

Prediction of the benefits of selection for resistance to footrot in sheep

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

The University of Edinburgh

2008



Abstract

The aim of this thesis is to quantify the benefits of selection for resistance to an important sheep disease in Britain. Specific aspects addressed are *i*) the choice of the specific disease based on economic costs and potential savings from selection, *ii*) genetic parameters for the disease, such as the heritability (h^2) and the genetic and phenotypic relationships with production traits, *iii*) prediction of the response to selection on a trait that is measured in only two classes (healthy or diseased), accounting for variable exposure and prevalence, and *iv*) modelling of the combined effect of increased genetic resistance and reduced pathogen burden as a result of selection.

It is shown that the major sheep diseases in Britain, in terms of annual costs to the British sheep industry are gastro-intestinal parasites, footrot, Chlamydial abortions (enzootic abortions of ewes) and Toxoplasmosis, with estimated annual total (variable) costs of £84M (£84M), £24M (£12M), £20M (£1M) and £12M (£9M). A commercial service for selection against gastro-intestinal parasites already exists in Britain and elsewhere, and footrot is identified as an opportunity to make substantial savings to the industry. Footrot is a highly contagious disease, caused by the bacteria *Dichelobacter nodosus*, which is influenced by environmental factors. It affects the skin between the digits of a hoof resulting in lameness. Vaccines exist, but are expensive and have short protection periods.

Resistance to footrot has been reported to show additive genetic variability, and this is confirmed in this thesis. A total of 4340 Scottish Blackface on 5 farms and 726 mule ewes in 3 flocks were scored repeatedly for lesions that are indicative of footrot by a team at SAC. Results showed that in these adult sheep lesion scores are heritable, with the h^2 typically around 0.2 (for footrot 0.19 in SBF, 0.12 in mules; for severe footrot 0.26 and 0.19 respectively). This simple binary score turned out to be as effective as more complex criteria that considered the severity of lesions. Phenotypic correlations between successive scores in the same animals were generally close to 0, but genetic correlations were higher. The repeatability of footrot

lesion scores was very low, i.e. not much higher than the heritability. Therefore repeated measures or traits that combine a number of scores on the same animal over time are expected to be considerably more effective than single measurements. The heritability of resistance to footrot appeared to depend on the prevalence, with higher heritabilities at higher prevalences; in the SBF flocks with the highest prevalence (0.30) the h^2 for footrot was 0.36, compared to 0.06 in the flock with lowest prevalence (0.10). Additionally, 1199 weaned SBF lambs in 2 flocks were scored once; analyses showed the absence of a genetic component for lesions scores in these lambs.

The relationship between footrot and production was investigated using data from an Australian trial in which 1267 Merino sheep were artificially challenged with footrot and were weighed on a regular basis over two consecutive trials. A general theory was developed describing the relationship between the disease and weight gain, defining new traits such as the maximum weight loss as a result of disease. From data on animals that were not affected by footrot throughout each trial, normal growth curves were calculated and applied to affected animals to predict their growth had they remained healthy, so that weight loss as a result of footrot could be predicted. Animals with average footrot severity in the two trials suffered weight losses of 0.5 to 2.5 kg live weight, but most animals regained lost live weight later as footrot healed following vaccination. The estimate of the heritability of the magnitude of weight loss, adjusted for the severity of footrot was about 0.30 and 0.15 in the two trials. In trial 1, when animals were still growing, there was a strong negative correlation between weight loss and the weight at the start of a trial ($r_g = -0.67$), indicating that at equal severity of footrot, larger animals cope better with the disease. Selection for increased resistance to footrot is therefore expected to lead to a lower impact on weight in affected animals, and in general selection for improved resistance is predicted not to have any detrimental effects on growth.

Predictions of the response to selection generally assume that traits are normally distributed, or can be transformed to a normal distribution. Special theories exist for the prediction of the response to selection on a binary trait (e.g. healthy or diseased),

for the case that selection is based only on observations on individuals or the case where observations are available on groups of relatives, but not on a combination of both sources. In sheep breeding, this combination is very relevant, and a theory was therefore developed to predict the response to selection on a binary trait, combining own performance of selection candidates and information on relatives. The theory generally agreed well with stochastic simulations using a selection index. With a disease prevalence between 5 and 25%, a heritability on the underlying scale of 0.3 and other conditions as typically seen for British sheep, selection on the disease trait alone and including half sibs' information is predicted to half the prevalence in every round. This conclusion changed only little if account was taken of variation in prevalence among flocks or incomplete and varying exposure of animals to the disease. Unless exposure was below 40% (i.e. over 60% of susceptible animals would appear healthy and be misclassified as resistant), progress is still predicted to be over 75% of that with full exposure, so that considerable genetic progress can still be made.

Selection for resistance to an infectious disease not only improves resistance of animals, but also has the potential to reduce the pathogen challenge faced by contemporaries, especially when the population under selection is the main reservoir of pathogens, as is the case for footrot. A model was developed to describe the epidemiological cycle that animals in affected populations go through: susceptible, latently infected, diseased and infectious, recovered and reverting back to susceptible through loss of immunity, and the rates at which animals move from one state to the other, alongside effects on the pathogen population. The equilibrium prevalence was estimated as a function of these rates. The response to selection for increased resistance was predicted using a threshold model and epidemiological models with and without reduced pathogen burden. Models were standardised to achieve the same genetic response to one round of selection. The model was then applied to footrot. The only epidemiological parameters with major impacts for prediction of genetic progress were the rate at which animals recover from infection and the notional reproductive rate of the pathogen. There are few published estimates for these parameters, but plausible values for the rate of recovery would result in a response to

selection, in terms of changes in the observed prevalence double that predicted by purely genetic models in the medium term (e.g. 2-5 generations).

It is concluded that footrot is a disease of economic importance, with additive genetic variability. Selection for resistance can be effective if based on simple binary scores, especially if animals are scored repeatedly. The response to such selection can be predicted with a newly developed theory for binary traits, which also covers situations when exposure to infection is variable. Selection for resistance is expected to result in animals that can better cope with the disease, in terms of reduced weight loss. A new epidemiological model predicts likely responses to selection, showing a considerable additional decrease in the prevalence of footrot compared to purely genetic predictions. It is concluded that selection for increased resistance to footrot can be expected to be successful in reducing costs of the disease to the British sheep industry.

Declaration

I declare that this thesis is my own composition. I wrote the manuscript and all analyses were conducted by myself, unless stated otherwise.

Drafts of all chapters were reviewed by Steve Bishop and Bill Hill, and I followed their suggestions and incorporated their comments. Chapter 5 is based on a trial conducted under supervision of Herman Raadsma and he supplied data and helped with interpretation of results. Chapter 6 is based on data collected by a team at SAC led by Jo Conington. She and Lutz Bünger made valuable contributions to this chapter.

Publications related to this thesis

Nieuwhof, G.J. and Bishop, S.C. 2004. Opportunities for breeding for disease resistance in British sheep. *Proc. EAAP*, Bled, Slovenia.

Nieuwhof, G.J. and Bishop, S.C. 2005. Costs of the major endemic diseases of sheep in Great Britain and the potential benefits of reduction in disease impact. *Anim. Sci.* **81**: 23-29. (Based on Chapter 2)

Nieuwhof, G.J., and Bishop, S.C. 2005. Opportunities for breeding for disease resistance in British sheep. *Proc. BSAS*, York, p 49.

Nieuwhof, G.J., and Bishop, S.C. 2005. Selection for disease resistance as a quantitative trait. In *The Third International Symposium on the Genetics of Animal Health*, Iowa State University Ames, Iowa USA July 13-15 2005 (ed. S.J. Lamont, M.F. Rothschild, D.L. Harris). CAB International.

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Nieuwhof, G.J., Conington, J., Bünger L. and Bishop, S.C. 2008. Genetic aspects of resistance to footrot in sheep. *Proc. BSAS*, Scarborough.

Nieuwhof, G.J., Bishop, S.C., Hill, W.G. and Raadsma, H.W. 2008. The effect of footrot on weight gain in sheep. *Animal* **2**: 1427-1436. (Based on Chapter 5)

Nieuwhof, G.J., Conington, J., Bünger, L., Haresign, W. and Bishop, S.C. 2008. Genetic and phenotypic aspects of resistance to footrot in sheep of different breeds and ages. *Animal* **2**: 1289-1296. (Based on Chapter 6)

Nieuwhof, G.J., Conington, J. and Bishop, S.C. 2009. A genetic epidemiological model to describe resistance to an endemic bacterial disease in livestock: application to footrot in sheep. *Genet. Sel. Evol.* **41**: 19-30. (Based on Chapter 7)

Acknowledgements

When, in 1995, I joined the then Institute for Animal Research in Zeist (the Netherlands) Julius van der Werf asked if I was finally going to start my PhD. I was not, but he planted the idea in my head. It was not until 2003 when the British Sheep Strategy Council decided they wanted a PhD student to investigate the genetics of disease resistance in sheep that things came together. The Sheep Strategy Council asked me to draft a plan for this student and find a supervisor. The supervisor was easily found, but he did not think we would be able to find a student. When the MLC agreed for me to undertake this study alongside my day job and to co-fund it, the work leading to this thesis could start.

Many people have stimulated me to undertake this thesis, by setting an example (Pieter Knap, Egbert Knol), by being supportive (the late Mike Attenborough, Duncan Pullar), by pointing out the importance to the industry (Jonathan Barber, Sam Boon, the late Peter Johnson) or simply by challenging me that I could never complete a PhD in five years (Heather Leask, Huw Jones).

Certain parts of this thesis have only been possible in cooperation with other scientists. The data for chapter 5 were collected by a team led by Herman Raadsma. Jo Conington was in charge of the project that led to chapter 6, and she and Lutz Bünger have played an important role in the analysis and interpretation. Neil Hudson has been invaluable in accessing literature from all over the world (even some in foreign languages).

At the start I was told that completing a PhD is a matter of stamina rather than science, but I have to disagree. My supervisors have made this a worthwhile experience throughout. Their many comments on my ideas and early drafts have always been constructive. From Bill Hill I have learned to quantify ideas so that they become testable hypotheses. Steve Bishop has been a rich source of ideas and inspiration.

