Breeding for improved disease resistance in ruminants

S.C. Bishop
The Roslin Institute and Royal (Dick) School of Veterinary Studies
University of Edinburgh
Midlothian EH25 9PS
United Kingdom

Abstract
Breeding for enhanced resistance to infectious disease is an effective means of improving the health, fitness and robustness of ruminant livestock. The most amenable endemic diseases to genetic selection are likely to be mastitis, bovine leukaemia, gastrointestinal (GI) parasitism, tuberculosis (TB) and paratuberculosis in cattle; and mastitis, GI parasitism and footrot in sheep. For bovine mastitis, selection on clinical signs or somatic cell count (SCC) is well established; however the longterm wisdom of decreasing SCC is often questioned. A solution may be to decompose SCC into baseline and response variables, along with a liability to become infected, and select for reduced liability. Genetic markers are often sought for mastitis resistance, but the complexity of the host-pathogen interactions may mean that individual markers are of insufficient value, requiring whole-genome approaches. Bovine TB is an emerging zoonotic threat, and a disease of major importance in some geographical regions. Studies are currently underway to assess options for breeding cattle for increased resistance. In particular, identification of cases and controls from herds with disease outbreaks may allow efficient genome scans. Paratuberculosis is a similar bacterial disease, but its prevalence is currently unknown and improved diagnostic tests are required before effective genetic approaches can be contemplated. For nematode resistance and footrot in sheep, readily measured indicators of relative resistance are available, and observed genetic gains may be larger than predicted by genetic theory, due to decreased contamination from selected animals. Although it has yet to be explored, this result is also likely to apply for several dairy cattle diseases. In summary, selection for increased resistance to specific diseases may have considerable benefits for cow health, welfare and robustness. However, this conclusion is dependent upon the disease prevalence, the higher the prevalence the greater the benefits of selection and the greater the impact on robustness.

Keywords: disease resistance, genetics, selection, epidemiology, ruminant

Introduction

This paper considers issues related to breeding cattle for improved disease resistance, as a means of improving robustness. General issues related to the importance of diseases and disease resistance, the benefits of genetically improving resistance and prioritising diseases are discussed. The paper will then explore options for breeding cattle for resistance to various important infectious diseases and draw parallels from experiences in sheep.

Background

The competitiveness of livestock industries in Europe is determined by productivity and quality values, with quality values including food quality, food safety and animal welfare. Sustainable and socially acceptable animal production methods and the prevention of human disease are also becoming more important. Infectious disease has impacts on animal production at all of these levels, as well as having a major impact on animal welfare and robustness. Disease costs

are estimated to account for 10-20% of turnover in developed countries. This figure does not take account of the devastating impact that outbreaks of exotic diseases, such as foot and mouth disease or bluetongue, have on the livestock industry and the wider national economy. Disease-related suffering of animals is increasingly recognised as an important welfare issue, and food-borne and other zoonotic pathogens pose a major risk to human health. Our ability to control many infectious diseases of livestock is also threatened by the emergence of pathogens resistant to antimicrobial and anti-parasitic drugs, as well as the stricter regulations governing chemical residues in animal products and the prophylactic use of antibiotics.

On a global scale, inadequacies in animal production are a significant contributory factor to food shortages and poverty in the developing world. With demand for animal products predicted to increase by 50% by 2020, mostly as a consequence of human population expansion in developing countries, this situation is likely to deteriorate. Disease is one of the most important constraints to animal production in these regions, with financial losses due to disease amounting to 35-50% of turnover. This situation largely reflects absence or unsustainability of disease control measures.

More effective and sustainable methods of disease control are required to deal with these problems, particularly with the emergence of drug-resistant pathogens. Recent advances in animal genomics and immunology and in the understanding of host-pathogen interactions provide new opportunities to develop more effective control strategies. The focus of this paper is the selection of animals for increased genetic resistance to disease, leading to healthier, more productive and more robust animals.

Benefits of selection for resistance

Benefits of selection for resistance depend upon the epidemiological context of the disease. A framework within which the benefits may be calculated was presented by Bishop and Stear (2003) and further elaborated by Gibson and Bishop (2005). Essentially the distinction must be made between endemic diseases, i.e. those whose presence is easily predicted, and epidemic diseases, i.e. those that can spread rapidly through the population. Epidemic diseases will be generally absent from livestock populations, therefore genetic selection for resistance would aim to reduce risks of epidemics, or their severity should an epidemic occur. For endemic diseases, the aim of a selection program is to breed animals that are more resistant to a disease that is predictable in its occurrence. As well as improved productivity, welfare and robustness, impacts may include a reduced abundance of the pathogen or parasite in the population or environment, leading to further benefits. This has been quantified for nematode resistance (Bishop and Stear, 2003) and footrot (Nieuwhof, Conington and Bishop, unpublished results) in sheep.

