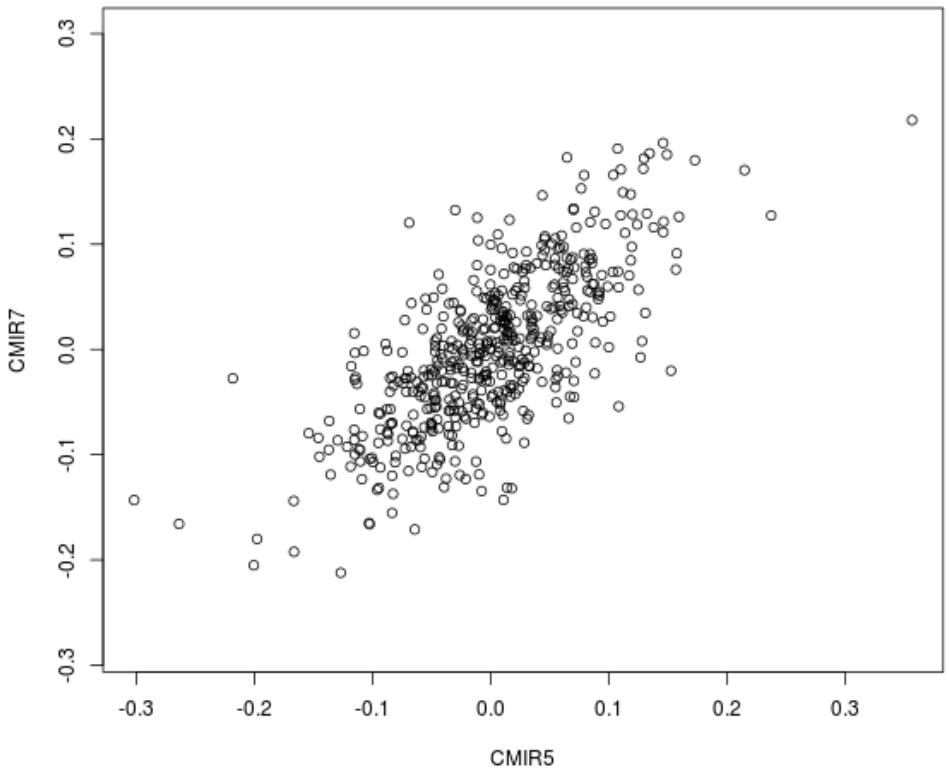

Figure 3. Scatterplot showing the relationship between CMIR7 and CMIR5 residual values. The phenotypic correlation between CMIR5 and CMIR7 was estimated at 0.75 ± 0.02.

5.2 Relationships between immune competence, stress-responsiveness and temperament traits

Correlations between immune competence and temperament were investigated in the current study. Results suggested that immune competence is favourably genetically correlated with temperament with genetic correlations between both AMIR and FT and CMIR and FT being strongly positively correlated. Favourable correlations were also observed between immune competence and crush score; however, correlations were only considered to be weak. Combined these results suggest that selection for immune competence will also select for improved temperament traits. Previous studies have demonstrated that calm animals (high FT, low CS) perform better in the feedlot environment as evidenced by their higher average daily weight gains and lower mortality as compared to their nervous (low FT, high CS) counterparts (Fell et al. 1999). Although no significant effects of CIR7 phenotype group on temperament traits were observed, high CIR7 animals had higher FT's (~0.71s) as compared to their average (~0.67s) and low CIR7 (~0.63s) counterparts. Crush scores were similar between high, average and low CIR7 phenotype animals.

Correlations between immune competence and the stress-responsiveness traits hapto and WtGain were also investigated. Results indicated that AMIR and WtGain were weakly positively genetically correlated (0.24 ± 0.3) and CMIR and WtGain were not correlated (-0.10 ± 0.33). However, the large errors associated with the correlation estimates mean the results are difficult to interpret. Although

not statistically different a trend in group WtGain differences were observed with high CIR7 animals having the highest WtGain (0.44 ± 0.11 kg/day) followed by average CIR7 animals (0.34 ± 0.04 kg/day) and low CIR7 animals having the lowest WtGain (0.31 ± 0.10 kg/day). Weight gain during the weaning period was monitored as an indirect measure of an animal's ability to cope with the management-induced stress. Therefore WtGain results may suggest that immune competence and stress coping ability are favourably correlated; however, further studies will be required to validate this hypothesis.

Haptoglobin is an acute phase protein whose expression is up-regulated during periods of heightened stress. Therefore increases in serum haptoglobin concentration can be used as a stress response indicator. Results of the current study suggest that the immune competence traits, AMIR and CMIR7 are not phenotypically or genetically correlated with increases in serum haptoglobin associated with the stress of yard weaning. This was an unexpected result based on WtGain data which suggested immune competence may be favourably correlated with stress-coping ability. When interpreting these results it is important however to consider that acute phase proteins such as haptoglobin play an important role in innate immunity and as such their levels are expected to increase in response to immune challenges such as vaccination as well as stress. As calves were vaccinated at the commencement of yard weaning in the current study, to allow the immune competence of animals when under stress to be assessed, increases in serum haptoglobin detected post-weaning are likely to be due to the combined effects of stress induced by the yard weaning process and stimulation of the immune system through vaccination at the commencement of weaning. This effect was confirmed in a pilot trial conducted prior to this study in which calves were vaccinated with 7in1 (test) or saline (control) at the commencement of yard weaning and the influence of vaccination on haptoglobin responses assessed 3 days post weaning. Unfortunately the confounding influence of vaccination on haptoglobin responses induced by the stress of the yard weaning process could not be avoided in the current study if we wanted to assess the immune competence of animals when under stress. The use of alternative indicators of stress responsiveness such as serum cortisol or serum amyloid A were considered when designing the current project; however, serum cortisol responses are rapid and very dynamic, requiring very strict timing of sampling which was not practical when testing large numbers of animals on commercial farms and measurement of serum amyloid A at the scale required here was cost prohibitive. The influence of vaccination on these alternative indicators would also require investigation. On this basis it was decided to proceed with measurement of haptoglobin as a stress response indicator in the current project. In future studies we plan to investigate the use of faecal cortisol as a stress response indicator. Measuring cortisol in faeces is expected to allow more accurate baseline cortisol levels to be determined at the commencement of weaning and provide more flexibility in sample timing as compared to measuring serum cortisol.

While acknowledging the confounding effects discussed above, increases in serum haptoglobin observed during yard weaning in the current study were positively genetically correlated with the growth traits YW (0.29 ± 0.20) and FW (0.64 ± 0.28) but negatively genetically correlated with the fat cover traits Rump (-0.47 ± 0.32) and Rib (-0.68 ± 0.3) suggesting that increased stress responsiveness may be associated with faster growing but leaner body phenotypes. Interestingly, hapto was strongly negatively genetically correlated with WEC (-0.94 ± 1.25) suggesting that increased stress-responsiveness is associated with reduced resistance to internal parasite challenge; however, the large error associated with the estimate makes interpretation difficult. Hapto was favourably

genetically correlated with CS (0.43 ± 0.42), unfavourably correlated with FT (0.41 ± 0.41) and not correlated with WtGain (0.07 ± 0.41); however, the large errors associated with these correlation estimates make interpretation difficult.

5.3 Relationships between immune competence and production traits

It has long been considered that resistance to disease in livestock may incur a production cost as a consequence of nutrients being redirected from production to support immune function. However counter-balancing this cost of resistance is the metabolic cost of disease (reviewed by Colditz 2002; Colditz, 2008). Chronic activation of immune defence pathways during chronic subclinical infection leads to reduced efficiency of production. In the current study we investigated correlations between immune competence traits and production traits. Results suggested that immune competence traits are weak to moderately negatively genetically correlated with growth traits, as evidenced by the genetic correlation between AMIR and WW (-0.38 ± 0.26), AMIR and FW (-0.44 ± 0.20), CMIR7 and WW (-0.45 ± 0.27) and CMIR7 and FW (-0.23 ± 0.22). This finding was supported by the slightly reduced WW, YW, FW and CWT observed in high CIR7 animals as compared to their average and low CIR7 counterparts; however, it is noteworthy that differences between immune phenotype groups were not statistically different for any of the growth traits measured and productivity losses due to health associated mortalities at the feedlot were not captured when calculating the LSmeans for FW and CWT (for further discussion see section 9.1.7.5). Therefore although genetic correlation estimates suggest that selection for immune competence may incur minor productivity losses, such losses are offset by the reduced mortalities observed in high and average CIR phenotype animals as compared to their low CIR counterparts. Such results also suggest that selection for production traits with little or no emphasis on health and fitness traits will reduce immune competence over time leading to an increase in the incidence of disease. Supporting this notion, antagonistic or unfavourable genetic correlations are known to exist between production traits and the incidence of many common diseases in livestock (Rauw *et al*., 1998). It is also important to recognise, that genetic progress can be made simultaneously in traits even when those traits are unfavourably genetically correlated. An example of which comes from the sheep industry where genetic progress in reducing fibre diameter while simultaneously increasing fleece weight, traits which are unfavourably correlated, has been successful (Taylor and Atkins, 1997).

In previous studies investigating links between immune competence and growth, high immune responder pigs were found to have higher growth rates relative to their average and low immune responder counterparts, significantly reducing the time taken to reach market weight (Mallard *et al*., 1998a). In housed dairy cattle, multiparous high AMIR responder cows were found to have significantly higher milk production compared with their low immune responder counterparts; however, in first-parity cows, milk production was higher in low AMIR responder animals than in average or high immune responder cows (Wagter *et al*., 2003). While in pasture reared dairy heifers, high and average AMIR responder animals were found to have higher average daily weight gains as compared to their low AMIR responder counterparts (Aleri 2015). Common to these studies was the intensification of the production systems investigated whether animals were housed or on pasture and the increased disease challenges that come with intensification. In the current study, calves were reared and backgrounded in extensive pasture based production systems before entering the feedlot at approximately 18 months of age. Once at the feedlot, calves remained in their herd cohorts throughout feedlot finishing and were only mixed with unfamiliar cattle at the commercial

feedlot (after a minimum of 100 days in the feedlot environment) where herd cohort size was significantly smaller than pen capacity. Therefore the stress and increased disease challenges imposed by mixing with unfamiliar animals was minimised. We expect that any production costs incurred by selecting for enhanced immune competence to be reduced when animals are exposed to a more challenging environment.

Favourable associations between immune competence and reproductive traits in dairy cattle have been reported (Thompson-Crispi *et al.*, 2012b). In a study across 42 herds in Canada, favourable associations were observed between immune competence and number of artificial services, and time from first service to conception. In the current study, results suggested that immune competence traits are weak to moderately positively genetically correlated with the fat cover traits, RUMP and RIB suggesting that selection for immune competence will also select for increased fat cover. It is well established that maintaining body condition score in breeding females is a critical factor in achieving reproductive success and therefore we speculate that immune competence and fertility traits may be favourably genetically correlated. Of animals immune competence tested in this study, live scan data was only available on steer progeny from the ASBP and therefore associations between immune competence and fat cover in heifers could not be investigated. However as part of the ASBP, heifer progeny are retained in co-operator herds until their first calving and the reproductive traits conception rate and days to calving recorded. As these heifers represent half-sibs to the steers immune competence tested in the current study, associations between immune competence and reproductive performance can be inferred by calculating immune competence genomic estimated breeding values (gEBVs) for sires used in the ASBP and looking at associations between these gEBVs and reproductive performance in their heifer progeny. We are currently exploring this approach and plan to validate links between immune competence and reproductive performance in future studies.

5.4 Relationships between immune competence and other traits

All steer progeny from the ASBP are feed efficiency tested at the Tullimba feedlot using the GrowSafe monitoring system. NFI-f represents an animal's feed intake at a standard weight and rate of weight gain. A weak unfavourably genetic correlation between CMIR7 and NFI-f (0.36 ± 0.23) was observed in the current study. However, AMIR and NFI-f were not genetically correlated (0.00 ± 0.04) and no differences in NFI-f were observed between high, average and low CIR phenotype group animals.

Worm egg counts were conducted on all immune competence tested calves to investigate associations between immune competence and resistance to internal parasites. Multi-drug resistance of common internal parasites is a major issue for the sheep industry and is becoming an increasingly important issue for beef cattle producers backgrounding feeder cattle on pasture. Results suggested that the immune competence traits AMIR and CMIR7 are not genetically correlated with WEC. However significant differences in WEC were observed between CIR7 phenotype groups with high CIR7 phenotype animals having a lower logWEC (2.90 ± 0.17) than their average CIR7 (3.38 ± 0.06) and low CIR7 (3.31 ± 0.16) phenotype counterparts, suggesting high CIR7 animals may have enhanced resistance to internal parasites. WEC values observed in the current study were generally low. Further studies in high parasite load environments are required to confirm the association between immune competence and internal parasite resistance.