Mijn ouders moet ik bedanken voor de steun die ze me gegeven hebben gedurende mijn verschillende opleidingen, zonder welke ik nooit aan dit proefschrift had kunnen beginnen.

Combining a PhD with a young family is only possible with the unconditional support from home. Lieve Corlien, bedankt voor je steun en liefde. Nadia and Justin (I better address my children in English), you have known me as a student for most of your life, it is time to catch up on those lost weekends!

And, Julius, I am finally going to Australia.

Gert Nieuwhof

1 April 2008

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Chapter 1. General introduction

1.1 Background

Over the past decades British sheep breeders have successfully applied performance recording to genetically improve the efficiency of their flocks. Most emphasis has been on increased production in terms of growth rates and higher proportions of lean in the carcass in terminal sire breeds (Amer *et al.*, 2007), with the more recent introduction of maternal traits in the breeding goal in other breeds (Conington *et al.*, 2001; Mekkawy, 2008a,b).

Economic pressure and concerns from society are shifting emphasis to reduction in costs of production, increased food safety, improved animal welfare and lower carbon footprints (FABRE-TP, 2006). Improved resistance of sheep to disease can, in principle, contribute to all these new goals. It is encouraging therefore that there are many reports of host genetic variation in disease resistance, for a variety of diseases, as well as of a number of genetic markers or polymorphisms associated with variation in resistance (Axford *et al.*, 2000; Bishop, 2003; Archibald and Bishop, 2006).

Within practical British sheep breeding the most notable example of application of these opportunities is the selection for scrapie resistance based on PrP genotypes. While scrapie is only a minor disease in terms of costs to the sheep industry (Bennet and Ijpelaar, 2003), a National Scrapie Plan was launched in 2001 because at the time there were fears of links with BSE and hence food safety (Defra, 2003).

Since 2001 British breeders have had the opportunity to select for resistance to gastro-intestinal parasites based on faecal egg counts, which is an accurate estimator of worm burden and thus resistance (Nieuwhof and Evans, 2002). Similar programmes exist in Australia and New Zealand, but uptake seems limited given the apparent benefits. Genetic tests for other disease related traits in sheep are available in some countries; these include tests for facial eczema (a non-infectious disease), gastro-intestinal parasites and footrot.

Successful programmes to increase resistance to diseases are operated in other livestock species. In dairy cattle there is a widespread effort to reduce the incidence of mastitis, through selection against high somatic cell counts and clinical mastitis (Interbull, 2008), while tests for various genetic defects are also used routinely (Nieuwhof *et al.*, 2008). Poultry breeding companies use a marker test for susceptibility to Marek's disease (Nieuwhof *et al.*, 2008), while for pigs there are tests for resistance to *E. coli* (Dekkers, 2004).

A number of genetic markers for production traits have also been used successfully, such as tests for meat quality and stress in pigs (Fujii *et al.*, 1991) and double muscling in cattle (e.g. Dunner *et al.*, 2003) but these are beyond the scope of this thesis.

1.2 Aim

Against this background, the aim of this thesis is to identify opportunities for selection for increased resistance to infectious diseases in sheep and explore the benefits and consequences of such selection for the British sheep industry.

Given the existing data recording and breeding structures and proven track record of the technology, the focus will be on quantitative approaches using phenotypic observations and genetic relationships among relatives.

Compared to the standard production traits, such as growth, resistance to an infectious disease has a number of particularities:

1. The trait is expressed only if there is a pathogen challenge, and even then animals may be affected for only a limited period of time, depending on actual exposure to the pathogen, treatment, recovery and development of permanent or temporary immunity.
2. Diseased animals will affect contemporaries because they are infectious. Increased resistance can therefore lead to a lower pathogen challenge for

contemporaries, especially when the host species of interest (e.g. sheep) is the main source of pathogens.

3. Unless an indicator trait with a continuous scale exists (like faecal egg counts) disease status is scored in a limit number of classes, often only two (healthy/diseased).
4. The benefits of increased resistance may be difficult to quantify, as disease costs include preventive measures, treatment and lost production, and some measures may affect more than one disease. Financial values for animal welfare, food safety and environmental impact may be difficult to obtain.
5. There is a risk that pathogens adapt to the increased resistance in host species, thereby negating some of the benefits of increased resistance.
6. There may be a competition for resources between production traits and disease resistance, so that increased resistance may be at the expense of production traits.

Some of these issues, especially those to do with exposure, diagnosis and the potentially negative correlations with production, have led to questions with regard to the potential of breeding for disease resistance (Stear *et al.*, 2001). Many of these issues will be addressed in this thesis.

1.3 Outline

In chapter 2 of this thesis, costs of the major sheep diseases in Britain are analysed and gastro-intestinal parasites and footrot are identified as the diseases for which the greatest benefits would be obtained from increased host resistance. Since a breeding programme against gastro-intestinal parasites already exists, there is most potential in developing a system for footrot and the thesis further focuses on this disease.

In chapter 3 a general approach is developed to predict the response to selection on a binary trait (such as affected or not by footrot) and considering the importance of inclusion of scores on relatives. The effect of differences in prevalence among flocks and consequences of non-exposure of some animals in the population are investigated in chapter 4.

Genetic parameters for footrot are estimated in chapters 5 and 6. The issue of the relationship between resistance to footrot and growth is addressed in chapter 5, and the importance of repeated measurements and flock prevalence is considered in chapter 6.

The additional benefits of improved genetic merit for resistance to footrot through decreased environmental pathogen burden are quantified in chapter 7 by means of a novel genetic-epidemiological model.

Chapter 8 contains a general discussion followed by conclusions and guidelines for a practical breeding programme.

Chapter 2. Costs of the major endemic diseases of sheep in Great Britain and the potential benefits of reduction in disease impact

2.1. Introduction

Diseases of livestock receive increasing interest from both producers, who want to control costs, and policy makers interested in animal health and sustainability of livestock production. Current costs of diseases in sheep in Great Britain and, consequently, opportunities to reduce costs are poorly documented.

In a survey among farmers, shepherds, veterinarians and others, the Moredun Foundation (1997) identified internal parasites, sheep scab and footrot as important diseases in sheep. Various types of abortions also ranked high. Bennett and Ijpelaar (2003) estimated on-farm direct costs for eight contagious diseases, but excluded internal parasites, footrot and scab. In their study, highest costs were estimated for abortions. Annual on-farm costs of Chlamydial abortions were estimated at £20 M (excluding costs to human-health), and for toxoplasmosis at £12 M in Great Britain.

Whilst there is much data available on disease costs, these data are invariably incomplete and do not necessarily indicate the benefits of disease control. Total annual costs for medicines and veterinary expenses estimated in 180 ewe breeding flocks were £3.80 per ewe in 2002/03 (Promar International, 2003) and £0.48 per store lamb in 45 flocks, equating to about £64 M annually for the British sheep industry. But this ignores the costs of the farmer's labour and reduced performance. McLeod (1995), for instance, shows that in Australia the production losses due to gastro-intestinal parasite infestations in sheep are more important than the control costs, while for lice and blowfly the opposite holds. However, as pointed out by McInerney (1987), the potential costs savings from eliminating a disease do not equal the total costs of a disease. Important reasons are that the process of elimination will have its own costs, and preventive measures may need to be taken to control the disease re-establishing.

The aim of this study is to estimate the benefits of a reduction in the severity of the effects of a disease on individual sheep or in the incidence of a disease for GI parasites, footrot and sheep scab to the British sheep industry. First, the total costs of these diseases will be estimated using the method used by Bennett and Ijpelaar (2003) for other diseases. This approach also allows estimation of the benefits of reductions in disease incidence or severity of the effects. This thesis will not investigate how a reduction in disease incidence or severity can be achieved and maintained; it is simply assumed that this is technically possible.

2.2. Materials and Methods

In this section we will first describe the method of cost calculation as developed by Bennett *et al.* (1999b), followed by a short description of relevant cost factors for the diseases considered and the application of the model to the target diseases.

2.2.1. Methodology

The system of Bennett *et al.* (1999b) is based on actual probabilities of an animal contracting a disease and associated costs of prevention, treatment and reduced performance. The costs per animal are then multiplied by the number of animals at risk. The cost calculation framework is based on the formula:

$$C = L + T + P$$

where: C = total costs per year, L = annual loss in expected output and wasted inputs, T = annual treatment costs and P = annual prevention costs.

The components (T , L and P) are calculated by multiplying the number of animals that could be treated or are at risk with the probability of actually being treated or affected and the costs per animal. The number of animals at risk normally distinguishes between lambs and ewes, but could (if data were available) also be used to distinguish between breeds or production systems that are more or less at risk. Probabilities and cost estimates will be based on literature values and industry

expert opinion. The availability of this information will dictate the degree of refinement that is possible. Bennett's calculations are presented in Excel spreadsheets.

The division of costs into prevention, treatment and production costs, in principle, allows calculation of the effect of reduced disease incidence or severity of disease effects. This calculation can be done if we assume that a modest reduction will not affect preventive measures, but has a direct effect on treatment costs and production losses.

2.2.2. Relevant cost factors

A general description of GI parasites, footrot and sheep scab can be found in Martin and Aitken (2000).

Gastro-intestinal parasites are a continuous challenge to lambs which will only temporarily be suppressed by anthelmintic treatment. Reduction in performance is therefore a part of the costs of the disease, alongside costs associated with anthelmintic treatment (medicines and labour).

Footrot is a highly contagious disease affecting the skin between the digits of a hoof resulting in lameness. Vaccines exist, but are expensive and have short protection periods (Zhou *et al.*, 2001). Treatment includes footbaths, removal of the affected hoof and the use of antibiotics, but it may be necessary to cull affected animals (Egerton, 2000). Based on various surveys (Grogono-Thomas *et al.* 1998; Wassink and Green, 2001; Clements *et al.*, 2002) it is estimated that in Britain about 3% of lambs are affected annually, with an incidence in ewes about twice that in lambs (Clemens *et al.*, 2002). Recently, a new more virulent form of footrot was identified and called contagious ovine digital dermatitis (Codd) (Wassink *et al.*, 2003). Little is known about the current incidence and costs of Codd and it is therefore not included in these calculations.