Independent of how an improvement in disease resistance is achieved, i.e. either by genetic or environmental means, the economic benefits of the improvement require careful consideration. A method to calculate these benefits was presented by Bennett *et al.* (1999), and illustrated for several endemic sheep diseases by Nieuwhof and Bishop (2005). Essentially, total annual disease costs may be estimated as the sum of annual losses in expected output and wasted inputs, annual treatment costs and annual prevention costs. Improving disease resistance doesn't necessarily reduce all cost categories proportionately, as the necessary prevention costs may remain unchanged. For example, in Great Britain, annual costs for nematode infections and footrot were estimated to be £84 million and £24 million, respectively. Whilst nematode costs are linear to the severity of infection, approximately half of the footrot costs are due to

preventive measures which are not influenced by marginal improvements in resistance. Therefore, the relative marginal benefit of improvements in resistance is greater for nematode infections than for footrot. Similarly for dairy cattle, economic benefits may not be directly proportional to the total disease costs.

Opportunities to Select for Resistance

To perform effect selection for disease resistance it is necessary to prioritise diseases; unless an attempt is being made to select for general disease resistance it is unlikely that it will be possible to simultaneously select for resistance to more than a small number of diseases. A method of prioritising diseases, based on aspects of disease importance, has been outlined us (Davies, Genini, Bishop and Giuffra, unpublished results). Six disease-based assessment criteria were defined: industry concern, economic impact, public concern, threat to food safety or zoonotic potential, impact on animal welfare and threat to international trade barriers, and subjective scores were assigned to each category for each disease according to the relative strength of available evidence. Evidence for host genetic variation in resistance was determined from available published data, including breed comparisons, heritability studies, QTL studies, evidence for candidate genes with significant effects and host gene expression analyses. Combined, these enable a qualitative but robust ranking of the amenability of diseases for host genetic studies and eventually for genetic improvement.

From these analyses, the top ranking dairy cattle diseases were, in order, mastitis, bovine leukaemia, gastrointestinal (nematode) parasitism, paratuberculosis and bovine tuberculosis. Many important epidemic diseases, such as foot and mouth disease, were lower ranked because of the difficulty of obtaining host genetic information and hence the associated lack of evidence for host genetic variation. It is interesting to note that these diseases are already the focus of much research. When compared across livestock species, mastitis was the second highest ranked disease overall, only beaten by *Salmonella* infections in chickens.

Opportunities in Cattle

Three examples are illustrated and discussed for dairy cattle, where genetic selection has been, or potentially could be, used to breed animals for increased disease resistance.

Mastitis

Mastitis, inflammation of the mammary gland, is usually caused by bacterial organisms such as *Staphylococcus spp.*, *Streptococcus spp.*, *Pseudomonas spp.*, *Mycoplasma spp.* and various coliforms such as *E. coli*. Mastitis incidence in the dairy industry has been estimated at 30% of cows per year, and each case has been estimated to cost between 150 to 300 euros per diseased cow. Therefore, it is a disease of considerable importance.

Selection for increased milk yield will generally worsen the incidence of mastitis, due to the unfavourable genetic correlation between milk yield and mastitis susceptibility. Therefore, efforts to reduce mastitis, or prevent its incidence from rising, are a part of most dairy cattle evaluations. Currently, selection to reduce the incidence of mastitis is based on udder conformation, somatic cell count (SCC) and mastitis infection history. SCC and clinical mastitis generally have low heritabilities, usually in the range 0.05 to 0.15. Mastitis resistance is probably due to structural attributes of the udder or teat, as well as immune responses. This is suggested by the observation that mastitis incidence is correlated with aspects of udder conformation (up to 0.37; Van Dorp *et al*., 1998) as well as SCC (ca. 0.7; e.g. Carlén *et al*., 2004, Heringstad *et al*., 2006).