5.5 Associations between immune competence and feedlot health

Detailed health records for all steers entering the commercial feedlot (n=839) were obtained and analysed to assess the influence of immune competence phenotype on feedlot health. As described above steers were categorised as low (n=98), average (n=653) or high (n=88) immune responders for CIR7 and group differences in disease incidence and mortalities observed at the feedlot analysed. Results showed that incidence of disease was highest in low CIR7 phenotype animals (15.3 cases / 100 animals), followed by average CIR7 animals (10.3 cases / 100 animals) and lowest in high CIR7 animals (10.2 cases / 100 animals); however, due to low overall disease incidence observed differences between groups were not significant. A favourable association between immune competence phenotype and number of mortalities was also observed with 6.1% mortalities recorded in low CIR7 phenotype animals, 1.2% mortalities in average CIR7 animals and no mortalities observed in high CIR7 animals. Mortalities in low CIR7 animals were significantly higher than in their average ($p = 0.005$) and high ($p = 0.030$) CIR7 phenotype counterparts. We hypothesise that when selecting animals based on immune competence that maximum benefit will be achieved by eliminating low responder CIR phenotype animals rather than selecting high responder CIR phenotype animals. Therefore the number of mortalities were compared in high and average CIR7 phenotype animals combined versus low CIR7 animals. Although total mortalities observed were low at 1.7%, the difference in mortality rate between high/average CIR7 phenotype animals and low CIR7 animals was highly significant ($p = 0.003$). Combined these results suggest that significant health associated cost benefits can be achieved by identifying low CIR animals and either eliminating them from the herd or targeting them for pasture rather than feedlot finishing. Animal health can be improved through both implementation of genetic selection strategies aimed at breeding animals with improved disease resistance, as we propose here, and also through targeted management practices and it is in combination that these approaches have the potential to dramatically improve animal health in the feedlot.

An attempt was made to quantify the potential benefits of selecting for immune competence, realised through a reduction in health related costs at the feedlot. Health-associated costs due to lost production costs at the feedlot as a result of health related mortalities, replacement cost of animals which died due to illness and disease treatment costs were estimated at $3.53, $28.24 and $103.36, (per head) for high, average and low CIR7 phenotype animals, respectively. Highlighting the significant economic benefits which can be achieved by identifying low CIR phenotype animals and eliminating them from the feedlot sector, results showed that low CIR7 phenotype animals represented only 11.7% of all animals but accounted for 35% of estimated health associated costs incurred at the feedlot. Results indicated that high CIR7 animals had the highest number of lost production days due to illness (Table 15) and the highest disease treatment costs (Table 20). This is a consequence of animals identified as having a high CIR7 phenotype being able to recover from illness, as evidenced by the fact that no mortalities were observed in the group, and should be considered a favourable outcome. It is important to note that the health associated cost benefits calculated here did not incorporate the direct labour costs associated with administering disease treatments and monitoring of animals nor the opportunity cost associated with having a sick animal or an animal which dies taking up pen space which could otherwise have been used to house a healthy animal which was gaining weight and generating income for the feedlot. It could also be expected that low CIR phenotype animals may act as a disease reservoir increasing disease risk for

pen mates. On consideration of these additional factors, the economic benefits of selecting for immune competence in terms of reduced health associated costs calculated here are likely conservative.

Health data collected in the current study was from steers which were 1) vaccinated against both respiratory and clostridial diseases prior to feedlot induction, 2) remained in their herd cohorts throughout feedlot finishing at both Tullimba and the commercial feedlot, 3) were only mixed with unfamiliar cattle at the commercial feedlot (after a minimum of 100 days in the feedlot environment) where herd cohort size was significantly smaller than pen capacity minimising the stress and increased disease challenges imposed by mixing with unfamiliar animals and 4) were feedlot finished at feedlots which both traditionally experience a low incidence of disease. Combined, these factors created a low disease risk environment. Therefore the economic benefits from reduced health costs calculated here when selecting for immune competence can be considered representative of the benefits expected in a low disease risk feedlot environment. We hypothesis that the economic benefits from reduced health associated costs will be even greater in higher disease risk environments where animals are not vaccinated prior to feedlot induction and cattle are mixed with unfamiliar animals from a variety of sources including saleyards at feedlot entry and recommend evaluating this in future studies.

Based on results of the current study we hypothesise that even in a low risk feedlot environment the economic benefits of selecting for immune competence, realised through reduced health associated costs at the feedlot are clearly evident. Based on the unfavourable genetic correlations observed between immune competence traits and growth traits, results suggest that selection for immune competence traits will incur a cost in productivity. However, when the increased mortalities observed in low CIR phenotype animals are factored into calculations (“Deads-in” method as described by Gaylean and Elam, 2009), results show that as a group, high CIR phenotype animals are as equally productive as their average and low CIR counterparts in the feedlot environment. Using the “Deads-in” method to compare feedlot exit weights between immune competence phenotype groups at the end of feedlot finishing, the feedlot exit weights for high, average and low CIR7 phenotype animals were calculated as 812, 811 and 808 kgs, respectively. When interpreting these results it is important to consider that no differences in feed efficiency were observed between immune competence phenotype groups (Table 9).

In addition to reducing direct health associated costs, selection for immune competence is expected to improve animal welfare and reduce reliance on antibiotics to treat disease. Consumers are increasingly conscious of the health and welfare of the animals producing their food and are demanding the highest possible standards of animal welfare through purchasing choices. Consumers are also increasingly concerned with the use of antibiotics in food-producing animals. Maintaining consumer confidence in beef products will be critical to the future profitability of the beef industry.

6 Conclusions/recommendations

6.1 Conclusion

Results of the current study demonstrate that even in a low risk feedlot environment, where animals are vaccinated prior to entering the feedlot and are not mixed with unfamiliar animals at feedlot induction, the benefits of selecting for immune competence realised through reduced health associated disease and mortalities are significant. Furthermore, we hypothesise that in higher disease risk feedlot environments the health benefits of selecting for immune competence will be even greater than those described here.

Strategies aimed at reducing the incidence and impact of disease in Australian feedlots such as that described here have the potential to:

- Increase productivity in the feedlot
- Reduce disease treatment costs
- Improve animal health & welfare
- Reduce use of antibiotics in the food-chain
- Improve consumer confidence in the Australian beef industry

6.2 Objectives achieved

Specific indicative tasks were to:

- Develop an appropriate panel of antigens based on currently used commercial vaccines to measure general immune responsiveness, including measures of innate and adaptive (both antibody and cell-mediated) immune responsiveness. **ACHIEVED**
- Develop an immunisation protocol and timing for assessing general immune function – e.g. during yard weaning in order to replicate some of the stressors that animals experience at feedlot entry. **ACHIEVED**
- Collect phenotypic data on immune status in pasture and feedlot environments. **ACHIEVED**
- Measure other host defence variables such as response to ACTH challenge and acute phase protein response to social stressors. **ACHIEVED**
- Estimate associations between immune status, host defence variables and performance in pasture and feedlot environments. **ACHIEVED**
- Estimate genetic parameters for immune status, host defence variables and performance in pasture and feedlot environments. **ACHIEVED**
- Explore genetic markers for immune responsiveness traits and for immune responsiveness traits associated with feedlot performance. **YET TO BE ACHIEVED.** All ASBP calves immune competence tested in the current project have been fully genotyped allowing genetic markers for immune responsiveness traits to be investigated in future studies.

6.3 Future projects

Future projects will aim to:-

- Confirm the benefits of selecting for immune competence in higher disease risk environments where animals are not vaccinated prior to feedlot induction and cattle are mixed with unfamiliar animals from a variety of sources including saleyards at feedlot entry.
- Generate gEBVs for immune competence for sires used in the ASBP to infer associations between immune competence and reproductive performance.
- Refine testing protocols, minimising the number of farm visits required and time taken to conduct testing.
- Develop field based tests to replace laboratory assays, providing same day results during testing and removing the need to transport serum samples to the laboratory.
- Explore genetic markers for immune responsiveness traits

6.4 Publications and conference proceedings (see appendix for articles without a link)

Hine BC, Mallard BA, Ingham AB, Colditz IG. (2014) Immune competence in livestock. In 'Breeding focus 2014 – Resilience'. (Eds. S. Hermesch and S. Dominik) pp. 49-64. (Animal Genetics and Breeding Unit, University of New England, Armidale, NSW, Australia) ISBN 978-1-921-597-65-7.

Colditz IG, Hine BC. (2015) A consideration of biological responses related to resilience in farm animals. *Animal Production Science*. http://dx.doi.org/10.1071/AN15297

Hine B, Wiiffels G, Ingham A, Colditz I. Potential benefits of selecting for improved resilience in Northern beef cattle. (2016) *"In Proceedings of the Northern Beef Research Update Conference"*, Rockhampton, QLD, Australia 15th – 18th August, 2016. Improving animal health and welfare for productivity in Northern Australia section pp 70-76.

Dominik S, Hine, B. Selection for immune competence in beef breeding programs modelled on potential reductions in the incidence of bovine respiratory disease. (2016) In 'Breeding focus 2016 – Animal Welfare'. (Eds. S. Hermesch and S. Dominik) (Animal Genetics and Breeding Unit, University of New England, Armidale, NSW, Australia).

7 Key messages

7.1 Key project findings

- Heritability estimates for the immune competence traits, AMIR and CMIR7 are considered moderate, suggesting a reasonable rate of genetic gain can be expected when selecting for immune competence.
- The immune competence traits AMIR and CMIR7 are strongly positively genetically correlated.
- Immune competence traits are favourably genetically correlated with temperament traits.
- Average daily weight gains during the yard weaning period suggest that immune competence and stress coping ability are favourably correlated.
- Immune competence traits are weak to moderately negatively genetically correlated with growth traits. This negative association is in agreement with the reduced disease resistance seen in other livestock species following selection for production traits. Although differences between immune competence phenotype groups were non-significant, feedlot exit weight (based on "Deads-out" and adjusted for feedlot entry weight and days on feed) was calculated at 817, 815 and 824 kgs for high, average and low immune competence phenotype animals, respectively. However, when the influence of mortalities on productivity were considered feedlot exit weight (based on "Deads-in" and adjusted for feedlot entry weight and days on feed) was calculated at 812, 808 and 811 kgs for high, average and low immune competence phenotype animals, respectively, suggesting that as a group, high immune competence phenotype animals are as equally productive as their average and low responder counterparts in the feedlot environment.
- Immune competence traits are weak to moderately positively genetically correlated with the fat cover traits which may have implications for reproductive performance in females.
- Significant differences in WEC were observed between immune competence phenotype groups with high immune competence phenotype animals having a lower logWEC (2.90 ± 0.17) than their average (3.38 ± 0.06) and low (3.31 ± 0.16) immune competence counterparts.
- Incidence of disease was highest in low immune competence phenotype animals (15.3 cases / 100 animals), followed by average immune competence animals (10.3 cases / 100 animals) and lowest in high immune competence animals (10.2 cases / 100 animals); however, due to low overall disease incidence observed differences between groups were not significant.
- Number of mortalities at the feedlot were highest in low immune competence phenotype animals (6.1%), followed by average immune competence animals (1.2%) and lowest in high immune competence animals where no mortalities observed.
- Health-associated costs due to lost production days at the feedlot as a result of health related mortalities, replacement cost of animals which died due to illness and disease treatment costs were estimated at $3.53, $28.24 and $103.36, (per head) for high, average and low immune competence phenotype animals, respectively.

- Low immune competence phenotype animals represented only 11.7% of all animals entering the feedlot but accounted for 35% of the estimated health associated costs incurred at the feedlot.

7.2 Acknowledgements

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9 Appendix

9.1 Appendix A

Immune competence in livestock

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Abstract

Selection for production traits with little or no emphasis on health-related traits has led to an increase in the incidence of disease in many of our livestock species. Currently we are developing testing procedures to assess 'general immune competence' of beef cattle, dairy cattle and sheep on-farm. Immune competence traits will be combined with measures of temperament and ability to cope with management induced stress to estimate an animal's resilience. By exploring associations between resilience and important production traits we aim to develop breeding strategies which will identify animals highly suited to their production environment.