Sheep scab is an allergic reaction of the skin to a mite, which is transmitted from sheep to sheep. Estimates of its prevalence suggest that 10% of UK flocks (Farmers Weekly, 2003a) or 30% of Scottish flocks are affected (Farmers Weekly, 2003b), but the within-flock incidence is unclear. An estimate in a single flock suggests that about 15% of the animals present are affected to the extent that their performance is reduced (Sargison *et al.* 1995). Scab, along with other ecto-parasites can be controlled by dipping and injections with endectocides. Dipping has lower costs but has environmental and human health implications.

2.2.3. Data sources and calculations

The first requirement in the application of the model is an estimate of the sheep population at risk. The number of ewes was based on the June 2003 census for Wales, Scotland and England, i.e. 16.4 million breeding ewes. The number of lambs reared annually was estimated based on an average litter size of 1.09 lamb per ewe present, which is commonly used by MLC to predict lamb numbers.

There are no national statistics for the diseases considered and the annual incidence is therefore based on surveys reported in the literature. Where more than one estimate exist, the average of a high and a low incidence was used, this was particularly the case for footrot. Sheep scab mainly occurs in winter, when about 30% of lambs born in that year are still present on the farm (Nix, 2003), hence only this 30% is considered at risk.

Estimates of physical losses in production as a result of a disease are limited and vary by disease. Where multiple estimates existed, the average of the low and high estimate was used. The extent of preventive measures and treatment of infected animals were again based on surveys. Where possible data were used from peer-reviewed scientific literature, but in a number of cases incidence rates, prevention and treatment regimes were poorly documented. In such cases estimates were based instead on views from specialists, i.e. expert opinion, either in direct consultation or as expressed in the farming press. Unit costs of production losses, medicines, labour and other items were taken from Bennett and IJpelaar (2003) where available, and

otherwise obtained from experts or the Farmpharmacy website (www.farmpharmacy.co.uk).

Estimates for reductions in the final weight of lambs due to GI parasite infestation range from 6.2 to 23% (Coop *et al.*, 1985; Mackay *et al.*, 1998). The costs for one anthelmintic treatment are estimated as £0.20 for medicines (based on <http://www.farmpharmacy.co.uk>) and £0.159 for labour (Bennett disease spreadsheets). Anthelmintic usage is based on one survey that indicated that lambs are treated 3.5 times and 70% of ewes once annually (Sargison and Scott, 2003). It is also assumed that gastrointestinal infestation of ewes does not significantly affect pregnancy and lactation.

It is assumed that ewes infected with footrot will have a reduced lamb output of 18%, and the same reduction is assumed for growth in lambs (based on estimates by Symons, 1978 and Stewart *et al.*, 1984). Based on various sources, the average cost for preventive measures are calculated at £0.85 per ewe (including any lambs present at the time). Likewise, treatment costs for affected individuals are £2.24 per lamb and £2.42 per ewe, including the costs of culling 3% of affected animals.

The calculations are based on the premise that infection with sheep scab leads to a 53% reduction in growth rate (Kirkwood, 1980) and a 10% loss in birth weight (Sargison *et al.*, 1995). It is also assumed that dipping and other preventive measures are taken on 54% of the animals, costing £0.43 per treatment (Liddel, 2001) plus labour (£0.15 per treatment) and investment in a diptank costs £0.10 per ewe per year (Nix, 2003).

As set out by McInerney (1987), the potential cost savings of eradication of a disease are not equal to the total costs. This is particularly true if only a small reduction in disease severity (e.g. level of parasite infestation) or incidence is achieved, for instance through improved resistance of host animals, because this will not automatically lead to a proportionate reduction in preventive measures. For the purpose of this study we will assume that a reduction in the severity of the effects of

the disease on individual sheep or in the incidence of a disease will only affect costs for treatment (including culling) and production losses (these can therefore be considered to be variable costs). Since the costs of prevention are not affected by a reduced severity or incidence, for our purpose these costs can be considered fixed. Benefits of a reduction in disease can then be expressed on a per ewe or per lamb basis, by dividing the total variable costs by the number of animals. It should be noted that this would be an average at industry level, and not apply equally to all flocks. For illustration, benefits of a reduction in disease impact are estimated for a 10% reduction in disease severity or incidence.

2.3. Results

2.3.1. Total costs

Table 2.1 shows that the total costs for gastro-intestinal parasites, footrot and sheep scab are estimated at £84, £24 and £8 million per annum, across the entire British sheep industry. The high costs for GI parasites are mainly for loss of growth with estimated annual costs of £64 M. The costs of anthelmintic treatment are estimated at £20 M.

The costs for footrot are more evenly spread over the various cost sources; with costs for lost performance and treatment of affected animals (including some culling) estimated at £7 M and £4 M respectively, while £14 M is spent on prevention, which includes footbaths and trimming.

For sheep scab a 15% proportion of animals (ewes and over-wintered (store) lambs) affected within the 10% of affected flocks, in combination with a 53% reduction in performance (based on Kirkwood, 1980) gives negligible annual costs of £0.8 M. This is in stark contrast with the costs of prevention, estimated at £7.5 M.

The range of costs figures in Table 2.1. is based on the most extreme estimates and reflects the expected minimum and maximum costs associated with each disease. These are further described in the Discussion section of this chapter.

Table 2.1 *Numbers of animals affected and annual cost components for gastro-intestinal parasite infestations, footrot and sheep scab in British sheep, classified by cost type.*

Parameter	GI parasites	Footrot	Sheep scab
Number affected (M)			
Ewes	-	1.0	0.2
Lambs	17.9	0.5	0.1
COSTS (£ M)			
Costs of growth reduction	63.7	1.5	0.8
Costs of reduced lamb output	-	5.3	-
Costs of treatment and control	20.3	3.6	-
Costs of prevention	-	13.9	7.5
Total costs	84.0	24.4	8.3
Range of costs	48 - 120	14 - 37	8 - 11

In Table 2.2 costs are broken down into the constituent cost factors; with lost income including costs associated with culling of ewes (e.g. for footrot this is £1.2M)). The table gives the range of costs based on combining all lowest and all the highest estimates for incidence, treatment and effects of the disease. For sheep scab only higher estimates were considered. From this table, it is clear that for GI parasites labour and medicines play a minor part in the total, whilst lost production makes up over three quarters of total costs. For footrot, lost income is still important but less so than medicine costs. For sheep scab, the costs of medicines (all preventive) comprise 60% of total costs. For none of the diseases is labour a major component of total costs.

2.3.2. Impact of reductions

Based on data published by Coop *et al.* (1982) and Coop *et al.* (1985), a near-linear relationship appears to exist between infestation level (measured faecal egg count, FEC) and reduction in performance. Assuming a linear relationship between FEC, performance and anthelmintic requirements, a 10% reduction in FEC levels would decrease costs by 10% or £8.4 M per annum.

Table 2.2 *Annual costs in £ M (range) for gastro-intestinal parasite infestations, footrot and sheep scab in British sheep, classified by cost factor.*

Parameter	GI parasites	Footrot	Sheep scab
Labour (£ M)	11.7	4.1 (3.3 – 4.6)	1.8
Medicines (£ M)	8.6	11.2 (8.3 – 14.7)	5.0
Structures (£ M)	-	1.0 (0.7 – 1.3)	0.8
Lost income (£ M)	63.7 (27 -99)	8.0 (1.8 -16.0)	0.8 (0.8 – 3.7)
Total costs (£ M)	84.0 (48 – 120)	24.4 (14.1 – 36.5)	8.3 (8.3 – 11.3)

For sheep scab the benefits of a reduction in incidence are less clear, because most costs are associated with prevention. A small reduction in disease incidence may not lead to a lower use of preventive measures, especially if this reduction is equally distributed over flocks. A 10% reduction in incidence would therefore only lead to cost savings of £ 80K per annum. If the small reduction were to be achieved by complete elimination of the disease from a small number of flocks (within the same geographic area and with adequate biosecurity) then, theoretically those flocks could cease preventive measures altogether, and national costs savings would be linear to the proportion of flocks no longer taking these preventative measures (assuming similar average flock sizes). However, dipping for sheep scab is aimed at a reduction of other ecto-parasites at the same time and this will make cessation of dipping less likely.

For footrot, costs are a combination of prevention, treatment and lost performance. A small reduction across flocks in the incidence of footrot would reduce treatment costs and performance loss, which total £10 M. And for instance a 10% reduction in incidence across flocks would therefore have national benefits of £1.0 M annually. If this reduction was achieved by eradication of the disease in certain flocks, considerable additional benefits could be had by reduction of preventive treatments, like footbaths, in these flocks, but in the UK climate eradication seems highly unlikely. Hoof trimming would still be required to some extent, even in the absence of the disease.

Table 2.3 shows the average costs for the three diseases. Total and variable costs are assigned to ewes or lambs and expressed per ewe and lamb. As described above, for small changes in disease impact it is the variable costs that will be largely affected by the decrease in disease impact.

Table 2.3 *Total and variable costs (range) for gastro-intestinal parasite infestations, footrot and sheep scab expressed per animal.*

Parameter	GI parasites	Footrot	Sheep scab
Average total cost per ewe (£)	-	1.32 (0.81-1.93)	0.22 (0.22-0.26)
Average total cost per lamb (£)	4.70 (2.66-6.69)	0.15 (0.05-0.27)	0.26 (0.26-0.39)
Average variable costs/ewe (£)	-	0.48 (0.13-0.87)	0.00 (0.00-0.04)
Average variable costs/lamb (£)	4.70 (2.66-6.69)	0.15 (0.05-0.27)	0.05 (0.05-0.17)

2.4 Discussion

This study has provided estimated costs of three major endemic infectious diseases of the British sheep industry, using the method described and applied to various other diseases by Bennett *et al.* (1999a) and Bennett and Ijpelaar (2003). This system is simple and flexible, but has a number of shortcomings, which do not invalidate it, but should be borne in mind when calculating benefits of alternative disease controls.