QTL associated with mastitis resistance traits have been reported on almost all of the 29 bovine chromosomes, in a variety of populations and breeds including US, German and Dutch Holsteins, Finnish Ayrshire, Swedish Red and White, Danish Red and Norwegian Cattle (see reviews: Khatkar *et al*., 2004; Rupp and Boichard, 2003). This large number of QTL suggests that gene-assisted selection, using causative mutations underlying these QTL, may be inefficient if each of these mutations explains only a small proportion of the observed variation in SCC or clinical mastitis. Possibly a whole genome approach using a dense single nucleotide polymorphism array ('SNP chip'), i.e. genome-wide selection (Meuwissen *et al*., 2001), may be advantageous in this case.

However, there is also likely to be considerable benefit in redefining traits describing mastitis resistance, and this may also address concerns as to whether continued selection for reduced SCC is a long-term solution to mastitis. SCC is used as an indicator of mastitis, with high SCC values indicating that an animal is likely to be infected. However, SCC measurements on a group of animals comprise a mixture distribution trait describing baseline SCC in unaffected animals as well as elevated SCC in infected animals. The concern is that reducing SCC too far may reduce baseline SCC levels, hence an animals ability to respond to infection. In actual fact, the trait that is of interest to the breeder is liability to mastitis. Therefore, a rational aim when considering SCC data is to decompose it into baseline SCC values for uninfected animals, response SCC values for animals that are infected, along with the probability that a particular animal falls into one distribution and not the other. This concept was introduced by Odegard *et al*. (2005), and the quantitative genetic properties of such mixture distribution traits were formalised by Gianola *et al*. (2006). The primary selection criterion arising from this data decomposition is the liability of an animal to be affected by mastitis. The secondary question is whether to increase or decrease SCC; however, this question must be asked separately for baseline and response SCC. To answer this, it is necessary to calculate genetic correlations between SCC and mastitis liability, separately for baseline and response SCC.

The fact that mastitis is caused by different species of bacteria raises further issues of potential importance. Can these separate categories of infection be teased apart and is it beneficial to do so? Further, for the infectious (as opposed to 'environmental') sources of mastitis, further insight may be gained by assessing cow liability to mastitis in relation to the force of infection. For example, are there genetic influences on the order in which animals become infected, and do genetic effects alter as disease prevalence changes? If these effects exist, they may point to additional epidemiological benefits from selection for increased resistance. However, it may require considerable quantities of detailed data to assess these effects.

Bovine Tuberculosis

Bovine tuberculosis (TB) is an infectious and contagious disease of cattle caused by *Mycobacterium bovis*, characterised by the development of tubercles in any organ of the body. Aerosol exposure is the main route of infection, and wildlife reservoirs of infection are often implicated in the disease epidemiology. This is particularly the case in the UK, where badgers are a source of infection, and New Zealand where opossums are similarly implicated. Significant economic loss occurs due to the loss of stock. Bovine TB is zoonotic and may be transmitted to humans through unpasteurised milk and dairy products. Worldwide, annual costs to agriculture due to bovine TB are estimated around $3 billion (Garnier *et al*. 2003). In the UK, as an example, the costs incurred in attempting to eradicate TB in 2005 were £90 million

and it is estimated that could be as much as £1 billion between 2008 and 2013 (The Veterinary Record 2008).

Although published evidence of genetic variation in the host resistance to TB in cattle is currently weak (i.e. little has been published), substantial evidence exists in deer (Mackintosh *et al*., 2000), mice and humans (Hill 2006; Fortin *et al*. 2007). It would be biologically surprising if similar host genetic variation did not exist for cattle. However, current control measures, along with the associated data collection procedures, provide an opportunity to explore host genetic variation. At present, control is through routine skin testing of all cattle and immediate culling of any animal exhibiting a positive reaction. This information is recorded, at least in the UK. Therefore, combining information from databases containing TB test results and databases containing pedigree information provides the opportunity to quantify host genetic variation, at least for skin test reactions if not for TB resistance itself. This process has been successful in the UK (unpublished data), potentially enabling the ranking of bulls for TB resistance. Further, linking these data to milk recording data further allows relationships between TB resistance and performance to be explored.

SNP chip technology can also be used to assist in the identification of animals with increased resistance to TB. Similar to the identification of animals responding to routine skin testing, cases and controls can also be identified from high prevalence TB herds, defining cases on either skin test results or clinical signs of disease. These cases and controls can then be genotyped using a high density SNP chip, and overall genetic merit for TB resistance can be predicted, akin to the genomic-wide selection strategy outlined by Meuwissen *et al*. (2001). Currently (2008), this approach is being implemented using data recorded in Northern Ireland. Using these approaches, it is technically possible to provide both phenotype and genotype-derived estimated breeding values for TB resistance for dairy cattle bred in high TB risk areas.