Introduction

The immune system is composed of tissues, cells and molecules which work together to protect the host animal against disease. Effective host defence is reliant on the immune system's ability to detect a wide variety of agents, to distinguish whether such agents are part of the body or foreign (self versus non-self), to determine whether non-self agents are commensals or threats, and to eliminate the potentially infectious agents or pathogens. Livestock, with the exception of those raised in specialised facilities, are exposed to a myriad of pathogens on a regular basis. Such pathogens possess the inherent ability to evolve rapidly, and as a consequence, adapt quickly to changes in the environment, and continually develop new strategies to avoid detection and elimination by the host's immune system. To detect and eliminate pathogens, the immune system has developed a diverse range of defensive responses that work together and which can be broadly categorised as either innate or adaptive responses. When a pathogen is first encountered, the innate immune system is activated. In the initial phases of the innate response, pre-formed anti-microbial substances, present in bodily fluids and secretions, begin to weaken and kill the pathogen while sending signals to alert the adaptive immune system of impending danger. As these responses advance, innate effector cells recognising common pathogen-associated signatures become activated, setting in motion a signalling cascade that triggers defence mechanisms aimed at eliminating the pathogen. Should a pathogen breach these initial lines of defence and damage the host, mechanisms are in place to trigger adaptive immune responses. In contrast to innate responses which are largely non-specific, fast acting and not substantially enhanced by repeated exposure to

the same pathogen, adaptive responses are highly pathogen-specific, slower to develop and continually refined upon repeated exposure to the same pathogen. Adaptive responses have an important memory component, which enables the effector functions of the adaptive immune system to be deployed more rapidly and with increasing specificity upon re-exposure to a pathogen.

The immune system is the body's main defence against disease, however some commonly used terms describing an individual's response to disease should be considered. Different disciplines and research studies use the related terms of disease resistance, tolerance, resilience and robustness in slightly different ways and therefore the precise relationship between these terms may be context specific. For the purpose of this paper the following distinctions will be made between these separate, yet related, terms as they pertain to disease. Disease resistance is considered as the host's ability to limit or eliminate pathogens using a variety of host defence reactions including physiological, behavioural and immunological responses (Colditz, 2008). Morphological traits can also make an important contribution to disease resistance as evidenced by the relationship between breech conformation and resistance to flystrike in Merino sheep (Greeff *et al*., 2014). These various defence mechanisms work in conjunction to block pathogen invasion or destroy the invader. However, the host can also defend itself by limiting the damage caused by the pathogen using mechanisms that prevent self-harm or modulate escalating immune responses (Schneider and Ayres, 2008). This is termed disease tolerance, or in other words, an ability to minimise the effects of infection at a given level. This terminology can be further refined by identifying individuals that maintain productivity in the face of a disease challenge. This is generally referred to as disease resilience (Bishop and Morris, 2007). A key difference between disease tolerance and disease resilience is that disease tolerance often implies a permanent state of infection where repeated exposure to a particular pathogen reduces sensitivity to its effects, whereas disease resilience is generally considered a more transient state of infection where the host eventually clears the infection with little or no effect on production. Finally, the term robustness is defined as the ability of the individual to maintain its functions in the face of internal and external challenges (Kitano, 2007). Robustness therefore is quantified by performance of various traits, such as growth, fertility, and carcass characteristics, as well as response to disease.

Both the ability to resist infection and the ability to tolerate the effects of disease are likely contributors to an animal's ability to maintain productivity when faced with a disease challenge. Therefore disease resistance and disease tolerance can both be considered to contribute to disease resilience (Bishop, 2012). In considering whether to target, disease resistance or disease tolerance, as the basis for improving animal health in selective breeding programs, there are no simple answers. It is important however to realize that disease resistance and disease tolerance are generally negatively correlated, and are based on different underlying host mechanisms and genes, and have different impacts on the evolving pathogen (Simm and Triplett, 1994). Because disease resistance and disease tolerance are often negatively genetically correlated, individuals identified as susceptible to disease tend to be more tolerant. Conversely, individuals with resistant genotypes tend to be less tolerant. The implication of these factors is outside the scope of this discussion; however, it highlights the importance of considering the preferred final outcomes for both the host and pathogen when establishing selection strategies to improve animal health. The research described here focuses on general disease resistance because in many cases of infectious disease it is critical to eliminate the causal agent in order to prevent mortality and unintended pathogen transmission to the environment or to other hosts. Furthermore, animals identified using

appropriate strategies as having enhanced general disease resistance are likely to be resistant to a wide-range of pathological agents.

When developing strategies aimed at improving animal health, it is important to recognise that disease resilience is just one component of general resilience. Just as disease resilience can be considered as the ability of an animal to maintain productivity in the face of disease challenge, general resilience can be considered as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Livestock are exposed to a variety of environmental challenges in their production environment including abiotic extremes, social and management-induced stressors and disease challenges. The contribution of immune competence to general resilience will be discussed in further detail later in the chapter.

Immune competence

Immune competence can be considered as 'the ability of the body to produce an appropriate and effective immune response when exposed to a variety of pathogens' (Wilkie and Mallard, 1999). Weak responses may allow pathogens to persist or overcome host defences leading to morbidity and mortality. Inappropriate responses to self antigens (an antigen being any substance that provokes an adaptive immune response can lead to autoimmune diseases, while inappropriate responses to harmless antigens can lead to allergic responses. It is also critical that when faced with a pathogen challenge, the body mounts the most effective type of response to control that pathogen. Some pathogens have devised means by which they enter cells of the body (intracellular pathogens) while others remain in the environment external to cells (extracellular pathogens). Elimination of intracellular pathogens generally requires that infected cells be destroyed. This job is carried out by phagocytes, which are specialised cells with the ability to ingest harmful agents and infected cells, and by cytotoxic cells, which are capable of inducing programmed cell death in target cells. Collectively, the actions of such cells are described as 'cell-mediated immune responses'. In contrast, extracellular pathogens and soluble antigens are more effectively controlled by 'antibody-mediated immune responses'. Antibodies bind to pathogens and soluble antigens in the extracellular environment, preventing them from damaging or entering cells and tagging them for destruction by immune cells. As the immune system is constantly challenged by both intracellular and extracellular pathogens it is critical that individuals have a balanced ability to mount both cell-mediated and antibody-mediated immune responses. Equally responses must be of a magnitude that effectively eliminates pathogens without causing self harm.

Immune Competence – An Important Selection Trait

Selection for production traits with little or no emphasis on health and fitness traits has led to an increase in the incidence of disease in many livestock industries. Antagonistic or unfavourable genetic correlations exist between production traits and the incidence of many common diseases in livestock (Rauw *et al*., 1998). For example, the genetic correlation between milk production and the incidence of mastitis in dairy cattle has been estimated at between 0.15 to 0.37 (Lyons *et al*., 1991; Uribe *et al*., 1995; Van Dorp *et al*., 1998). Thus progeny of parents with high genetic potential for milk production have a higher incidence of mastitis than progeny of parents with low genetic potential for milk production. In pigs, selection focussed on high productivity has led to an increase

in susceptibility to stress and disease (Prunier *et al*., 2010). In sheep, recent production focussed breeding has been achieved in an environment where chemicals have been available to control the major pathogens, gastrointestinal nematodes. A comparison of progeny sired by contemporary rams or from semen collected over 30 years ago shows advances in many productivity traits during this time however natural resistance to nematodes has declined significantly (Shaw *et al*., 2012). Such findings suggest that continued selection based on productivity alone will result in further increases in the incidence of disease in livestock species. The animal production sector is becoming increasingly aware of this issue and is actively seeking solutions to the problem.

Changes in community attitudes are also contributing to a renewed focus on breeding production animals that have an enhanced natural ability to resist disease. Consumer awareness of practices that impact the health and welfare of food-producing animals is increasing, as is concern regarding the use of antibiotics to control disease in livestock and the potential food contamination issues that arise from their misuse. However, it must also be acknowledged that selection for increased productivity remains a key profit driver for our livestock industries. Alternative strategies that address these consumer concerns while reducing the incidence of disease, and as a consequence, production losses and treatment costs associated with disease are therefore required. It is therefore proposed that a possible genetic solution is to combine production traits and immune competence traits into a weighted selection index with the aim of breeding high-producing animals with enhanced general immune competence (Mallard *et al*., 1998a; Wilkie and Mallard, 1999).

Selecting for Resistance to Specific Diseases versus Selection for General Disease Resistance

Breeding strategies targeted at increasing resistance to specific diseases in livestock have proven very successful. Such strategies include breeding sheep with enhanced resistance to specific internal parasites (Le Jambre *et al*., 1971), dairy cattle with enhanced resistance to mastitis (Heringstad *et al*., 2000) and beef cattle with increased resistance to brucellosis (Adams and Templeton, 1993) and to cattle ticks (Frisch *et al*., 1998). Based on the knowledge that the host immune system tailors responses to the type of pathogen encountered, it could be expected that selection of animals based on their resistance to a specific disease may inadvertently increase their susceptibility to other diseases. For example, selection of animals based on their resistance to an extracellular pathogen, largely controlled by an antibody-mediated immune response, might inadvertently increase their susceptibility to intracellular pathogens, largely controlled by cell-mediated immune responses. In support of this concept, it has been reported that cell-mediated and antibody mediated immune responses are negatively genetically correlated in dairy cattle even though they work in coordination to protect the host (Hernandez *et al*., 2006; Thompson-Crispi *et al*., 2012b). An inverse relationship between antibody production and macrophage function, an important component of cell-mediated immunity, was first reported in Biozzi mice selected for high and low antibody production (Hale and Howard, 1981). A similar relationship has since been reported in cattle selected for resistance or susceptibility to *Brucella abortus* (Price *et al*., 1990). Furthermore, a recent study in dairy cattle has demonstrated that cattle which test positive for tuberculosis, which is largely controlled by cell-mediated immunity, have a lower incidence of mastitis, largely controlled by antibody-mediated immunity (Edwards, 2014). In contrast to these findings, monocyte function was found to be similar in pigs selected for high and low overall immune responsiveness (Groves *et al*., 1993). Although such findings suggest more research is required to assess the long term effects of selection for resistance

to a specific disease on susceptibility to other diseases in livestock, long term benefits can be expected from adopting breeding strategies based on enhancing general disease resistance of livestock as an alternative to, or in conjunction with, enhancing resistance to specific diseases of significant economic importance to the livestock industries.

Assessing Immune Competence

Genetic variation in the ability to resist disease is due to a large number of additive genetic effects which together regulate innate and adaptive immune responses (Wilkie and Mallard, 1999). It has been estimated that greater than 7% of all known genes in the mammalian genome are involved in immune function (Kelly *et al*., 2005). Although the underlying genotype involves complex interactions between many genes, by inducing immune responses and objectively measuring such responses in livestock, general immune responsiveness of individual animals can be assessed (Wilkie and Mallard, 1999) (Fig 1.). This was first demonstrated amongst livestock species in Yorkshire pigs, where measures of innate and adaptive immunity (both antibody and cell-mediated) were combined to generate estimated breeding values (EBVs) for general immune responsiveness and to rank boars and gilts as high, intermediate and low immune responder (IR) phenotypes for use in future breeding programs (Mallard *et al*., 1992). This strategy aimed to simultaneously improve the ability of animals to mount both antibody and cell-mediated responses, and as a consequence, enhance general disease resistance. Following the inbreeding of high, intermediate and low IR phenotype pigs for several generations it was found that high IR pigs had superior antibody responses to test antigens and several commercial vaccines (Wilkie and Mallard, 1999), a lower frequency of non-responders when vaccinated with inactivated influenza vaccine (Wilkie and Mallard, 1998) and higher antibody avidity, a measure of the strength of the antibody-antigen interaction (Appleyard *et al*., 1992), than their intermediate and low IR counterparts. Although such findings provide overwhelming evidence to suggest that selection successfully enhanced general immune responsiveness in high IR pigs, when challenged with *Mycoplasma hyorhinis,* these pigs displayed more severe arthritis than LR pigs, suggesting that high IR phenotype pigs may be more prone to generating inflammatory responses (Magnusson *et al*., 1998). However, in the same study, high IR pigs were found to have less severe peritonitis, less severe pleuritis and produced serum antibody against *M. hyorhinis* both earlier and to a higher level than did their low IR counterparts and therefore survived better. Thus the tradeoff between lameness and survival may be defensible in this case.