These include:

1. Costs are based on actual costs and include inefficiencies.
2. Effects beyond farm gate, for instance on market prices, are ignored (it may be expected that eventually consumers rather than producers will reap most of the benefits from improvements through lower prices for lamb).
3. Costs to animal welfare, human health (zoonoses) and the environment are ignored.
4. Disease-associated costs cannot always be attributed to one particular disease.
5. The total costs are not equal to the avoidable costs. For instance, eradication of the disease does not result in benefits equal to the current costs (McInerney, 1987).
6. Future developments are ignored (e.g. anthelmintic resistance).

Some of these shortcomings were adjusted in later applications by Bennett and IJpelaar (2003), especially by including estimates for human health and animal welfare costs. We have further tried to avoid inefficiencies, like certain anthelmintic treatments of ewes. In particular, the benefits of reductions in disease impact or incidence were estimated by only including lost performance and treatment cost, but not preventive measures. Benefits that have been ignored throughout are those associated with effects of disease on human health, animal welfare and the environment.

Prices for lambs vary from year to year and within a year, due to seasonality of production. Prices will also change if any improvements in disease resistance result in a significant increase in lamb output. Following Bennett and IJpelaar (2003) we have used a border price for lamb of £0.61 per kg live weight. The border price is based on global supply and demand, and is less sensitive to changes in British supply. For comparison, Amer (unpublished results) based on an analysis of live auctions in the UK between 1995 and 2000 calculates that within a season a negative trend exists of 7.6 pence per animal per day. Costs of production are 4 pence per animal per day (grass fed). At equal prices, the value of faster growth would be £0.26 per kg at a fixed age and at decreasing prices £0.74 per kg. This is based on healthy animals growing 0.156 kg per day and ignores decreased efficiency and carcass quality that would occur in animals affected by disease.

The highest costs for GI parasites are not medicine or labour, but lost performance. We used an estimate of 14.6% reduction in live weight, resulting in a cost of £64 M. This estimate is based on the average of the lowest (6.2% weight reduction, Coop *et al.*, 1985) and highest (23% reduction, Mackay *et al.*, 1998) estimates and the average is close to weight reductions estimated by Coop *et al.* (1985) of 12% and 17% for high infestation levels, with or without anthelmintic treatments. The range in weight reductions is very wide. This reflects the difficulty in measuring the impact of GI parasites on performance. Coop *et al.* (1982 and 1985) used lambs that were kept clean until the start of the experiment at 15 and 17 weeks of age and given exact doses of larvae. Mackay *et al.* (1998) observed effects within a system, so that the

challenge and treatments better reflect normal conditions, but they are also less well controlled. There is a difference in financial terms between the low and high estimate of £72 M annually. The highest cost estimate for GI parasites would therefore be £120 M, the lowest £48 M annually, about twice as much as the second most costly disease.

For footrot, the high estimate for the annual incidence was based on the prevalence in the month with the highest incidence. Since the average duration of an infection is less than a year, this would lead to an underestimate of the true incidence, which is the number of new cases occurring over a one-year period. On the other hand, when considering costs, the interest is mainly in those infections that lead to reductions in performance, be it growth or fertility. Preliminary analysis from a survey (Wassink *et al.*, 2001) shows that the distribution of the 'month with the most footrot' was spread very evenly over the year. It appears therefore that the risk of acquiring footrot is the same for ewes at any stage of the reproductive cycle and lambs of any age, including those stages and ages when reproduction and production are affected by the disease.

The lowest estimate for prevalence of footrot is 2% in lambs and 4.5% in ewes, high estimates are 4% and 8% respectively (Grogono-Thomas *et al.*, 1998; Wassink and Green, 2001). The extreme estimates for the impact on production are a reduction of 6.7% as the lowest (Symons, 1978) and 30% as the highest (Stewart *et al.*, 1984). Combining all low and all high estimates, the total costs for lost production are between £2 M and £16 M. Likewise differences between lowest and highest costs for prevention and treatment for footrot of £6 M and £2 M can be calculated. A combination of all the lowest estimates gives a lower bound to the costs of £14 M and similarly the upper bound costs are £37 M.

The incidence and effects of scab are poorly documented and those available most probably present an underestimate of the real costs. If we accept the estimate of 10% of flocks being infected, but with a much higher prevalence of infection within these flocks, e.g. 60% rather than 15%, this will quadruple the losses, but only from £0.8 M to £3.0 M. And this is based on a 53% growth reduction, considerably higher than

the estimate by Rehbein *et al.* (2000), who report a 39% reduction in growth. In absence of data, no estimates were included for losses of lambs, be it through non-conception, abortion or pre-weaning deaths, but this may not have a great impact. For instance, if 10% of the 1.5% affected ewes lose a litter, this would cost just £700 K per annum. It seems likely therefore that other important effects of scab exist that are yet to be well documented. If a new Moredun survey undertaken in 2004 confirms the high ranking of scab, this would warrant further investigations into the impact of this disease.

The classification of costs in different factors, like labour, medicines, structures and lost production, allows a closer analysis of the sensitivity of the results to factor costs. For instance, the costs of farm labour are difficult to estimate, and will depend on the possibilities of finding alternative use. The value may be zero if no alternatives are found, but can be considerable if labour is the limiting factor with regard to expansion of production. Table 2.2 shows that labour costs make up a small proportion of total costs, and uncertainties about its value are therefore of limited importance. In the case of GI parasites costs of medicines, which may be difficult to estimate due to the wide variety of products on offer, play a minor role, but for most other diseases medicine costs are important. As is clear from the estimates for GI parasites, and as discussed above for sheep scab, lost production can be by far the most important source of costs. However such costs are poorly documented and economic analyses of sheep diseases should therefore focus on improved estimates of production losses.

It is instructive to compare our estimated disease costs to those obtained by different methods. The total costs of prevention, treatment and control for the three diseases considered, i.e. total costs excluding lost production, are £51 M per annum. Bennett and co-workers ([http://www.apd.rdg.ac.uk/AgEcon/livestockdisease/sheep/Sheep disease spreadsheets.xls](http://www.apd.rdg.ac.uk/AgEcon/livestockdisease/sheep/Sheep%20disease%20spreadsheets.xls)) estimate the prevention, treatment and control costs for 7 diseases at £39 M per year, bringing the total to £90 M annually. This is somewhat more than the estimate of £64 M from Promar International (2003), a company that collects financial data, including the total costs for veterinary interventions and

medicines. An important part of the difference is farm labour, which Promar ignores, and is estimated at £17 M for the three diseases considered in this study and another £6 M for the diseases considered by Bennett and Ijpelaar (2003) (corrected for 2003 ewe and lamb numbers). We consider that Bennett and Ijpelaar (2003), by assuming a 24.5% vaccination rate overestimate the costs of Chlamydial abortion by £8 M annually. Taking this into account, it is estimated that £5 M of the annual costs suggested by Promar International could be attributed to other treatments and diseases, inefficiencies and costs that cannot be assigned to one particular disease, like flock health plans.

A broad ranking of the perceived importance of various diseases and health conditions was given by a survey undertaken by the Moredun Research Institute. The Moredun survey (Moredun, 1997) was conducted among 3303 members of the Moredun Foundation and the ranking was based on 972 responses to the question: 'Which of the following do you recognise as the five major threats to animal health and welfare?' Scores for each disease were calculated by weighting first ranking with 5, second with 4 etc. The highest ranking perceived threats were: sheep scab, footrot, anthelmintic resistance, Chlamydial abortion, pasteurellosis, parasites (internal), nutritional deficiencies and toxoplasmosis. The list of threats included 'anthelmintic resistance' and 'parasites (internal)' as separate categories, however these could be considered to be different manifestations of the same issue. The combination of these two would rank third in the most conservative approach (assuming the same people scored the two with similar ranks), or first if the respondents chose only one category and not the other.

The question asked in the Moredun survey used the word 'threats' and included animal welfare, this may lead to a different ranking from the purely economic approach used in this study and by Bennett and Ijpelaar (2003), and would probably include a risk factor. There is a general agreement of the importance of gastrointestinal parasites and footrot relative to Chlamydial abortion, toxoplasmosis and pasteurellosis. However, sheep scab ranks differently using the two approaches, ranking highest (or second highest) in the Moredun survey, but only seventh in

combined results from Bennett and Ijpelaar (2003) and the current work. One reason for this may be that, at the time of the survey, the prevalence of sheep scab had increased rapidly after the deregulation of dipping, and it may therefore have been perceived as more of a threat than costs alone would justify.

The secondary aim of this study was to ascertain potential cost savings from reductions in severity or incidence of the various diseases. This is different from the total costs of a disease, and should help to focus efforts on diseases with highest potential for cost savings. The actual mechanism of reduction is beyond the scope of this study, and consequently so are the costs associated with the technology used to reduce disease impact. However, it is essential that such costs are included before decisions are made.

Throughout, costs have been divided into preventive measures and costs of an animal actually having contracted the disease. Gastro-intestinal parasites affect essentially all grazing animals, and this is unlikely to change. Improvements would therefore need to come from lower worm burdens. The only available estimates suggest a linear relationship between worm burden and costs (and zero costs at zero worms), and a linear relationship was therefore assumed between FEC and costs. For the other diseases, reductions in the number of animals affected has to be the main goal, and as costs per affected animal are fixed this reduction gives a proportionate reduction in lost production and treatment costs. This type of disease is more amenable to eradication, especially at flock level, and the potential cost savings from eradication may therefore approach total costs, with the exception of the costs of eradication itself and continued efforts to stop reintroduction.

2.4.1. Conclusions

Of the sheep diseases considered, infestation with gastro-intestinal parasites had the highest estimated costs of £84 M per year (range 48-120 M per year). If the assumptions underlying the calculations are correct, cost savings that can be made are linear with infestation levels. The second most costly disease, of those investigated, is footrot with total annual costs estimated at £24 M (range 14-37 M). A

reduction in incidence of footrot will not have a linear response in benefits, because a proportion of costs are for preventive measures, and this will have to be maintained unless the disease is completely eradicated from certain flocks. For instance, a 10% reduction in incidence, spread equally across affected flocks, would lead to predicted annual savings of £1.0 M. There appear to be few direct economic benefits from small to moderate reductions in the incidence of sheep scab, because most identifiable costs are for preventive measures.