Paratuberculosis

Paratuberculosis, or Johne's disease, is a bacterial infection of the gastrointestinal tract cause by *M. avium sub. paratuberculosis*. It is characterised by chronic diarrhoea, persistent weight loss, decreased milk production and eventually death. The disease is not treatable and vaccinations do not prevent infection. Therefore, economic losses are substantial in both the dairy and beef industries. Conflicting opinions have been published which indicate a potential link between the causative agent (i.e. *M. avium sub. paratuberculosis*) and Crohn's disease in humans (a severe and incurable inflammatory bowel disease), via the consumption of infected dairy products (Chiodini and Rossiter, 1996; Bakker *et al*., 2000).

Studies of infection status of cattle have indicated that susceptibility to paratuberculosis appears to be heritable, with heritability estimates ranging from 0.06 to 0.18 (Koets *et al*., 2000; Mortensen *et al*., 2004; Gonda *et al*., 2006). A QTL affecting susceptibility has been mapped recently in US Holsteins to BTA20 (Gonda *et al*., 2007). However, application of genetic approaches to paratuberculosis, similar to those used for TB, is hindered by difficulties in diagnosing infected or diseased animals. Diagnosis is a major difficulty, being time-consuming, expensive and prone to error, and is the rate limiting step in any study of host genetics using field data. Development of new diagnostic tests remains a critical area requiring further research investment; if this is successful then genetic approaches may well be successful for this disease as well.

Lessons from Sheep

Nematode Resistance

Nematode infections constitute a major disease problem to domestic livestock worldwide (Perry *et al*., 2002), with most grazing livestock being at risk from nematode parasite infections. Growing lambs with immature immune responses are particularly vulnerable to nematode infections, with even sub-clinical infections causing marked decreases in productivity (Coop *et al*., 1982 and 1985). Effective control of gastrointestinal nematode parasites is becoming difficult, mainly due to the well-documented evolution of drug resistance in nematode parasite populations (e.g. Jackson and Coop, 2000; Waller, 1997), which threatens sustainable sheep production throughout the world. Although nematode problems are generally less severe in cattle, they nevertheless constitute a problem in calves and lactating cows.

Genetic selection is increasing viewed as a means of helping to control nematode infections in sheep. Many studies have quantified within-breed heritabilities, usually using faecal egg count (FEC) as the indicator of relative nematode resistance (see summary by Bishop and Morris, 2007). In almost all cases FEC, once appropriately transformed, is a moderately heritable trait and one which responds to selection. Genome scans to detect QTL are now well advanced in many countries, again summarised by Bishop and Morris (2007). With the exception of a QTL near the interferon gamma locus on chromosome 3, a feature of these studies is the difficulty in detecting QTL that are consistent between studies. As with mastitis, selection based on either phenotypic data or whole genome results obtained using a dense SNP chip would appear to be the most promising ways of achieving genetic progress.

An important feature of selection for nematode resistance is the interaction between host genotype and disease epidemiology. As described in the Introduction, altering host genotype can also change the force of infection faced by the population. In this case, by creating a population of animals that is more resistant to infection the larval contamination on pasture will tend to decrease. This, in turn, will lead to reduced parasite challenge to all animals, furthering the benefits of selection. This phenomenon was quantified *in silico* by Bishop and Stear (1997 and 1999), with experimental verification provided by Gruner *et al*. (2002) and Leathwick *et al*. (2002).

The key lesson from nematode resistance is that the total benefits from selection can be larger than those arising directly from genetic change in the host, i.e. there may well be additional environmental or epidemiological benefits as well. This benefit would clearly arise for cattle selected for nematode resistance, but in principle it could also arise for other diseases as well, including TB and contagious mastitis.

Footrot

Footrot is a common cause of lameness in both lambs and mature sheep, and it is considered to be one of the major welfare problems in sheep. Footrot is a highly contagious bacterial disease caused by *Dichelobacter* (*Bacteroides*) *nodosus*. In addition to the welfare concerns, it is also a major cause of economic loss and currently it is estimated to have economic costs to the UK sheep industry of £24 million per annum (Nieuwhof and Bishop, 2005). Lameness in dairy cattle has some similarities as a disease, with severity being a function of both structural properties of the hoof and infectious agents.