More recently, research efforts have been focussed on developing protocols to assess general immune responsiveness in dairy cattle, similar to those used in pigs, and on investigating associations between immune responsiveness phenotypes and the incidence of disease in large-scale commercial dairy farms. This strategy involves immunising animals with antigens that stimulate either strong antibody or cell-mediated immune responses, and then measuring both types of response. The responses are then used in combination to rank animals for general immune responsiveness (Heriazon *et al*., 2009a; Heriazon *et al*. 2009b). Although this ranking strategy does not incorporate measures of innate immunity, in contrast to the strategy used in pigs, it is acknowledged that strong adaptive immune responses are underpinned by strong innate immune responses (Fig 1.). In fact, macrophage function, including both phagocytosis and nitrous oxide production, seems to be stronger in high responder dairy cows (B.A. Mallard, *pers. comm*.) as does TLR2 expression, a receptor involved in the recognition of a wide array of microbial molecules

(Wagter-Lesperance *et al*., 2014). Therefore such a strategy can still be expected to identify animals with enhanced general immune responsiveness and, as a consequence, general disease resistance. Researchers have utilised this testing strategy to investigate the influence of hybrid vigour on general immune responsiveness in purebred and crossbreed dairy cattle (Begley *et al*., 2009, Cartwright *et al*., 2012), the influence of age and pregnancy status on general immune responsiveness in dairy heifers (Hine *et al*., 2011), leukocyte (white blood cell) populations in high and low IR dairy heifers (Hine *et al*., 2012) and the influence of geographical location on immune response profiles of Canadian dairy cattle (Thompson-Crispi *et al*., 2012a).

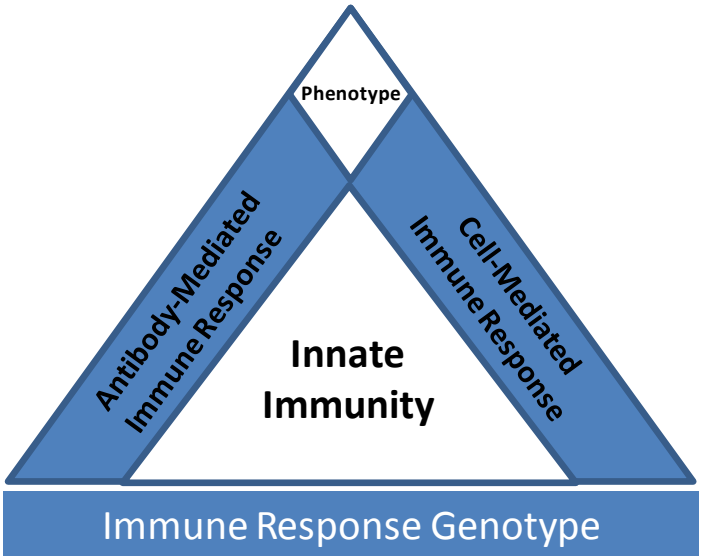

Figure 1. Genetic variation in the ability to resist disease is due to a large number of additive genetic effects which together regulate innate and adaptive immune responses (Source: adapted from Wilkie and Mallard 1999)

Heritability of Immune Competence Traits

The practicality and efficiency of the immune response testing protocol, developed by Mallard and colleagues for use in dairy cattle, has permitted the testing of large numbers of commercial dairy cows across diverse geographical locations in North America in order to estimate the heritability of immune responsiveness traits (Thompson-Crispi *et al*., 2012b). The heritability of a trait refers to the proportion of the observed variation between animals which can be directly attributed to differences in genetics. Genetic gains can be made quickly in highly heritable traits, whereas genetic progress in traits with low heritability, while still achievable, is expected to be proportionally slower. The heritability of antibody and cell mediated immune responsiveness in commercial dairy cattle has been estimated at 0.16-0.41 (with a standard error (SE) of 0.09-0.11, depending on time of sampling and antibody isotype measured) and 0.19 (SE = 0.10), respectively (Thompson-Crispi *et al*., 2012b). These estimates are in line with those reported in pigs selected for general immune responsiveness for eight generations, where the heritability of antibody and cell-mediated immune responsiveness was estimated at 0.27 and 0.16, respectively (Wilkie and Mallard, 1999). Heritability estimates of these traits in the initial cohort of Canadian Holstein sires owned by the Semex Alliance (http://www.semexusa.com/) are in the range of 0.3 to 0.48 (B.A. Mallard, *pers. comm*.). These heritability estimates are considered moderate and they are comparable with the heritability of

many highly selected production traits in livestock species (Safari and Fogarty, 2003). Therefore, reasonable genetic gains in general immune responsiveness traits can be expected when the traits are incorporated into livestock breeding programs.

Selection for Immune Competence – Associations with Disease Incidence, Reproduction and Productivity

Knowledge of associations between enhanced general immune responsiveness and incidence of disease, rates of reproduction and productivity in commercial livestock operations is critical to the success of selection strategies aimed at breeding high-producing animals with enhanced general immune responsiveness. In an early study conducted on both research and commercial dairy farms, it was reported that cows classified as high for antibody-mediated immune responsiveness had a lower incidence of mastitis when compared with average or low responders using data pooled across herds. High antibody responder cows also responded better to the commercial *Escherichia coli* J5 mastitis preventative vaccine (Wagter *et al*., 2000). It should be noted however, that in the same study, cows classified as high antibody responders had the highest incidence of mastitis in one of the three herds tested, with all mastitis cases in these cows recorded in first-parity cows rather than multiparous cows. This finding was limited to the research herd tested and was not observed in the two commercial herds tested. Disease incidence records carefully and systematically collected on commercial farms provide valuable data to quantify the success of selecting for improved general disease resistance (Guy *et al*., 2012). A more recent study reported incidence rates of clinical mastitis in 41 herds across Canada in dairy cattle classified as high, average or low for general immune responsiveness (Thompson-Crispi *et al*., 2013). Results from this study revealed that the average cases of mastitis reported per 100 cow years in high, average and low IR cows were 17.1, 27.9 and 30.7, respectively and that severity of mastitis cases was greatest in low IR cows. Associations between disease incidence and general immune responsiveness have also been investigated in a large commercial dairy herd in Florida (Thompson-Crispi *et al*., 2012c). Results showed that the incidence of mastitis was higher in average IR cows compared to high IR cows. Mastitis incidence tended to be higher in low IR as compared to high IR cows; however, the difference was not statistically significant. Although observed differences in the incidence of metritis and ketosis between IR phenotypes were not significant, displaced abomasums and retained foetal membranes were observed more frequently in low IR cows. The considerable research effort aimed at developing a strategy to assess general immune responsiveness and evaluating the success of that strategy to reduce the incidence of disease in commercial dairy herds has culminated in the licensing of the High Immune Response technology to the Semex Alliance. The Semex Alliance has been marketing semen from dairy sires with EBVs for enhanced general immune responsiveness in North America since January 2013 and is currently marketing this semen globally. Recent data collected from large commercial dairy farms in the United States demonstrated that daughters of Immunity+ sires have lower incidence of mastitis (8.8% versus 15.8%) and pneumonia (6.8% versus 9.1%) than do daughters from non-Immunity+ bulls in the same herd (Data courtesy of Jay Shannon, Sire Analyst, Semex Alliance).

It has long been considered that resistance to disease in livestock may incur a production cost as a consequence of nutrients being redirected from production to support immune function. However counter-balancing this cost of resistance is the metabolic cost of disease (reviewed by Colditz 2002;

Colditz, 2008). Chronic activation of immune defence pathways during chronic subclinical infection leads to reduced efficiency of production. Enhanced immune responsiveness is expected to avoid the penalty to production that accompanies chronic immune activation and therefore may lead to improved productivity. In support of this concept, high IR pigs were found to have higher growth rates relative to their intermediate IR and low IR counterparts, significantly reducing the time taken to reach market weight (Mallard *et al*., 1998a). The relationship between antibody-mediated immune responsiveness and milk production has also been investigated in dairy cows. Among multiparous cows, high IR animals were found to have significantly higher milk production compared with low IR animals; however, in first-parity cows, milk production was higher in low IR animals than in average of high IR cows (Wagter *et al*., 2003). Favourable associations between general immune responsiveness and reproductive traits in dairy cattle have also been reported (Thompson-Crispi *et al*., 2012b). In a study across 42 herds in Canada, favourable associations were observed between general immune responsiveness and number of artificial services, and time from first service to conception. Clearly more research is required to determine associations between general immune responsiveness and important reproduction and production traits in livestock species. It is important to recognise however, that regardless of the outcome of these studies, genetic progress can be made simultaneously in traits even when those traits are unfavourably correlated. An example of this comes from the sheep industry where genetic progress in reducing fibre diameter while simultaneously increasing fleece weight, traits which are unfavourably correlated, has been successful (Taylor and Atkins, 1997).

Phenotype to Genotype

General immune responsiveness is a complex trait under polygenic control, having many genes each contributing to the variation observed in the trait (Wilkie and Mallard, 1999). Therefore it will be difficult to identify individual genes which have a major effect on general immune responsiveness which can be selected for in commercial populations of livestock. The use of EBVs or genomic based estimated breeding values (GEBVs) may help to overcome this issue by simultaneously selecting for genes contributing to the general immune responsiveness trait without the need to identify individual contributing genes (Thompson-Crispi *et al*., 2014). Estimation of GEBVs for traits is based on genetic markers across the genome that have a statistical association with those traits. Genome-wide association studies (GWAS) can be undertaken to explore associations between genetic markers and traits of interest. Various GWAS have been conducted in livestock to evaluate genetic differences in production, reproduction and health traits (Cole *et al*., 2011; Do *et al*., 2014). Recently, a GWAS was conducted to evaluate general immune responsiveness in Canadian Holstein cattle (Thompson-Crispi *et al*., 2014). This study identified several significant genetic markers, candidate genes and pathways associated with antibody and cell-mediated immune responsiveness in dairy cattle. Based on these findings it may be possible to calculate GEBVs for general immune responsiveness traits which could be incorporated into selection indices. However, studies based on larger reference populations are required to validate this approach. Associations between genetic markers and traits can differ between breeds and even between lines within breeds and therefore validation across multiple populations will be required.

Immune Competence as a Component of Resilience

Resilience can be described as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Livestock respond to challenges from infectious agents and other environmental stressors through immunological, physiological and behavioural defence reactions. These three modalities of host defence are highly integrated and their activation uses resources that would otherwise be directed towards production (Colditz *et al*., 2002). Research over a number of years has highlighted that the level of activity of the immune system is associated with an animal's ability to thrive in the face of environmental stressors and can be an indicator of future health and performance (Schmid-Hempel *et al*., 2003). Such findings highlight the important contribution of immune competence to resilience.

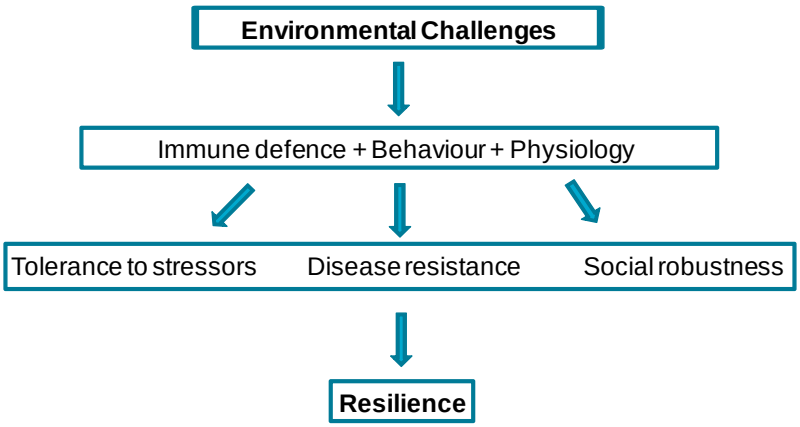

Figure 2. Resilience can be considered as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Measures of disease resistance, tolerance to stressors and social robustness can be used in combination to predict an animal's resilience

The resilience of individual animals can be predicted by combining measures of their general immune competence, stress responsiveness and behaviour or temperament (Fig. 2). Livestock management practices, such as weaning, social mixing and animal handling, provide opportunities to simultaneously assess the various components of host defence contributing to resilience. For example, yard weaning of beef calves provides an opportunity in which to simultaneously assess the ability of calves to cope with the stress induced by the weaning process, the ability of calves to respond to immunological challenges whilst under stress and also assess the temperament of calves. It is well recognised that stress, both physiological and metabolic, negatively impacts on immune function. For example, the incidence of disease in dairy cows is highest during the periparturient period when cows are under physical and metabolic stress (Mallard *et al*., 1998b). Incidence rates of bovine respiratory disease in feedlot cattle are highest in the first few weeks after entering the feedlot when cattle are under stress as a consequence of adjusting to a new environment (Schnieder *et al*., 2009) and the stress of late pregnancy and early lactation induces a relaxation in immunity to gastrointestinal parasites in sheep during the periparturient period is well documented (Salisbury *et al*., 1970). Such findings suggest that assessing immune competence in animals when under stress may improve our ability to identify animals able to resist disease challenges during subsequent periods of heightened exposure to environmental stressors. When combined with measures of stress responsiveness and temperament, general immune responsiveness when under stress is expected to

be a good predictor of resilience in livestock. Development of protocols to assess resilience phenotypes in livestock species will allow selection of animals better adapted to the environmental challenges associated with their respective production environments.