Chapter 3. Prediction of the response to selection on a binary trait measured in candidates and their half sibs

3.1. Introduction

Selective breeding has been applied successfully to many species and traits. The accuracy of selection and the genetic progress can be predicted if traits are normally distributed, such that regression equations are linear, or can be transformed to a normal distribution. For certain traits, like litter size or diseases, traits are scored in a limited number of classes and often only in two, for instance affected and healthy. An example of such a disease is footrot in sheep. In Chapter 2 it was shown that this disease causes important losses to the British sheep industry, even though prevalence is normally low at 5 to 10%. Since susceptibility to footrot is known to be heritable (Raadsma *et al.* 1994), there is opportunity to reduce the incidence of footrot through selective breeding. Nieuwhof and Bishop (2005a) estimated that in a multitrait selection programme, including the standard production and reproduction traits, the genetic progress from one round of selection in resistance to footrot would lead to annual savings of £2.7 M per year for the British sheep industry if applied by all breeders. Since they ignored the binary character of the trait this is probably an overestimate (Falconer and Mackay, 1996). At a low prevalence, limited information is available for effective selection on own performance, and the challenge is to combine observations on the candidates for selection with information on their relatives.

The potential for selection on binary traits can be calculated, as a first approximation, by ignoring the fact that the trait is discrete and assuming that the regression is linear. This prediction breaks down, however, increasingly as selection becomes more intense and the trait more highly inherited (McGuirk, 1989). An alternative is to use a threshold model, in which it is assumed there is an underlying normally distributed trait ('liability') and that there is a threshold value, above which the observed trait has one value (e.g. affected) and below it the other (e.g. healthy). Under this model, the regression of breeding value on phenotype or of offspring on parent is linear on the liability scale, and the response to selection on the observed scale can be obtained

from normal integrals. Robertson and Lerner (1949) and Dempster and Lerner (1950) developed this concept and showed the relationship between heritability on the observed scale and that on the liability scale.

For selection on own performance, the response can be predicted based on the heritability of the liability and the effective selection intensity (Falconer and Mackay 1996). The effective selection intensity depends solely on the proportion of candidates with the desirable phenotype (i.e. healthy) if only healthy animals are selected. If all healthy and some diseased animals are selected it is the average of the selection intensities in the two groups, weighted by the number of animals in the two groups.

Foulley (1992) extended the prediction of genetic progress to more general cases, illustrated for half-sib groups, assuming that true genetic merit and estimated breeding value for the trait have a joint normal distribution. The latter will clearly not be the case if a breeding value for a binary trait is based on only one or a few observations, but it will become an increasingly good approximation if there are observations on large sets of half-sibs.

In meat sheep breeding schemes, information will generally be available on a variety of relatives of both sexes, including parents, grandparents, full and half sibs, and the animal itself. While this should contribute to the accuracy of selection and genetic progress, predictions of genetic progress for this type of scheme have not been developed. The opportunities to increase resistance to disease by genetic selection, based on various sources of information and prevalence of the disease are investigated in this chapter, including the use of a selection index. A two-stage approach, in which initial culling is solely on the animal's own phenotype and subsequently information is available on the animals half sibs, is used to predict genetic progress.

3.2. Material and methods

3.2.1. Principles

Robertson and Lerner (1949) showed that the relationship between the heritability of a binary trait (h_{01}^2) and that of the underlying continuous trait or liability, assumed to have a standardised normal distribution (h_L^2), is approximated by:

$$h_L^2 = p(1-p)z^2 h_{01}^2 \quad (1)$$

where p is the prevalence of the binary trait and z is the ordinate of the standardised normal distribution corresponding to p . The term $p(1-p)$ is the phenotypic variance of the binary trait. The response in liability to selection on own performance R_L can be predicted based on the heritability and the selection intensity (i). In this case i depends on the selected fraction (f) relative to p , for instance the effective selected fraction f' is equal to $1-p$ if $f \leq (1-p)$. The consequent change in the prevalence can then be computed from the change in mean on the liability scale, assuming the threshold remains constant (e.g. Falconer and Mackay, 1996). In view of the non-linearity of offspring-parent regression on the all-or-none scale, this is usually a more precise prediction of genetic change than simply $ih_{01}^2[p(1-p)]^{0.5}$.

Foulley (1992) considered selection based on relatives' performance and showed that genetic progress R can be predicted as:

$$R^\pm = \Phi\{(\mu \pm i\rho h_L) [(1-i(i-\eta)\rho^2 h_L^2)^{-0.5}] - \Phi(\mu) \quad (2)$$

for the cases where selection is for increased (R^+) or decreased (R^-) prevalence, with $\Phi(\mu)$ being the cumulative distribution of the standardised normal distribution evaluated at the initial prevalence, η is the threshold for the standardised normal distribution corresponding to the fraction selected, i is the corresponding selection intensity and ρ is the accuracy of selection. The correction term $[]$ in (2) defines the impact of selection on variance in liability in the next generation. Foulley considered selection of sires on the performance of their half-sib progeny. In the current study, the half sibs, rather than their sires, are the selection candidates, and this can be accommodated in (2) by appropriate adjustment of ρ .

Falconer and Mackay (1996) show that for combined individual and sibs' performance the between family additive and phenotypic variation are rV_A and tV_P

respectively and the within family variations are $(1-r)V_A$ and $(1-t)V_P$, with r =relation between HS (0.25), t =the intraclass correlation, V_A = the additive genetic variance and V_P = the phenotypic variance. The accuracy of selection can then be calculated as $r_{IH} = h[1+(0.25-t)^2(1-t)^{-1}(n-1)\{1+(n-1)t\}^{-1}]^{0.5}$. For a binary trait $(1-t)V_P$ is only an approximation of the within family phenotypic variance which is equal to $p_w(1-p_w)$ with p_w being the within family prevalence. This variance is different in different families and if p_w varies a lot the term $(1-t)V_P$ will be only a poor approximation.

A pragmatic solution to this is to assume two-stage selection in which, first, healthy candidates are selected, and then additional information from relatives is used to distinguish amongst equal ranking candidates. Two-stage selection is, in principle, less effective than one-stage selection because some animals may incorrectly be excluded at the first stage.

For a normally distributed trait, the genetic variance in liability is reduced as a result of selection at the first stage by $i_1(i_1 - x_1)\rho_1^2$ (3)

and the response to selection $R = \{i_1\rho_1 + i_2\rho_2[1 - i_1(i_1 - x_1)\rho_1^2]^{0.5}\}V_A^{0.5}$ (4)

where x_j , i_j and ρ_j are the truncation point for selection, the selection intensity and accuracy, respectively, at stage j . The reduction in variance also changes the heritability in the second stage, with an effect on the accuracy ρ_2 .

For a binary trait, the term $i_1\rho_1V_A^{0.5}$ in (4) is replaced by the rules from Falconer and Mackay (1996) to account for selection on OP in the first stage. The second stage utilises (2) with the adjusted additive genetic variance according to (3).

Assuming that a selected fraction of f is required after two stages of selection, in the first stage all $1-p$ healthy animals are selected. The second stage then depends on the relative values of $1-p$ and f :

- 1) If $1-p = f$ then there is no second stage selection.
- 2) If $1-p > f$ then the second stage selection is among the healthy animals based on HS performance
- 3) If $1-p < f$ then the second stage selection is among the diseased animals based on HS performance

3.2.2. Simulation procedure

Properties of these prediction equations, and the degree to which they successfully predict accuracies of selection and selection responses, were explored by means of simulation. For this purpose, realistic animal populations were based on the typical situation for British lamb production breeding flocks. A family structure was recreated by simulation of sets of 6 flocks, each comprising 180 ewes having 180 lambs. In each flock a total of 60 ewes were mated to 3 rams that were also used in two other flocks (so-called reference sires), producing 60 lambs. The remaining 120 ewes were mated to 4 stock rams (30 each), producing 120 lambs. The ewes and the stock rams had the same number of recorded offspring in one previous year, but reference sires did not. As a result each animal had 59 paternal half sibs, this structure with groups of 60 paternal half sibs will be referred to as 60HS. In an alternative structure, ten times as many rams was used on the same number of ewes, so that groups of only 6 half sibs (6HS) were created.

The genotypic value of all animals was simulated firstly by random sampling of sire effects of the selection candidates from a normal distribution, $N(0, 0.25h_L^2)$. Progeny deviations for 60 half sibs per sire, were then sampled from a normal distribution, $N(0, 0.75h_L^2)$, assuming random and unrelated dams. A continuous phenotypic value P was obtained by adding an environmental component, $N(0, 1 - h_L^2)$ to give a total variance of liability of 1.0. A binary phenotype P_T was formed by establishing the threshold value T so that $\Phi(T) = p$ and assigning a value of $P_T = 0$ to all animals below the threshold (healthy) and $P_T = 1$ to those above (affected).

For the estimation of breeding values, binary phenotypes (P_T) were pre-adjusted for fixed effects, which were assumed to be only the mean flock prevalence, so that $P_T' = P_T - p$, i.e. $P_T' = -p$ for $P_T = 0$ and $P_T' = 1 - p$ for $P_T = 1$. Weighting factors were obtained from standard selection index theory, depending on the scenario using either own performance (OP), HS performance or both and the appropriate heritability (i.e. h_{01}^2), calculated depending on prevalence according to (1). Following Falconer and Mackay (1996) for OP the weighting factor was $b_{OP} = h_{01}^2$,

for HS $b_{HS}=0.25h_{01}^2n/(1+(n-1)0.25h_{01}^2)$ and for the combined selection, the weighting on the OP $b_{cOP}=h_{01}^2-r^2h_{01}^4(1-h_{01}^2)/(a-r^2h_{01}^4)$ and on the HS $b_{cHS}=rh^2(1-h_{01}^2)/(a-r^2h_{01}^4)$, with $a=V_{Pn}/V_P=(1+(n-1)t)/n$, V_{Pn} = the phenotypic variance of an average of n individuals and the common environmental effect among HS is ignored so that $t=rh_{01}^2$. Candidates were selected at random from amongst those with identical EBVs. Simulation of each set of flocks was replicated 1000 times with a given prevalence.