Substantial genetic variation in resistance to footrot has been demonstrated by Raadsma *et al*. (1994), from deliberate challenges, and Nieuwhof *et al*. (2008), from field data. In particular,

Nieuwhof *et al*. (2008) found that data describing 'infected or not' was at least as heritable as data giving more detailed descriptions of the severity of infection, possibly because these data only describe the ~10% of animals that have clinical signs of disease and not the ~90% of animals that do not. A further finding from Nieuwhof *et al*. (2008) was that heritability of disease risk appeared to increase with flock disease prevalence, even when corrections were made for disease prevalence effects. This suggests that the greater likely force of infection in high prevalence flocks has allowed genetic variation in disease resistance to be more strongly expressed. Lastly, using modelling techniques, Nieuwhof, Conington and Bishop (unpublished results) demonstrated that total benefits arising from selection, i.e. genetic plus epidemiological, are usually larger than expected from genetic change alone, making selection for increased resistance an attractive option.

A key lesson from footrot is that hoof disorders, even when assessed using simple scoring systems are heritable traits which should respond to selection. When the disorder has an infectious component, responses to selection will be greater in higher prevalence herds or flocks and, once again, total gains may exceed those predicted by quantitative genetic theory alone.

Discussion and Conclusions

Infectious diseases are likely to affect the functional fitness and robustness of dairy cattle, with the impact depending upon the prevalence of the disease. Therefore, endemic diseases are likely to play a much greater role in robustness than sporadic diseases that pose epidemic risks. Of the major endemic diseases, mastitis is the most predictable and common disease with the greatest impact on cow health, welfare and robustness. Consequently, it has had the greatest research focus. However, previous methods of selecting for mastitis resistance have been somewhat clumsy and have ignored important aspects of the underlying disease biology. Therefore, it is likely that greater genetic progress can be made in terms of increasing resistance than has been achieved hitherto, due to a combination of more strategic data interpretation and use of new genomic technologies. Strategic data interpretation, i.e. separating concepts of baseline SCC, response SCC and liability to infection, in principle should enable genetic progress to be increased whilst at the same time addressing concerns about deleterious changes in animals' ability to respond to infection. In other words, decreasing mastitis liability whilst at the same time maintaining the ability of an animal to respond to infections (in general) is likely to be a key component of breeding more robust cows.

The other two dairy cattle diseases discussed, TB and paratuberculosis, are important for contrasting reasons. TB is a high risk disease with major impacts on animal welfare, robustness, etc, but only in specific and defined geographical regions. Therefore, breeding decisions can be specifically targeted to herds in those regions, for example avoiding the use of sires whose daughters are highly susceptible. In contrast, paratuberculosis is of unknown prevalence, with unknown geographical 'hot-spots', yet it potentially poses major constraints on the health, welfare and robustness of animals in affected herds. This makes it a high priority disease, however the initial research priorities should be focused towards diagnosis; only once satisfactory diagnostic tests are available can genetic solutions be effectively addressed.

Sheep provide valuable lessons for cattle in terms of breeding for resistance, particularly as sheep have a number of advantages over cattle in terms of obtaining data and testing breeding strategies. Their smaller body size, but larger flock size, means that data (apart from milk-related trait data) are more easily acquired than for dairy cattle, often in sufficiently large

quantities to enable within-flock selection. Further, breeders have greater opportunity to select for non-standard traits than in dairy cattle, hence flock-customised selection is feasible. A critical finding from the sheep studies is that there are often epidemiological benefits from selection for increased disease resistance that are realised in addition to the direct benefits predicted from genetic gain. These additional benefits make selection for increased disease resistance an attractive option under some circumstances. However, the corollary is that if the disease prevalence is low, then selection for resistance in that environment becomes inefficient with limited benefits, other than as an insurance against future disease outbreaks.

In conclusion, several opportunities exist to breed dairy cattle for increased resistance to endemic diseases. The opportunities are currently under-exploited and somewhat inefficiently implemented. A combination of techniques, i.e. interpreting existing data in more sophisticated ways, using new phenotypic information that is potentially available and applying new genomic tools, should enable considerably greater genetic progress in key traits. Further, under some circumstances, the benefits from genetic progress may be greater than anticipated from genetic theory alone. Decisions have to be made on the most appropriate diseases for genetic selection, however mastitis should remain a focus of attention and in some environments TB and paratuberculosis are likely to be important diseases as well. Increased resistance to these diseases will have multiple benefits on productivity, welfare and cow robustness. In particular, it should be possible to increase resistance to these diseases whilst simultaneously improving overall dairy cow robustness.

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