Summary

Selection for production traits with little or no emphasis on health and fitness traits has led to an increase in the incidence of disease in many livestock industries. A possible genetic solution to this problem is to develop breeding strategies aimed at enhancing general disease resistance of the animal while simultaneously making genetic gains in important production traits. Although immune responsiveness is a complex trait under polygenic control, general immune responsiveness can be assessed by inducing immune responses and objectively measuring such responses in livestock, allowing EBVs, and likely in the future, GEBVs to be calculated for individual animals. Selection for resistance to specific diseases carries the potential risk of inadvertently increasing susceptibility to other diseases. Selection of livestock for general immune responsiveness as an alternative to, or in conjunction with, selection for resistance to specific diseases reduces this risk and is expected to improve broad-based disease resistance. Extensive research in dairy cattle has demonstrated that animals with enhanced general immune responsiveness have a reduced incidence of disease in commercial herds. Furthermore, favourable associations between general immune responsiveness, production and reproduction traits have also been reported.

The ability to resist disease forms an important component of resilience, described as the ability to maintain productivity in the face of diverse environmental challenges. The resilience of livestock is becoming increasingly important as 1) selection pressure to increase productivity from livestock continues, 2) consumer awareness regarding the health and welfare of the animals producing their food increases and 3) consumer concern regarding the use of antibiotics in food-producing animals intensifies. The resilience of individual animals can be predicted using a combination of measures of general immune competence, stress responsiveness and temperament. Development of protocols to assess resilience phenotypes in livestock species will allow selection of animals better adapted to their production environment and help ensure the long-term future of livestock industries.

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9.2 Appendix B

Potential benefits of selecting for improved resilience in Northern beef cattle

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Introduction

Livestock face a variety of challenges from their production environment including exposure to infectious agents, abiotic extremes, social stressors as a result of herd hierarchy and mixing with unfamiliar animals and management induced stressors imposed by standard husbandry procedures and practices. Challenges vary between environments. For instance, in Northern Australia, beef cattle experience seasonal challenges from ticks and buffalo flies, extreme heat and humidity, variable feed quality and long transport distances to market. Following pasture backgrounding, many Northern Australian cattle are then finished through feedlots or are destined for live export exposing them to a new set of challenges. Identifying animals better able to cope with these unique challenges could 1) improve animal health and welfare 2) reduce reliance on the use of antibiotics and anti-parasitic drugs thus slowing the emergence of multi-drug resistance and 3) improve productivity. It is also important to consider the significant influence consumers can have on an industry.

Consumers are increasingly conscious of the health and welfare of the animals producing their food and are demanding the highest possible standards of animal welfare through purchasing choices. Consumers are also increasingly concerned with the use of drugs in food-producing animals and the potential residue issues they pose. Therefore, breeding strategies aimed at improving the health and welfare of animals and reducing reliance on drugs to treat disease are expected to improve consumer confidence, help maintain the social licence to operate and, improve industry profitability.

We define resilience as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Livestock respond to challenges from infectious agents and other environmental stressors through immunological, physiological and behavioural defence reactions. These three modalities of host defence are highly integrated, acting together to minimise the impact of challenges on the host (Colditz *et al*., 2002). The resilience of individual animals can be predicted by combining measures of their general immune competence, stress responsiveness, ability to tolerate climatic extremes and behaviour or temperament (Fig. 2). Livestock management practices, such as weaning, social mixing and animal handling, provide opportunities to simultaneously assess the various components of host defence contributing to resilience. For example, yard weaning of beef calves provides an opportunity to simultaneously assess the ability of calves to cope with weaning stress, the ability of calves to respond to immunological challenges whilst under stress and assess their temperament.

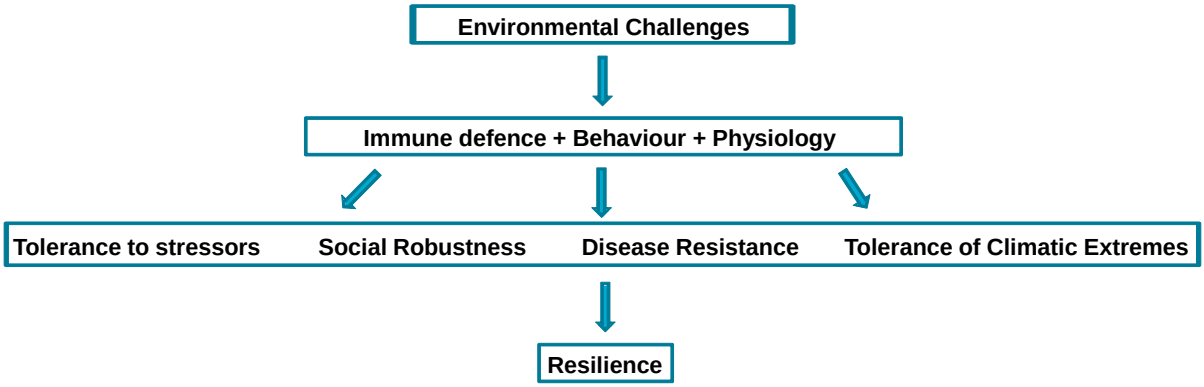

Figure 2. Resilience can be considered as the ability of an animal to maintain productivity in the face of diverse environmental challenges. Measures of disease resistance, tolerance to stressors, heat tolerance and social robustness can be used in combination to predict an animal's resilience

When assessing the resilience of livestock, the component measures used to define the resilience phenotype need to be tailored to the specific production environment. Here we propose a series of measures which could be used in conjunction to define resilience phenotypes specifically tailored for beef cattle grazing in various regions of Northern Australia.

Heat tolerance

The trend toward increased hot conditions in the cattle production regions of Australia is clear. Howden and Turnpenny, (1997) reported that for the Gayndah region (South East Queensland), the last 40 years has seen a 60% increase in days that cause heat stress in taurine cattle. With an intermediate warming scenario of an average temperature increase of 2.8°C by 2100, the number of heat stress days are estimated to increase to 139 days p.a. (as compared to the 58 heat stress days in the late 1990's). Furthermore, this region will face 92 days p.a. with high risk of heat related fatalities.

While the numbers and costs of cattle mortalities due to a discrete heat event can be calculated, total production losses over summers and on a national basis are difficult assessments. Sackett *et al.* (2006) estimated that Australian feedlots lose $16.5 million p.a. due to reductions in animal performance over summer.

The most obvious contribution to productivity loss in cattle from heat stress is decreased feed intake and subsequent slower weight gain. In beef cattle, there is a 0.4 kg/day average daily gain (ADG) depression for every 1°C increase in internal body temperature (Finch, 1986). A less obvious impact is the lower reproductive performance (Wheelock *et al.* 2010). All stages of bovine reproduction are affected by heat load.

Any stressor will redirect endocrine and metabolic processes toward maintenance of homeostasis and away from growth. The overt characteristics of heat stress: reduction of feed intake, reduced appetite and lassitude are the accumulation of the interactions of systemic endocrine, metabolic and inflammatory changes. The reduced feed intake most commonly experienced during heat stress has clouded much of the research and interpretation of the endocrine and metabolic effects that can be solely attributed to heat stress. However, the metabolic changes in heat stress cannot be explained by reduced feed intake alone. Heat-stressed ruminants fail to enlist the glucose saving mechanisms

used by underfed animals; i.e. do not consume their fat stores and become slightly insulin insensitive (Baumgard *et al.* 2011; Wheelock *et al.* 2010). It is likely, that to supply the glucose required for maintenance, protein in muscle is being catabolised to fuel gluconeogenesis in the liver.

There is now some evidence that the gut barrier function is disrupted in heat stress. The role of ruminal and intestinal dysfunction during heat stress in cattle was first proposed by Cronjé (2005). The disruption to gut function and integrity is a consequence of reduced blood flow to the viscera during heat stress, as the blood is directed to the skin and the mucosa of the respiratory tract for cooling. The lack of oxygen in the gut and liver, due to the reduced blood flow, compounds the situation thus setting off more inflammatory responses.

There has been research into different management tactics and tools with some adoption by producers and producer organisations (e.g. MLA, 2006). Based on research and their own experience, beef cattle nutritionists have manipulated buffering capacity, electrolyte balance and roughage: grain ratios of summer rations. These adjustments have met with success in some instances and not others, but this inconsistency is not understood.

Many researchers point to genetic selection as a means to equip the industry with heat tolerant breeds (Gaughan *et al*., 2010; Howden and Turnpenny, 1997). It is generally accepted that *Bos indicus* genotypes have greater heat tolerance than *Bos taurus* genotypes. There are exceptions. The Tuli, closely related to *Bos taurus* but tropically evolved, appears to have a high degree of heat tolerance (Hammond *et al*., 1998). This paper reported also that the rectal temperatures of Brahman cattle and Angus cattle (40.0 and 40.9°C respectively) were higher than the rectal temperature of Senepol cattle (39.6°C) under the same conditions.

Selective breeding for heat tolerance is a long and imprecise process but needs to be part of the answer. However, tools for detecting economically competitive heat tolerant phenotypes are limited because it is not understood which physiological parameters are most appropriate. Furthermore, the technology to measure these parameters in large numbers of animals in production environments is still under development or not yet in the pipeline.

Our current focus is on feedlot cattle where we are investigating inflammatory and metabolic responses to high heat load in growing steers in collaboration with Dr John Gaughan and team (University of Queensland, Gatton) (MLA B.FLT 0157). While the end-goal is to develop new nutritional and/or management approaches for alleviating heat stress in the feedlot, we are hopeful of discovering new parameters to define the heat-tolerant phenotype in *Bos taurus* cattle. This will provide tools for selective breeding and for assessing the suitability of animals for feedlot entry.

Tick resistance

Cattle tick (*Rhipecephalus microplus*) and tick borne disease (*Anaplasma marginale, Babesia bigemina, Babesia bovis*) have the highest economic impact of all diseases experienced in cattle in the north of Australia. A recent review commissioned by Meat and Livestock Australia estimated annual costs in excess of $160 million and attributed this to a combination of lost productivity and treatments (B.AHE.0010). Typical strategies used to control the incidence and severity of tick and tick borne disease are genetic improvement, chemical control, vaccination and management practices. A search of the patent literature over the last 10 years largely confirms the focus on these control strategies but identifies the occasional unconventional candidate. A breakdown of the results revealed a total of 68 patents of which 55 patents describing potential novel acaracides, 6 for

vaccine antigens, 3 genetic loci that could be significant for breeding approaches, and one each for probiotics, novel detection method, dsRNA (a form of chemical control) and freeze spraying (Derwent Innovation Index). Chemical control approaches have been highly successful when susceptible populations of ticks are targeted but increasingly ticks are showing high levels of resistance to acaricides. This issue has driven the ongoing search for new actives as identified in the patent search described above. Further complicating matters for producers are withholding times that must be applied following chemical application (limiting sale and movement of animals) and community concerns with the potential for residue contamination of foods and the environment.

Genetic control strategies are focussed on selective breeding programs that seek to include cattle that are tick resistant and / or eliminate those that are highly susceptible. This is largely achieved in industry by an indirect method through use of pure Indicine or crossbred Taurine and Indicine animals, as the Indicine breeds are reported to carry 5-10 times less ticks than taurine breeds (Jonsson 2014). Variation of resistance level within breeds does occur but it is difficult to take advantage of this fact as ranking animals for this trait in high numbers is not logistically or economically feasible. The main limitation being the intensive nature of recording tick levels on cattle, which is achieved via visual assessment of the animal. The tick burden is quantified as a score or as specific numbers of parasitising engorged adult ticks. Measurement of larvae is even more difficult given their near microscopic size and preference for difficult to access areas of the animal, that can place observers in harms way. The heritability of these traits is variable, ranging from 0.13 to 0.64 (Jonsson 2014), and this is most likely because the response mounted is complex, involves multiple functional pathways each of which may contribute at variable levels dependent on the different environmental or tick challenge methodology used.