3.2.3. Parameters

The heritability of liability was set at 0.3; but a heritability of 0.15 was also investigated for a few scenarios to check the importance of variation in resistance. Prevalences for the disease ranging from 0.05 to 0.9 were assumed, and the selection response for the liability was investigated for selected fractions of 10, 25 and 50%. In all cases, animals of the current year's lamb crop that contribute to estimation of a breeding value were also candidates for selection.

3.3. Results

3.3.1. Accuracy of Breeding Value Estimation

The correlations between true and estimated breeding value (the accuracy of selection), as estimated by standard selection theory, using an underlying heritability of 0.3 adjusted for prevalence as in formula (1), as well as that realised based on a binary trait are presented in Table 3.1 for the various prevalences and population structure scenarios.

For OP the realised accuracy is essentially equal to the expectation. It must however be noted that the estimated breeding values have a binary distribution (values being $-(1-p)h_L^2$ and ph_L^2). For the HS scenarios the realised accuracy falls short of the expectation, especially at more extreme prevalences and with 60HS. This may be because members of large groups of HS are related and their breeding value is mainly based on the same information, such that all HS with the same observed phenotype have exactly the same EBV. As expected, essentially the same accuracies were found for a prevalence of 10 and 90%. Predicted accuracies based on combined

within and between family selection are close to the realisations. The accuracy for a scenario with 60 HS is always considerably higher than that for 6 HS.

Table 3.1 *Expected and realised (s.e.) accuracy of selection (r_{IH}) depending on scenario and initial prevalence. Expected accuracy is calculated with standard selection index theory (including combined between and within family selection) and using the heritability for a binary trait (h_{01}^2) based on a continuous heritability (h_L^2) of 0.3 and the appropriate prevalence.*

Prevalence	0.05		0.10		0.50		0.90	
Scenario [†]	expected	realised	expected	realised	expected	realised	expected	Realised
OP	0.259	0.258 (0.029)	0.320	0.320 (0.028)	0.437	0.436 (0.024)	0.320	0.318 (0.026)
HS6	0.140	0.138 (0.038)	0.171	0.168 (0.038)	0.224	0.224 (0.037)	0.171	0.168 (0.038)
OP HS6	0.285	0.288 (0.033)	0.349	0.353 (0.031)	0.467	0.473 (0.027)	0.349	0.343 (0.030)
HS60	0.354	0.336 (0.075)	0.390	0.374 (0.070)	0.432	0.420 (0.067)	0.390	0.371 (0.069)
OP HS60	0.420	0.406 (0.064)	0.476	0.465 (0.055)	0.563	0.558 (0.044)	0.476	0.463 (0.054)

[†] OP = Own Performance, HS6 / HS60 = half sib family size of 6 / 60, OP HS6 / HS60 = own performance and a half sib family size of 6 / 60

3.3.2. Realised Genetic Merit and Responses to Selection

For normally distributed phenotypes, including liability, the average genetic merit of a selected fraction is predicted to be a linear function of the accuracy; but changes in prevalence are not linear because the relationship between liability and prevalence is non-linear.

Table 3.2 shows the average genetic merit on the liability scale of the top 10% selected on breeding value, for a continuous trait and a binary trait at different prevalences. With the exception of the scenario with a 90% prevalence, the genetic

merit of the top 10% under mass selection on the binary falls well short of that for a continuous trait, in spite of a correct estimate for the accuracy (Table 3.1). This is due to the binary distribution of the estimated breeding values. The effect of 5 HS on the response to selection is about equal to the effect of OP, while 59 HS have a much larger effect, disproportionate to the increase in accuracy (Table 3.1). As predicted by Foulley (1992), the selection differential is not symmetrical around a prevalence of 0.5.

Table 3.2 *Realised genetic merit (s.e.) on the liability scale of top 10%, selected on a continuous trait, or a binary trait with a frequency of the undesirable attribute of 0.05, 0.10, 0.50, or 0.90, depending on scenario*

Prevalence Scenario [†]	Continuous		Binary		
	0.05	0.10	0.50	0.90	
OP	-0.523 (0.051)	-0.037 (0.053)	-0.057 (0.054)	-0.239 (0.048)	-0.491 (0.057)
6 HS	-0.256 (0.065)	-0.036 (0.055)	-0.066 (0.055)	-0.201 (0.063)	-0.199 (0.066)
OP 6HS	-0.558 (0.052)	-0.067 (0.055)	-0.118 (0.054)	-0.378 (0.057)	-0.516 (0.052)
60 HS	-0.388 (0.125)	-0.263 (0.123)	-0.312 (0.125)	-0.370 (0.127)	-0.365 (0.130)
OP 60HS	-0.607 (0.090)	-0.282 (0.122)	-0.344 (0.121)	-0.503 (0.103)	-0.536 (0.097)

[†] see Table 3.1 for explanation of scenarios

Selection on Own performance. Table 3.3 compares the expected response to one round of selection of the top 10%, 25% and 50% of both sexes on OP with the realised response. When the selected fraction is equal to the proportion of desirable phenotypes (prevalence of 0.5 and 50% selected, prevalence 0.9 and 10% selected), the expected response is equal to that for selection on the continuous phenotype. In the first case, the realised response is also the same, but with a prevalence of 0.9 the

response is clearly less, presumably due to correlations among HS. The scenario with 6HS does not show this effect to the same extent (not shown), nor do scenarios in which HS are not considered candidates (Nieuwhof et al., 2006). Also, the proportion of healthy animals will only on average be equal to the selected fraction. In individual cases where, purely by chance, slightly more healthy animals are available this will not improve the selection result, but if there are too few healthy animals random selection among the diseased will have a major negative impact on the selection differential. Further note that expected and realised responses are the same for a prevalence of 0.1 and 0.9 if 50% is selected.

Table 3.3 *Predicted and realised (s.e.) response to one round of selection on Own Performance in terms of liability, depending on the selected proportion and original prevalence. Expectations are based on standard selection theory assuming normality for the continuous trait and the realised selection intensity based on selected fractions*

Selected fraction	10%		25%		50%	
Prev	Expected	Realised	Expected	Realised	Expected	Realised
Cont	-0.527	-0.523 (0.051)	-0.381	-0.382 (0.035)	-0.239	-0.240 (0.028)
0.05	-0.033	-0.037 (0.088)	-0.033	-0.036 (0.067)	-0.033	-0.035 (0.061)
0.1	-0.059	-0.057 (0.086)	-0.059	-0.058 (0.067)	-0.059	-0.058 (0.060)
0.5	-0.239	-0.239 (0.082)	-0.239	-0.240 (0.065)	-0.239	-0.230 (0.063)
0.9	-0.527	-0.491 (0.106)	-0.176	-0.173 (0.083)	-0.059	-0.056 (0.065)

HS selection. Table 3.4 shows the expected and realised selection response in terms of liability based on selection on a continuous trait (the liability) and a binary trait with selection in a family of 6 or 60 half sibs. For the continuous trait expectations

Table 3.4 *Predicted and realised (s.e.) response to one round of selection on HS in terms of liability for the scenario with families of 6 or 60 half sibs, depending on the selected proportion and original prevalence. Expectations are based on standard selection theory assuming normality ($i\pi_{IH}\sigma_H$) for the continuous trait and on formula (2) for the binary traits*

Selected fraction	10%		25%		50%	
Prev.	Expected	Realised	Expected	Realised	Expected	Realised
6HS						
Cont.	-0.258	-0.256 (0.065)	-0.187	-0.187 (0.041)	-0.117	-0.116 (0.030)
0.05	-0.135	-0.036 (0.077)	-0.098	-0.037 (0.049)	-0.061	-0.038 (0.036)
0.1	-0.164	-0.066 (0.077)	-0.119	-0.067 (0.051)	-0.075	-0.066 (0.037)
0.5	-0.215	-0.201 (0.080)	-0.156	-0.158 (0.054)	-0.098	-0.101 (0.038)
0.9	-0.164	-0.199 (0.084)	-0.119	-0.123 (0.054)	-0.075	-0.067 (0.039)
60HS						
Cont.	-0.437	-0.390 (0.125)	-0.317	-0.300 (0.085)	-0.199	-0.192 (0.067)
0.05	-0.341	-0.263 (0.134)	-0.247	-0.216 (0.093)	-0.155	-0.150 (0.071)
0.1	-0.375	-0.315 (0.136)	-0.272	-0.245 (0.091)	-0.170	-0.164 (0.073)
0.5	-0.415	-0.378 (0.137)	-0.301	-0.288 (0.097)	-0.189	-0.184 (0.076)
0.9	-0.375	-0.362 (0.138)	-0.272	-0.266 (0.096)	-0.170	-0.162 (0.073)

are very close to realised responses, but with 6HS the binary trait predictions of response are generally overestimated, particularly for low prevalence and intense selection. There are notable exceptions when prevalence and selected fraction sum to 1 and to a lesser extent when prevalence is 0.9 and 25% is selected. These are the exact cases for which selection on OP gives a relatively good response due to the binary character of the trait. With only 5 HS considered, the distribution of EBVs is not normal but discrete (with 6 classes) and this has an effect on the selection differential. If the heritability of resistance is ignored, for a prevalence of 0.05 the expectation is that on average in $0.95^5=0.77$ of families there are no diseased animals. A heritability larger than 0 leads to more extreme families with an even higher proportion having no diseased animals. Selection will be random within these families.

With 60 HS the realised selection response is up to 10% below the prediction for the continuous trait. This is due to correlations between EBVs of HS, and especially the fact that the OP of an animal is ignored for its own EBV. Realisations for selection on binary traits are generally well in line with expectations, with discrepancies occurring with lower prevalences and selection intensities.

Figure 3.1 shows the response to selection in terms of prevalence, for the 60 HS scenario, highlighting that on that scale the major overestimation occurs with moderate prevalences. This difference is due to the non-linear relationship between liability and prevalence. A change in liability at extreme prevalences will have a much smaller effect than when prevalence is around 0.5.

Combined OP and HS selection. Table 3.5 gives the selection results in terms of liability for the scenarios with observations on the animal and families of 6 or 60 half sibs. Predictions are based on combined between and within family selection and the two-stage approach. The predictions using the two-stage approach are always closer to the simulated response and also more so than when only HS were considered. For the OP6HS scenario important over-predictions of liability still occur, specifically where a higher selection intensity does not always lead to a higher response. While

this pattern is the same as for OP, the actual level of response is doubled compared to the OP scenario (Table 3.3), indicating that the 5 HS have contributed, but that there is a lack of variation in estimated breeding values for it to be effective at low prevalence.

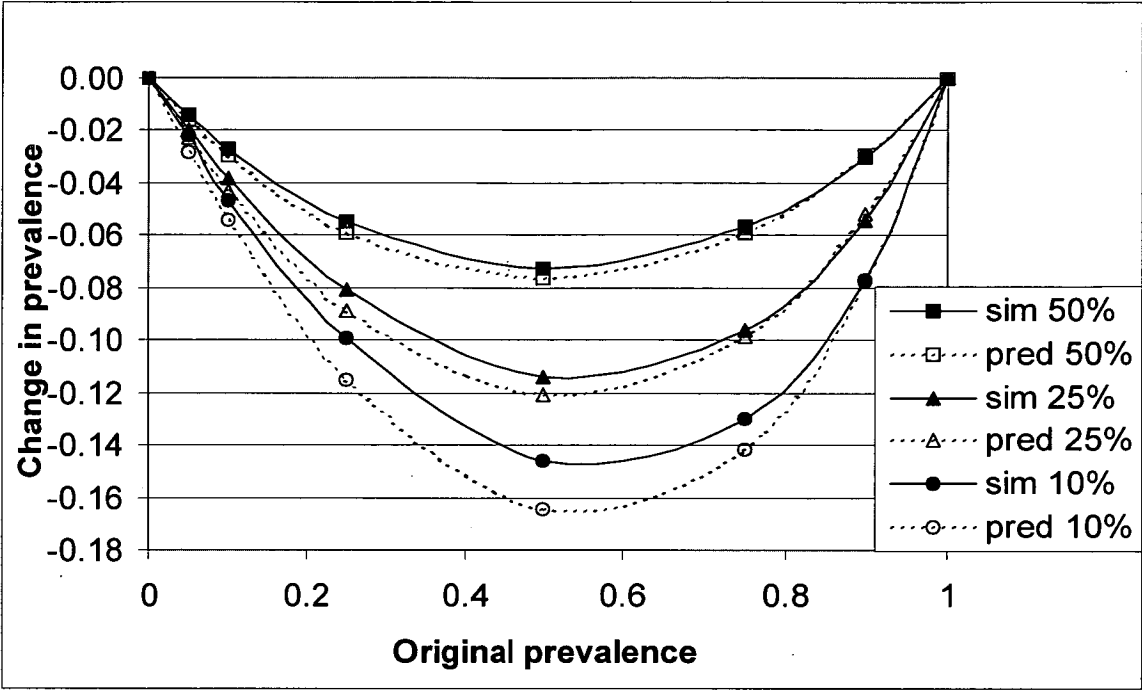


Figure 3.1 Response in prevalence to selection on 60HS depending on original prevalence and selection intensity as predicted (pred) and simulated (sim)

Figure 3.2 shows that in terms of prevalence the two-stage prediction is closer to the realised response than the liability would suggest.

When selection is on OP and 60 half sibs, Table 3.5 shows that the expected selection responses in liability based on combined between and within family selection is again inferior to the two-stage approach. Two-stage predictions and realisations from the simulations show generally good agreement, although some over-predictions still exist for low prevalences. Over-predictions occur because both the combined between and within family and the two-stage selection procedure assume that there is phenotypic variation (and phenotypes on a continuous scale) within the groups of HS. At very low and very high prevalences this is very limited,

especially for relatives of healthy animals. Selection among these animals will largely be random.

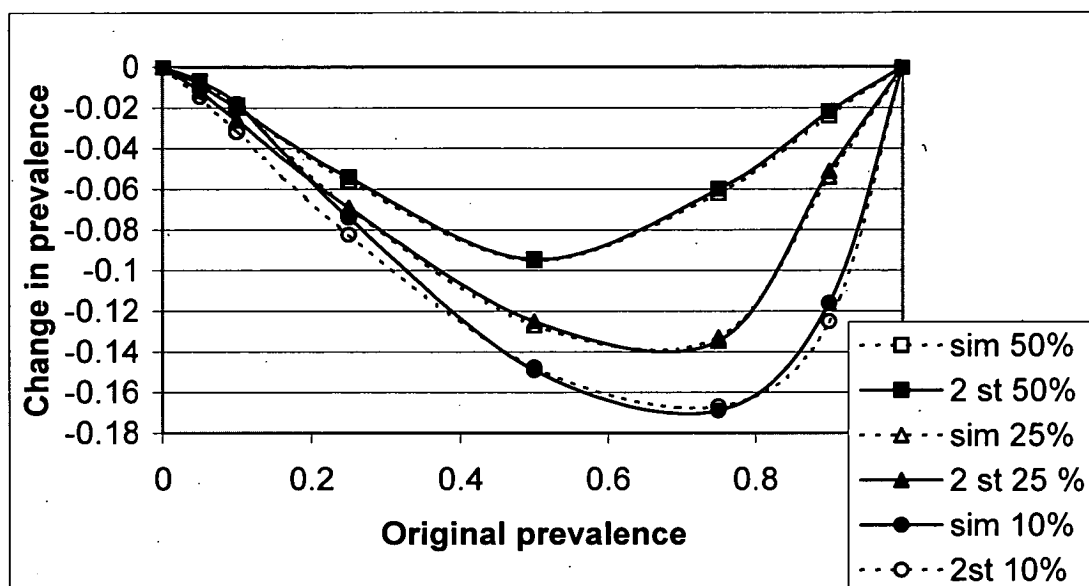


Figure 3.2 *Response in prevalence to selection on OP and 6HS depending on original prevalence and selection intensity as predicted with a two-stage approach (2 st) and simulated (sim)*

The combined between and within family method under-predicts progress for cases with high prevalence. This is a direct consequence of the implicit assumption of symmetry in response around a prevalence of 0.5, and the method now underestimates within family variation, especially for families with more than average unaffected animals.

Table 3.5 *Predicted and realised (s.e.) response to one round of selection in terms of liability and resulting prevalence for the scenario with own performance and families of 6 or 60 half sibs, depending on the selected proportion and original prevalence. Expectations are based on standard selection theory assuming normality for the continuous trait and on combined within- and between-family selection (Comb.) and two-stage (2 st.) for binary traits.*

Selected fraction	10%			25%			50%		
Prevalence	Comb.	2 st.	Real.	Comb.	2 st.	Real.	Comb.	2 st.	Real.
OP6HS									
Cont.	-0.553	-0.557	-0.558 (0.052)	-0.400	-0.404	-0.402 (0.036)	-0.251	-0.253	-0.253 (0.028)
0.05	-0.274	-0.162	-0.066 (0.078)	-0.198	-0.126	-0.067 (0.049)	-0.124	-0.090	-0.067 (0.036)
0.1	-0.335	-0.209	-0.118 (0.075)	-0.243	-0.166	-0.119 (0.052)	-0.153	-0.122	-0.119 (0.037)
0.5	-0.449	-0.379	-0.376 (0.076)	-0.326	-0.319	-0.321 (0.049)	-0.204	-0.239	-0.239 (0.035)
0.9	-0.335	-0.526	-0.516 (0.073)	-0.243	-0.250	-0.258 (0.055)	-0.153	-0.117	-0.120 (0.040)
OP60HS									
Cont.	-0.614	-0.614	-0.607 (0.090)	-0.445	-0.445	-0.441 (0.070)	-0.279	-0.279	-0.277 (0.062)
0.05	-0.403	-0.379	-0.282 (0.133)	-0.292	-0.285	-0.233 (0.092)	-0.183	-0.191	-0.167 (0.069)
0.1	-0.457	-0.420	-0.347 (0.132)	-0.331	-0.318	-0.272 (0.089)	-0.208	-0.216	-0.191 (0.070)
0.5	-0.541	-0.512	-0.503 (0.116)	-0.392	-0.394	-0.392 (0.084)	-0.246	-0.239	-0.259 (0.067)
0.9	-0.457	-0.526	-0.536 (0.110)	-0.331	-0.340	-0.349 (0.091)	-0.208	-0.184	-0.193 (0.073)

Interestingly, in a number of cases the two-stage approach also under-predicts the response. This is typically the case when the sum of the prevalence and selected

fraction is about equal to 1. In these cases, the two-stage approach actually fails to identify the top animals, as in the first stage it selects only healthy animals and discards some diseased animals which, based on their HS, are superior to some healthy animals. Or in other terms, the two-stage approach ignores the HS information and uses only OP. This can be verified by noting that in these cases the two-stage predictions are the same as those for OP in Table 3.3. Another type of overestimation occurs when there is a great shortage of healthy animals, and most of the selection is on HS among the diseased. At these high prevalences, the distribution of EBVs is highly skewed to the left (healthy animals) and more progress will be made than would be expected assuming a normal distribution. Figure 3.3 shows that in terms of change in prevalence the two-stage approach predicts the response to selection very accurately for this scenario, even when the response in liability is not predicted accurately.

The response to selection on OP and 60 HS in terms of liability and change in prevalence approximately halves if the heritability is 0.15 rather than 0.30 (Table 3.6, Figure 3.4).