The nature of host resistance to parasites is complex and involves many pathways (Campino 2006). The culmination of these pathways is reduced numbers of ticks, reduced viability or production of tick eggs. Resistance achieved via immunity is composed of both innate and acquired responses (Piper 2009, Kemp 1976). Antibody has been shown to be important in some studies but recent focus has been on the significance of the cellular response (Piper 2009). Genetic association studies have reinforced the importance of these pathways by identifying genes that are known to function in development of immune responses or wound repair, such as RIPK2 (Porto Neto 2012). Behavioural responses such as grooming, which is mediated by licking are important (Verissimo 2016). Other structural features of significance for enhancing cattle resistance to ticks include colour, hair density, and skin thickness (Shyma 2015).

We suggest that recent advances in technology should facilitate development of automated approaches for quantifying tick loads on animals and that this could be a productive area for future research. It may also be possible to measure resistance indirectly through an associated trait. In this respect, blood based immune parameters provide a further option. We have recently reported the use of blood based parameters for identification of worm resistant sheep allowing animals to be ranked following a single blood test (Andronicos 2014). Confidence in the value of such tests is enhanced by the observation that test results correlate well with conventional methods of counting parasite load (WEC in the case of worms). Significantly these phenotypes are amenable to pooling studies which greatly reduce the cost of genotyping studies and the method has been devised in a manner that allows both genotype and phenotype to be collected from a single sample. Given the importance of cellular responses to tick resistance in cattle we believe that application of a similar

approach in cattle may have great value in defining a new phenotype that can be routinely measured.

Temperament

It is easy to recognize that cattle differ in their behavioural reactions, for instance, to humans and to isolation from a group. When a behavioural response is expressed consistently on multiple occasions and in different situations it likely reflects the temperament of the animal. Cattle were domesticated from a wild progenitor, the auroch, which was hunted for food by humans. For these animals, fear of humans would have improved their chance of survival. During the process of domestication cattle were unintentionally selected for docility (Larson & Fuller, 2014); however, it was not until the 1970s that attempts were made to quantify the temperament of cattle and objectively breed for temperament traits. A number of methods for measuring temperament were explored including escape attempts of an animal isolated in a yard, flight distance when approached, and restlessness when held in a crush (Fordyce *et al.* 1982). The advantages of a standardised and automated method for measuring temperament led to the development of flight time, which is the time in seconds it takes an animal to travel a distance of approximately 2 metres when released from a crush (Burrow *et al.* 1988). The trait is moderately heritable and EBVs for flight time are available through Breedplan for Brahman and Santa Gertrudis sires while EBVs for docility, measured as restlessness in the crush or when held individually in a yard, are available for Limousins.

The behavioural responses we recognise as reflecting the temperament of the animal are accompanied by physiological responses such as release of the stress hormones cortisol and adrenalin. These hormones influence energy metabolism. It is therefore not surprising that favourable correlations exist between docile temperament (eg slow flight time), faster growth rate in the feedlot, more tender meat, and lower incidence of dark cutters (Kadel *et al.* 2006). Favourable temperament is also associated with a reduced occurrence of disease during feedlot finishing (Fell *et al*. 1999) but is not associated with resistance to internal or external parasites. In one study conducted during an AI program, more cows with a docile temperament were identified as in oestrus than cows with a poor temperament (reviewed by Haskell *et al.* 2014).

A second change in behaviour that is thought to have occurred early in the process of domestication was an increased capacity of cattle to habituate to the presence of humans and being handled (Wilkins *et al.* 2014). Whereas temperament is recognised by the consistency of a behavioural response over time, habituation is the change in response as the animal becomes accustomed to handling and to a new environment. A capacity to habituate underpins the training procedures used at weaning to teach young cattle to lead and move as a mob (Tyler *et al*. 2012). It has been proposed that genetic variation between animals in their capacity to habituate could be a valuable trait for selection (Wechsler & Lea, 2007); however to date, standardised tests for quantifying the capacity to habituate have not been developed. Further exploration of the genetics of habituation and its association with resilience of animals to environmental challenges is warranted.

Immune competence

Unfavourable genetic correlations exist between production traits and the incidence of many common diseases in livestock (Rauw *et al*. 1998). For example, the genetic correlation between milk production and the incidence of mastitis in dairy cattle has been estimated at between 0.15 to 0.37

(Lyons *et al*. 1991; Uribe *et al*. 1995; Van Dorp *et al*. 1998) and selection focussed on high productivity in pigs has led to an increase in susceptibility to stress and disease (Prunier *et al*. 2010). Such findings suggest that selection for production traits with little or no emphasis on health and fitness traits has the potential to increase the incidence of disease in livestock production systems.

The immune system is composed of tissues, cells and molecules which work together to protect the host animal against disease. Effective host defence is reliant on the immune system's ability to detect a wide variety of agents, to distinguish whether such agents are part of the body or foreign (self versus non-self), to determine whether non-self agents are commensals or threats, and to eliminate the potentially infectious agents or pathogens. Livestock, with the exception of those raised in specialised facilities, are exposed to a myriad of pathogens on a regular basis. Such pathogens possess an inherent ability to evolve rapidly, and as a consequence, adapt quickly to changes in the environment, and continually develop new strategies to avoid detection and elimination by the host's immune system. To detect and eliminate pathogens, the immune system has developed a diverse range of defensive responses that work together to protect the host. Immune competence can be considered as 'the ability of the body to produce an appropriate and effective immune response when exposed to a variety of pathogens'.

Animal health can be improved through both targeted management practices and the implementation of genetic selection strategies aimed at breeding animals with improved immune competence. In combination, these approaches have the potential to dramatically improve animal health. Health and welfare are intimately linked and therefore improving animal health is expected to result in improved welfare outcomes for livestock. The concept of breeding for 'general' disease resistance was first proposed by Wilkie and Mallard (1999) and has been used successfully to reduce the incidence of disease in pigs and dairy cattle (Mallard and Wilkie 2007, Mallard *et al*. 2014). This approach combines measures of both antibody-mediated immune responses (AMIR) and cell-mediated immune responses (CMIR) to assess 'general' immune competence (Figure 2). Extra- and intra-cellular pathogens are most effectively controlled by AMIR and CMIR, respectively, therefore individuals identified as having a balanced ability to mount both types of responses are expected to exhibit broad-based disease resistance. Based on this concept, Mallard *et al*. established a protocol to assess immune competence in dairy cattle which has enabled genetic selection strategies, aimed at breeding animals with enhanced 'general' disease resistance, to be developed and implemented in industry. We are currently developing a similar testing protocol, based on a different set of antigens to those used by Mallard, to assess 'general' immune competence in *Bos Taurus* beef calves in Southern Australia during yard weaning as part of a joint Meat & Livestock Australia and CSIRO funded project. As part of the project we are investigating the potential for genetic selection, aimed at improving 'general' immune competence, to reduce the incidence of disease in Australian beef cattle with a particular focus on reducing bovine respiratory disease (BRD) incidence in the feedlot environment.

Following extensive research to validate the benefits of breeding for improved 'general' disease resistance in dairy cattle, the global breeding company Semex Pty. Ltd. are now marketing semen from sires with estimated breeding values for immune competence (Mallard *et al*. 2014). Such advances are allowing dairy producers to place direct selection emphasis on traits aimed at improving the health and welfare of animals in their herds. We propose that the development of immune competence testing protocols specific for beef cattle in Northern Australia will allow beef

producers to select animals with improved general disease resistance, improving the health and welfare of cattle in their herds.

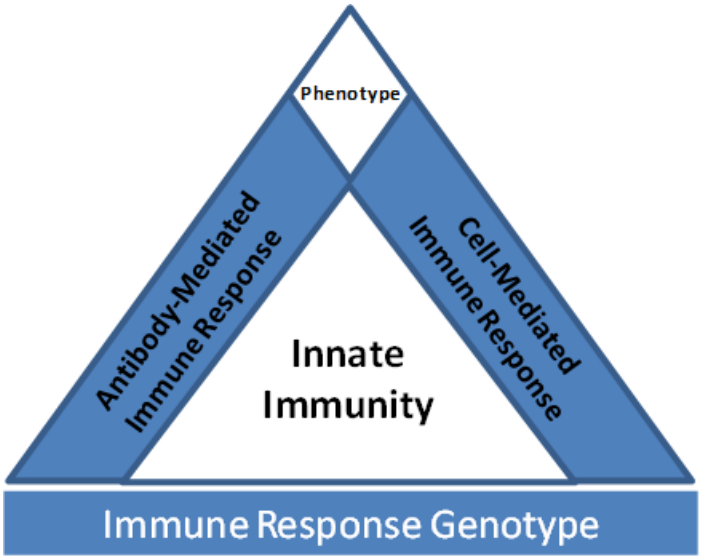

Figure 2. Genetic variation in the ability to resist disease is due to a large number of additive genetic effects which together regulate innate and adaptive immune responses (Source: adapted from Wilkie and Mallard 1999)

Summary

Future development of a resilience selection index specific to Northern Australia beef cattle will allow Northern cattle producers who are aiming to improve the resilience of their herds to make genetic gains in resilience traits. If improved resilience is correlated with an improved ability to cope with the challenges imposed by the feedlot and live export environments, feeder and live export cattle which are the progeny of high resilience indexing sires are expected to attract a premium for cattle producers.

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9.3 Appendix C

Selection for immune competence in beef breeding programs modelled on potential reductions in the incidence of bovine respiratory disease

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Abstract

Livestock industries are expected to intensify as land resources for agricultural production decline and global demand for animal protein increases. As a consequence, strategies aimed at sustainably improving the health and welfare of livestock will be critical to the future of our livestock industries. This study has made a first attempt at modelling the potential benefits of incorporating measures of immune competence in beef cattle breeding programs with the aim of improving general disease resistance, and as a consequence animal welfare. This study explores a variety of selection strategies and estimates their potential economic benefits based on data stemming from the dairy industry. Results demonstrated that the estimated heritability and predicted relationship between immune competence and growth traits strongly affect the potential gains which can be expected in immune competence and also overall response to selection. The economic values used in this study were conservative, suggesting that higher selection genetic responses and dollar returns are possible. For more accurate predictions, it will be crucial to obtain genetic and phenotype parameters for immune competence and correlations with other traits specifically for beef cattle. Research is currently underway to determine such parameters for beef cattle. The study also emphasises the need for robust economic values for traits, such as immune competence, where potential economic benefits of the traits are not just purely driven by the cost versus profit of the product, but also strongly influenced through public perception of the industry.

Introduction

Bovine respiratory disease (BRD) is the most common disease encountered in Australian feedlots, causing significant economic losses and animal welfare issues. It has been estimated that BRD costs the Australian feedlot sector in excess of $40 million annually, with losses estimated at up to $20 per head (MLA Project AHW.087). Bovine respiratory disease is a complex, multi-factorial disease caused by a variety of infectious agents and is most prevalent in cattle during periods of heightened stress such as the initial six weeks spent acclimatising to the feedlot environment. Commercial vaccines have been developed to protect cattle against particular agents contributing to the BRD disease complex, however providing protection against the full complement of potential BRD causing agents and achieving protective responses in all vaccinated animals is difficult to achieve. Strategies, aimed at reducing the incidence of BRD in Australian feedlots, are required to complement BRD vaccination programs.

The establishment of a protocol to assess immune competence in dairy cattle has enabled genetic selection strategies, aimed at breeding animals with enhanced ‘general’ disease resistance, to be developed and implemented in industry (Wilkie and Mallard 1999). This approach combines

measures of both antibody-mediated immune responses (AMIR) and cell-mediated immune responses (CMIR) to assess 'general' immune competence. Extra- and intra-cellular pathogens are most effectively controlled by AMIR and CMIR, respectively, therefore individuals identified as having a balanced ability to mount both types of responses are expected to exhibit broad-based disease resistance. A similar testing protocol, based on differing antigens, to assess 'general' immune competence in beef calves during yard weaning is being developed as part of a joint Meat & Livestock Australia and CSIRO funded project (Hine *et al.* 2014). Currently, the potential for genetic selection, aimed at improving 'general' immune competence to reduce the incidence of disease in Australian beef cattle with a particular focus on reducing BRD incidence in the feedlot environment, is being investigated.

The beef industry is actively working towards improving the health and welfare of animals in their production systems. Including immune competence in beef breeding objectives is expected to promote improved health and welfare through improving general disease resistance. It is hypothesized that combining selection for important production and reproduction traits with selection for health and fitness traits, such as enhanced 'general' immune competence in a selection index will enable beef cattle producers to breed highly productive animals with an enhanced ability to resist disease challenges encountered in their production environment. Such strategies are expected to result in significant long-term economic gains for producers through reduced disease treatment costs, reduced reliance on the use of antibiotics to treat disease, decreased production losses, reduced processing penalties, improved health and welfare outcomes for animals, lower mortality in the herd and improved consumer confidence in products of the beef industry.

In an effort to predict the potential benefits of incorporating selection for 'general' immune competence in breeding programs, hypothetical selection index scenarios have been modelled drawing on available information from the dairy sector.

Material and Methods

Breeding objective traits and selection criteria

A selection index can be used to investigate the effect of including novel traits in breeding programs. It consists of two main components. The first component is called "breeding objective", includes traits that drive profit and targeted to be improved through genetic selection. The second component is called the selection criteria and includes traits that can be routinely measured ("selection criteria") to inform the breeding objective traits. In some cases if the breeding objective trait is easy and cheap to measure, it also acts as the selection criteria for that trait. An example of such a trait is live weight. However, for breeding objective traits that are difficult to measure, correlated traits can be used as selection criteria to inform the breeding objective trait. For example, marble score can only be obtained at slaughter. To inform marbling score as a breeding objective trait, intra muscular fat content as assessed at scanning of live animals is used as a correlated selection criteria trait.

For this study a simplified breeding objective for a beef cattle stud operation that is selling bulls to commercial producers of feeder cattle (seed-stock producer) was defined based on three breeding objective traits which characterise growth, reproduction and carcase quality. Growth is represented

by sale weight (SW), which relates to live sale-weight at 17 months of age. Reproduction is represented by cow weaning rate (CWR), which relates to percent of cows that wean a calf from the total number of cows mated. This is calculated as annual percent pregnant x (1 – reproductive waste) (Fordyce et al. 2014). Carcase quality is represented by marbling score (MS). Marbling score is a visual beef quality grading system, scored from 0 (low marbling) to 9 (highly marbled), referring to the visible fat between muscle fibres in the rib eye muscle (AUS-MEAT Limited 2010). Immune competence (Immuno) was included in the breeding objective and represents a combined measure of an animal's ability to mount both antibody-mediated and cell-mediated immune responses (Hine *et al*. 2011).

Immuno was also measured as selection criteria. Other selection criteria traits included live weight measured 200 and 400 days of age (WT200 and WT400) and intra muscular fat (IMF) assessed on live animals using ultrasound scanning of the rib-eye between the 12th and 13th rib. Traits and their phenotypic and genetic parameters, including economic values for the breeding objective traits are summarised in Tables 1 and 2. Weight at 200 days and WT400, IMF and Immuno were recorded on the selection candidates themselves, their sires, their dams and their half-sibs. Number of records from the different information sources are shown in Table 1. It was assumed that each sire was mated to 50 females and 40 of these half-sibs would be measured for selection criteria. Marbling score is not recorded, but informed through IMF.

Table 1. Breeding objective traits (BO) and selection criteria (SC), their abbreviations and units, and the number of records collected on the selection candidate, its dam, sire and half sibs

Trait	Abbreviation	Unit	BO	SC	Information sources*			
					Own	Dam	Sire	Half sibs
Sale-weight	SW	Kg	Yes	No	0	0	0	0
Cow weaning rate	CWR	%	Yes	No	0	0	0	0
Marbling score	MS	Score	Yes	No	0	0	0	0
200 day weight	WT200	Kg	No	Yes	1	1	1	40
400 day weight	WT400	Kg	No	Yes	1	1	1	40
Intramuscular fat	IMF	%	No	Yes	1	1	1	40
Immune competence	Immuno	stddev	Yes/No	Yes/No	1	1	1	40

*Information sources are in relation to the selection candidate

The economic values for the breeding objective traits, heritabilities and genetic and phenotypic parameters for SW, CWR, MS, WT 200 and 400 and IMF were adopted from Archer *et al.* (2004). Parameters for Immuno and its relationships with other production traits were estimated based on studies in dairy cattle which have estimated genetic parameters of general immune competence (Thompson-Crispi 2012 and Thompson-Crispi *et al*. 2012). Some of the traits used in this study were not represented amongst the published information, and therefore assumptions had to be made. For example, genetic correlations between general immune competence and four reported reproductive traits (gestation length in heifers and cows, calf survival and calf size) were low and positive (ranging between 0.12 and 0.17) with one value low and negative correlation at -0.13 (Thompson-Crispi 2012). Consequently, it was assumed that Immuno and CWR have a low and positive correlation as was reflected in the majority of the dairy cattle estimates. Similar assumptions were made for other traits where published information was not available. The economic value for Immuno was based on

information from the Canadian Dairy industry, where estimated breeding values for general immune competence are available for sires whose semen is marketed by Semex Pty. Ltd. (Mallard et al. 2014). It has been demonstrated that progeny from high immunity sires (being one standard deviation or more above the mean for antibody and cell-mediated immune responsiveness) had 25% fewer incidences of calf pneumonia (Mallard *et al*. 2014).

For the purposes of this project it has been assumed that a similar reduction in BRD could be achieved in beef cattle in the feedlot environment which are progeny of high immunity beef sires. The economic value for Immuno used is this study is flexible and can be tailored to different feed lot systems based on their annual turn-over of occupancy to account for the increased incidence of BRD expected to be associated with increased turn-over.

Economic value ($/per year) = Cost of BRD per head x % reduction in BRD incidence expected in high immune competence animals x annual turn-over (1)

The annual cost associated with BRD has been estimated to be $20 per head (MLA Project AHW.087) and a 25% reduction in BRD incidence was assumed as outlined above. In this study, the economic value was derived for a feed lot operation with an annual turn-over of three times capacity. Based on these assumptions a 25% improvement per phenotypic standard deviation would be valued at $5 per feedlot occupancy. This results in an economic value of $15 per year for a feedlot system where occupancy is turned over 3 times per annum. The economic value of $15 served as the most realistic estimate for immune competence in the selection index scenarios outlined below. However, because of the uncertainty of what the real economic values is, a sensitivity analysis explored economic values that were 25% higher ($18.75) and lower ($11.25) than what was assumed to be the most realistic value.

Selection index scenarios

Six different scenarios were modelled to explore the effect of including immune competence in beef breeding programs on selection response. The selection index scenarios and the abbreviations used to describe them throughout the text are detailed in Table 3. All indexes include the three major breeding objective traits SW, CWR and MS. For the first selection index, immune competence was included as a breeding objective trait, but not measured as a selection criteria, with Immuno informed by other correlated trait responses (Index1). The second index included Immuno as a breeding objective trait as well as a selection criterion (Index2). The inclusion of Immuno as a selection criterion adds another source of information, which increases index accuracy, and as Immuno in the breeding objective and selection criteria are genetically highly correlated is expected to increase the opportunity to drive genetic gains in this trait.

Different variations of Index1 and Index2 used a range of genetic parameters and economic values to explore various scenarios which either favour progress in immune competence or provide little opportunity to progress this trait. The sensitivity of selection responses were tested for Indexes 1 and 2. Index scenarios with genetic parameters that do not favour progress in Immuno used a low heritability of h^2 = 0.1 for Immuno and unfavourable genetic correlations between Immuno and liveweight traits (SW, 200WT and 400WT). These scenarios are labelled with a "↓" to depict unfavourable parameters. Scenarios that use a heritability of h^2=0.3 for Immuno and favourable genetic correlations between Immuno with liveweight traits are labelled with a "↑" to indicate

favourable parameters. To test the sensitivity of responses to the economic value for Immuno, it was varied between $11.25 ($), $15 ($$) and $18.75 ($$$) and labelled with the dollar signs as shown.

Table 2. Genetic standard deviation (σ_G), economic values for breeding objective traits (EV in $) heritability ($h^2$ in bold) and genetic (above the diagonal) and phenotypic correlations (below the diagonal) for breeding objective traits and selection criteria

Trait	σ_G	EV ($)	EV*σ_G ($)	SW	CWR	MS	WT200	WT400	IMF	Immuno
SW	19.29	0.81	15.60	**0.31**	--	--	--	--	--	--
CWR	7.27	0.93	6.76	0	**0.05**	--	--	--	--	--
MS	0.44	0.01	0.00	0	0	**0.38**	--	--	--	--
WT200	9.49	--	--	0.68	0	0	**0.18**	0.75	-0.60	-0.20, +0.20
WT400	15.45	--	--	0.90	0	0	0.75	**0.25**	0	-0.20, +0.20
IMF	0.34	--	--	-0.02	0.09	0.72	0	-0.01	**0.12**	0.12
Immuno h^2=0.1	0.32	11.25, 15, 18.75	3.60, 4.80, 6.00	-0.20, +0.20	-0.12	0.12	-0.20, +0.20	-0.20, +0.20	0.12	**0.10**
Immuno h^2=0.3	0.55	11.25, 15, 18.75	6.19, 8.25, 10.31	-0.20, +0.20	-0.12	0.12	-0.20, +0.20	-0.20, +0.20	0.12	**0.30**

Abbreviations: SW: Sale weight, CWR: Cow weaning rate, MS: Marble score, WT200: 200-day weight, WT400: 400-day weight, IMF: Intramuscular fat, Immuno: Immune competence.

Table 3. Description of selection index scenarios

	Immuno Index1		**Immuno Index2**			
Abbreviation	$$↓	$$↑	$↑	$↓	$$↑	$$$↑
Immuno included in*	BO	BO	BO/SC	BO/SC	BO/SC	BO/SC
Heritability						
h^2=0.1 (↓)	✓			✓		
h^2=0.3 (↑)		✓	✓		✓	✓
Correlations (WT/Immuno)						
negative (↓)	✓			✓		
positive (↑)		✓	✓		✓	✓
Economic value						
$11.25 ($)			✓	✓		
$15 ($$)	✓	✓			✓	
$18.75 ($$$)						✓

*BO=Breeding objective trait, SC=Selection criteria

Two variations of Index1 were modelled, both assuming an economic value of $15 for a unit of improvement in Immuno. The first variation assumed favourable genetic parameters for progress in Immuno (Index 1 $$↑) i.e. positive correlations with weight traits and moderate heritability. The second variation of the index assumed unfavourable parameters for progress in Immuno (Index 1 $$↓) with negative correlations with weight traits and low heritability.

Four variations of Index 2 were modelled. The correlations between Immuno and liveweight traits were either positive or negative and economic values varied between low, medium and high. The variations included Index 2 $↑, Index 2 $↓, Index 2 $$↑ and Index 2 $$$↑ (Table 3).

Herd parameters

For the purpose of this study a hypothetical Angus stud herd with 450 breeding cows (n_s) was used. The male and female generation interval (L_m and L_f), which is the age of sires and dams at birth of their selected progeny was 2 years of age. Each bull is mated each year to 50 cows, which determines the number of half-sibs that are available for measurement. The calving and survival rates were estimated at 90%. Each year 23 males and 90 females were used as replacements giving a selection intensity (i) for males of 1.69 (i_m) and for females of 0.88 (i_f). Seventy two bulls are sold commercially and used by those purchasers for three years with each bull producing 150 progeny. Therefore, each year bulls produced from this stud have an estimated total number of 10,800 commercial progeny (n_c).

Response to selection

The response to selection, per head per round of selection, for the multiple trait selection index was calculated for each of the selection index scenarios. Results reported include the standard deviation of the breeding objective (SD_{BO}), the genetic gain as trait and dollar responses per round of selection, the standard deviation of the index (SD_{Index}) which describes the total dollar response per head per round of selection, as well as the index accuracy (Acc) which is the ratio of SD_{index} and SD_{BO} and illustrates how well the breeding objective traits are described by the selection criteria. To calculate the genetic gain per year (R), the response per round of selection was multiplied by the selection intensities for males and females and divided by the generation interval. The genetic gain per year per head was used in further calculations for discounted profit.

Discounted profit and net profit value

The discounted profit and net profit values were calculated to describe the long term value of the genetic gains made at the commercial herd level. The annual returns in year y were based on the genetic gain in dollars per year, starting in year 2 when commercial progeny of a sire are being born. Annual costs included health treatments at $30 per head and $10 per head to measure immune competence where applicable. It was assumed that for immune competence testing all animals in the herd are measured once. A discount rate of 7% per year was applied to returns and cost to calculate the discounted return in year y. The annual discounted profit per year was calculated by subtracting discounted annual cost from discounted returns per year. The annual discounted profit for each of the selection index scenarios was summed over an 11 year period to obtain the net profit value (NPV), providing a measure of profitability.

Discounted $returns_y = [(R_y + R_{y-1})*n_c]/(1+\text{discount rate})^y-1$, with R_y= genetic gain in year y, n_c = number of commercial progeny (2)

Discounted $cost_y = ((\text{health cost} + \text{measurement cost})* n_s)/ (1+\text{disount rate})^{y-1}$, with n_s = head of cattle in stud herd, y = year (3)

Annual discounted $profit_y$= discounted $returns_y$– discounted $cost_y$ (4)

Net profit value (NPV) = $\sum_{y=0}^{11} discounted\ profit_y$ (5)

Results

The results from calculations using the different selection index scenarios described above are summarised in Table 4. The standard deviation of the selection index (SD_{index}, representing the total dollar response per head per round of selection) was generally higher for variations of Index 2 compared to Index 1, as a result of including Immuno as a selection criterion in addition to being a breeding objective trait. The standard deviation of the selection index increased with increasing economic values for Immuno. As expected, overall responses for Immuno were higher when favourable relationships with liveweight and higher heritability values were modelled. The lowest total dollar response, was found for Index1 $$↓ with the maximum difference to the most profitable scenario (Index2 $$$↑) being $5.08 per head per round of selection. Increases in total dollar response were realised when the additional selection response in Immuno was higher than losses in the other breeding objective traits, i.e. sale weight and cow weaning rate.

For Index 1 with favourable relationships between Immuno and liveweight (Index1 $$↑) a positive response for Immuno could still be achieved, despite the fact that Immuno was not included as a selection criterion. This was a result of correlated responses, which was a consequence of the responses achieved in in live weight traits. Consequently, if the relationships with live weight traits were unfavourable (Index1 $$↓) response in Immuno was unfavourable.

Table 4. Standard deviation of the breeding objective (SD_{BO}), of the index (SD_{Index}), Index Accuracy (Acc) and trait responses per round of selection (in $) for the breeding objective traits sale weight (SW), cow weaning rate (CWR), marbling score (MS) and immune competence (Immuno) used in selection index scenarios

	SD_{BO}	SD_{Index}	Acc	SW	CWR	MS	Immuno
Index1 $$↓	16.64	6.24	0.37	6.82	0.00	0.00	-0.58
Index1 $$↑	19.94	7.93	0.40	6.80	0.00	0.00	1.12
Index2 $↑	18.94	9.18	0.48	6.54	-0.30	0.00	2.95
Index2 $↓	16.63	6.40	0.39	6.77	-0.02	0.00	-0.38
Index2 $$↑	19.48	9.73	0.50	6.02	-0.32	0.00	4.03
Index2 $$$↑	21.01	11.32	0.54	5.99	-0.38	0.00	5.71

The results in Table 4 demonstrate that when relationships between Immuno and liveweight traits are unfavourable (Index 1 $$↓ and Index2 $↓), it is easier to achieve higher profit by putting more emphasis on sale weight as is reflected in the trait response for sale weight. However, with favourable relationships, the emphasis on Immuno increases and therefore responses, accompanied by little decreased response for sale weight. The annual net profit value (NPV, Figure 1) emphasises the same trends that were observed in the index responses per round of selection over an 11-year time frame. Index1 $$↓ and Index2 $$↓ had the lowest NPV and the positive effect of higher economic values for Immuno is highlighted in the increase in NVP (Index2 $↑, $$↑ and $$$↑) (Figures 1 and 2).

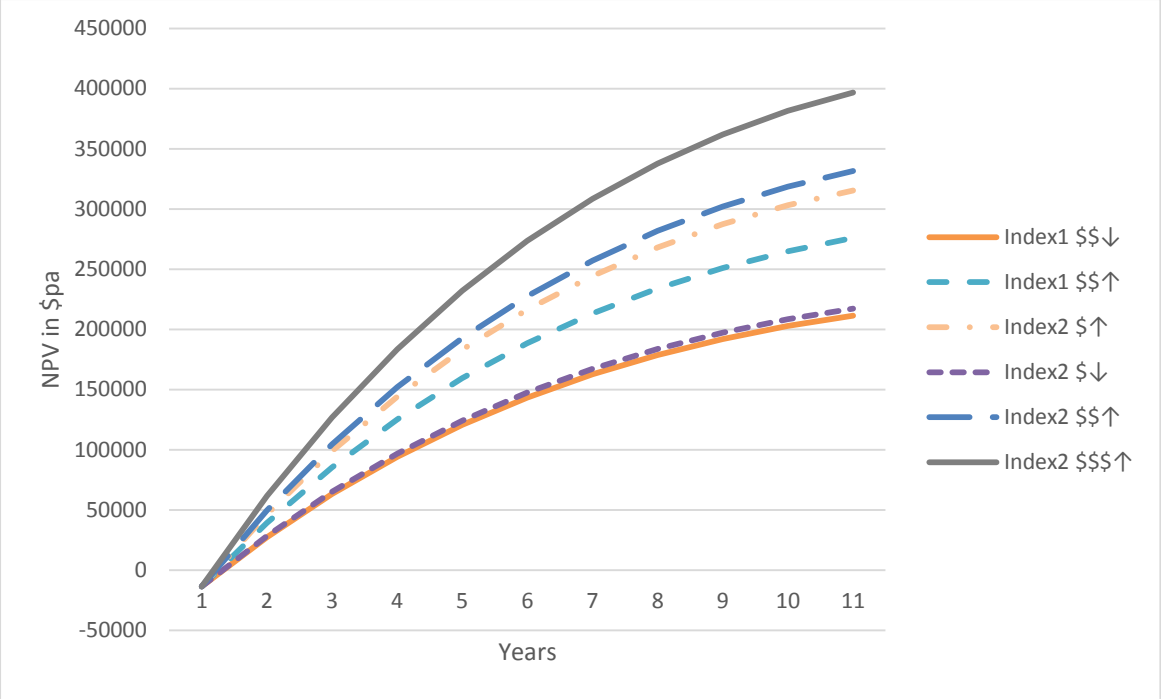

Figure 1. Annual net profit value (NPV) over 11 years for various selection index scenarios for a herd of 450 Angus breeding females

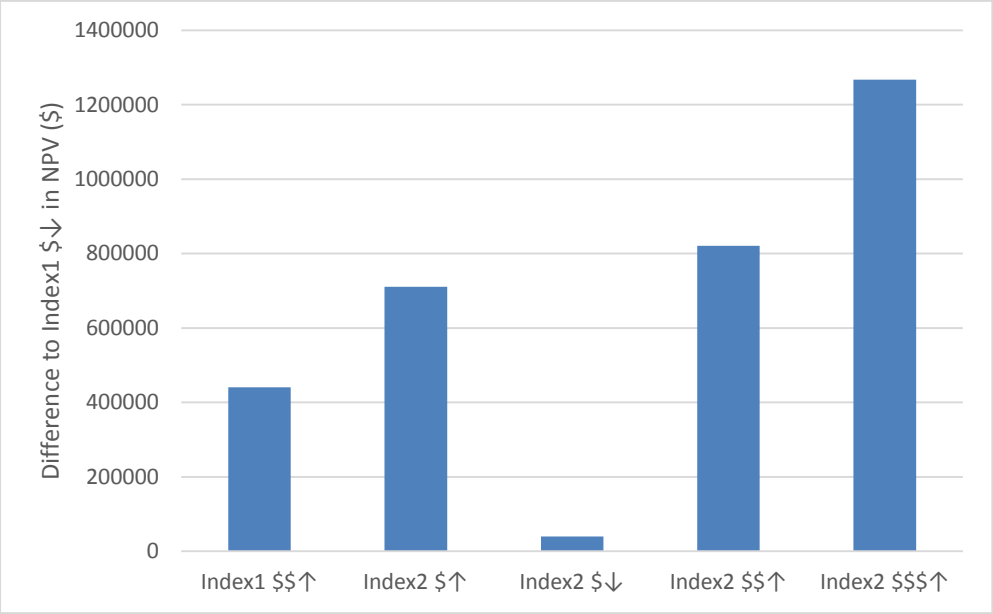

Figure 2. Difference in net profit value (total NPV in $) between Index1 $$↓ and other selection index scenarios

The total NPV over an 11 year time frame were compared to Index1 $$↓, which yielded the lowest total NPV (Figure 2). Index2 $↓ had only a slightly higher NPV compared to Index1 $$↓, highlighting that a small increase in profit can be gained by including Immuno as selection criterion even if the relationships with liveweight are unfavourable and Immuno has a low heritability. For Index2 $$↑, the results demonstrate that by including Immuno as selection criterion, the NPV can be increased substantially if relationships between liveweight and Immuno are favourable.

Discussion

Unfavourable genetic correlations exist between production traits and the incidence of many common diseases in livestock (Rauw *et al*., 1998). For example, the genetic correlation between milk production and the incidence of mastitis in dairy cattle has been estimated at between 0.15 to 0.37 (Lyons *et al*., 1991; Uribe *et al*., 1995; Van Dorp *et al*., 1998). Such findings suggest that selection for production traits in livestock with little or no emphasis on health and fitness traits has the potential to increase the incidence of disease in livestock production systems. One of the drives would have been the exponential increase in dairy cow milk production internationally over the last 50 years and a linear increase in the number of dairy cows (FAOstats, 2016). Based on this knowledge the Australian Beef industry is actively investing in research programs aimed at developing breeding strategies to improve the health, and as a consequence the welfare, of animals in their industry.

Animal health can be improved through both targeted management practices and the implementation of genetic selection strategies aimed at breeding animals with improved disease resistance. In combination, these approaches have the potential to dramatically improve animal health. Health and welfare are intimately linked and therefore improving animal health is expected to result in improved welfare outcomes for livestock. The concept of breeding for 'general' disease resistance was first proposed by Wilkie and Mallard (1999) and has been used successfully to reduce the incidence of disease in intensively farmed pigs and dairy cattle (Mallard and Wilkie 2007, Mallard *et al.* 2014). Following extensive research to validate the benefits of breeding for improved 'general' disease resistance in dairy cattle, the global breeding company Semex Pty. Ltd. are now marketing semen from sires with estimated breeding values for immune competence (Mallard et al. 2014). Such advances have allowed dairy producers to place direct selection emphasis on traits aimed at improving the health and welfare of animals in their herds. In the current study, the potential reduction in BRD incidence in feedlot cattle that could be expected as a result of incorporating measures of immune competence in selection indexes for beef cattle was predicted based on disease incidence data from dairy farms using sires with known EBVs for immune competence.

In the absence of known parameters, this study made a first attempt at modelling potential benefits of selection for immune competence in beef breeding programs. Although a lot of assumptions had to be made, this study explores potential benefits of breeding for improved immune competence by modelling extremes of high and low opportunity to improve the trait. The key outcome of the study was that response in Immuno can be driven more strongly, if it is used a selection criterion in addition to being included in the breeding objective. Adding Immuno to a selection index results in selection response in the trait at the cost of the responses in the other breeding objective traits due to competition for selection pressure. If relationships with other breeding objective traits are unfavourable and the heritability for Immuno is low, gains in Immuno were of insufficient value to compensate for the losses in the other traits. However, favourable genetic parameters for Immuno still compromised responses in other traits due to reduced selection pressure consequently being applied to those traits, but was offset through the gain in Immuno and the overall increase in the total dollar response. Accurate estimates of heritabilities for Immuno and correlations with other traits for beef cattle are necessary to make more informed predictions and are currently being generated. However the results of the current study provide first information on the expected trends.

The economic benefits of placing selection emphasis on a particular trait drives uptake by industry. Even though substantial responses could be achieved in Immuno in this study, it is safe to assume that the economic values for Immuno were conservative estimates, since they were only derived from the economic benefit in the feedlot sector and did not take into account reduced health associated costs in the stud operation. In addition increased consumer confidence in the beef industry as a result of improved animal welfare and reduced use of antibiotics is expected to significantly increase the economic value of improving general disease resistance of beef cattle.

Changing consumer confidence can have a significant effect on the profitability of livestock industries. Consumers are increasingly conscious of the health and welfare of the animals producing their food and are demanding the highest possible standards of animal welfare through purchasing choices. For example, the number of consumers opting to purchase eggs from free-range hens in preference to eggs from caged hens, based on welfare concerns, is increasing. This change in consumer preference has been the catalyst for dramatic changes throughout the egg industry and is evidence of the influence consumers can exert on farming practices. Consumers are also increasingly concerned with the use of antibiotics in food-producing animals. As a consequence, the practice of supplementing animal feed with antibiotics to prevent disease and promote growth is under increasing scrutiny and is unlikely to continue into the future. Therefore, breeding strategies aimed at improving the health and welfare of animals and reducing reliance on antibiotics to treat disease can be expected to also improve consumer confidence.

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