Table 3.6 *Predicted and realised (s.e.) response to one round of selection in terms of liability and resulting prevalence for the scenario with 60 half sibs and own performance, depending on the selected proportion and original prevalence. Expectations are based on standard selection theory assuming normality for the continuous trait and on a two-stage approach including formula (2) for binary traits for $h_L^2 = 0.15$*

Selected fraction	10%		25%		50%	
Prev.	Expected	Realised	Expected	Realised	Expected	Realised
Cont.	-0.359	-0.355	-0.260	-0.259	-0.163	-0.163
		(0.071)		(0.053)		(0.044)
0.05	-0.208	-0.165	-0.155	-0.137	-0.102	-0.097
		(0.099)		(0.069)		(0.051)
0.1	-0.237	-0.207	-0.178	-0.164	-0.118	-0.112
		(0.100)		(0.068)		(0.050)
0.5	-0.289	-0.298	-0.216	-0.226	-0.120	-0.145
		(0.086)		(0.060)		(0.046)
0.9	-0.263	-0.294	-0.189	-0.198	-0.107	-0.115
		(0.084)		(0.064)		(0.053)

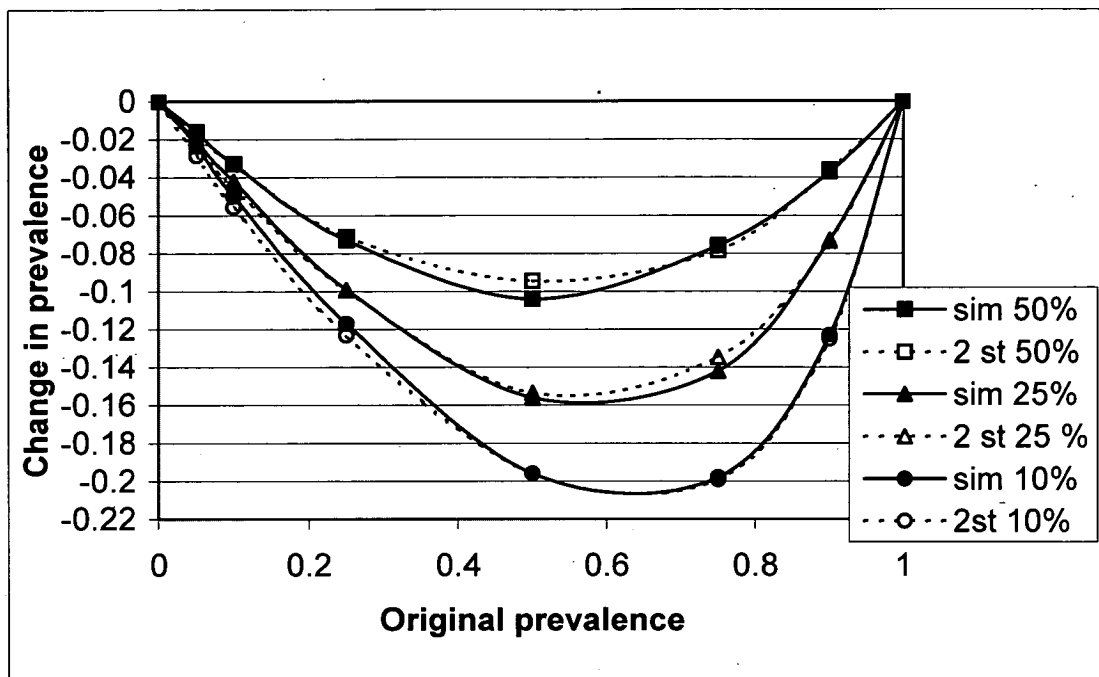


Figure 3.3 Response in prevalence to selection on OP and 60HS depending on original prevalence and selection intensity as predicted (2st) and simulated (sim)

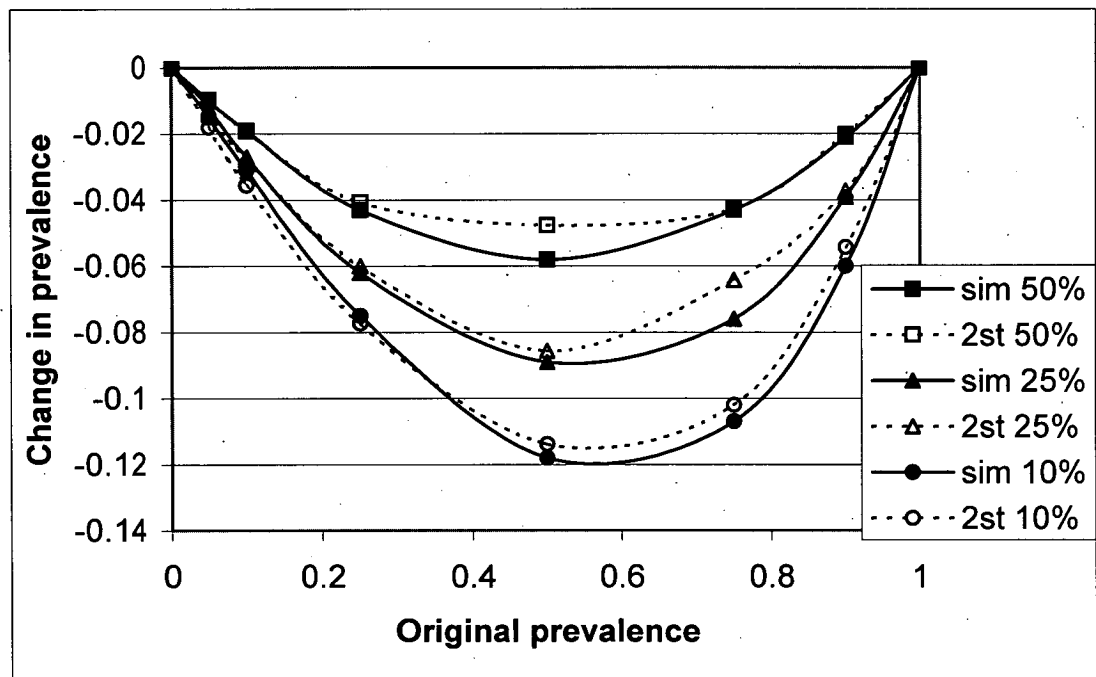


Figure 3.4 Response in prevalence to selection on OP and 60HS depending on original prevalence and selection intensity as predicted by the two-stage approach (2st) and simulated (sim) with heritability for liability (h_L^2) = 0.15

3.4. Discussion

In this study the response to selection on a binary trait was investigated for various scenarios combining different selection intensities and diseases prevalences. A method of predicting the response to selection based on two-stage selection theory was proposed. Results were verified using simulation.

There is a great variation in responses to selection in the various scenarios. As is normally the case in selection programmes, the response depends on the selected fraction for many scenarios, but not always if selection is on own performance only. Other factors determining the response are the prevalence and the use of information on relatives. It is clear that, in breeding schemes that do not rely on progeny testing for disease traits, both own performance and sibs' information make important contributions.

In the scenarios considered here each of the 6 flocks within a replicate would have the same prevalence, with there only being small differences as a result of sampling. In practice prevalences will vary from flock to flock, either due to the environment (affecting pathogen burden or animal resistance) or differences in genetic merit for resistance among flocks, and this may affect the response to selection. Some initial calculations (Nieuwhof and Bishop, 2005b) show that variations in flock prevalence can have positive or negative effect on progress, depending on the information used. This requires further investigation.

The relative weight of observations from different sources in the breeding value estimation was based on standard selection index theory using heritabilities on the observed scale (0/1). Where it later appeared that this adjustment was not fully correct (e.g. at low prevalences), the weighting factors would be incorrect and result in a sub-optimal index. In our study, this is relevant only in those cases where different sources were used (OP 6HS, OP 60HS), and even then in most cases the exact weighting had a very small effect (results not shown). In practice effects may be larger, as different animals have different numbers of relatives and various sets of

relatives, for instance missing (grand)parent observations and different numbers of full and half sibs.

It should be noted that the standard deviation of the responses to selection over 1000 replicates varies considerably, for instance from 0.051 for OP6HS to 0.130 for 60HS for the mean responses reported in Table 3.2 (which range from -0.036 to -0.536), with the lowest figure for scenarios with 6HS and the highest for scenarios with 60 HS. This implies that in a considerable number of cases, especially with few HS, on occasions no or very little progress will be made.

One way of further improving the success of breeding for resistance would be to get more exact information than one binary observation per animal. In the case of footrot, a scoring system has been developed that consists of 5 classes depending on severity, and a score would be given to each foot (e.g. Egerton and Roberts, 1971). The usefulness of this will be limited though, as the extra classes are used to subdivide the small class of affected animals, rather than the much bigger class of healthy ones. From a genetic selection point of view, gains from making the score more 'continuous' may be spurious, as it is apparently adding information, but to the wrong end of the distribution. Following Chang *et al.* (2004) it may be more useful to obtain repeated measures on both lambs and adults, which would circumvent the issue of exposure to some extent, but costs of this should be taken into account.

Prediction of response to selection on binary traits has been the subject of studies for a long time. This study confirms that ignoring the binary character of a trait and assuming normality may work reasonably in some cases, but not in others. Ignoring the binary character would lead to using the correct h_{01}^2 and phenotypic variance ($p(1-p)$) and genetic progress would be predicted as $ir_{IH}\sigma_H$, with both r_{IH} and σ_{H01} on the observed scale (0/1). Using this approach, the response to selection of the top 10% on the combination OP and 60HS at a prevalence of 0.50, (phenotypic variance is 0.25, $h_{01}^2 = 0.191$) would be -0.216, or a decrease in prevalence from 0.5 to 0.284. The simulated response, -0.392 in liability, leads to a new prevalence of 0.309 (Figure 3.3), which is similar. Much larger differences, however, would be obtained

with lower or higher prevalences. Using the same example, but now for a prevalence of 0.05 (phenotypic variance is 0.0475, $h_{01}^2 = 0.067$), the predicted response assuming normality would be -0.042 and the resulting prevalence 0.008 rather than the simulated 0.027 or two-stage prediction of 0.021 (Figure 3.3). Clearly, while a small bias does exist at a prevalence of 0.50, at more extreme values the assumption of normality leads to major errors.

The approach proposed by Foulley (1992) for family selection is based on a system in which the selection candidates do not contribute any data to the genetic evaluation. For meat sheep breeding, as applied in Britain, own performance of selection candidates plays an important role, which has two consequences when the formula is extended to this situation. First, all candidates descendant from the same sire will have an EBV that is largely based on the same observations – even with 60 HS there are only two EBVs within a HS group; one for healthy and one for diseased animals and selection within HS groups has only limited power. The second issue is that by only considering HS information, the animal's own performance is not included in its estimated breeding value estimation, while it does contribute to those of its HS. As an example, take the case of groups of 60 half sibs being considered for selection, and assume that a fraction p of a group of 60 has a phenotype of 1 and the others 0. Any animal's breeding value will be estimated based on 59 HS, i.e. $59p_i$ animals with phenotype 0, $59(1-p_i)$ animals with phenotype 1, so that there are only two distinct estimated breeding values within any group of 60. Since an animal's own observation is not included, the animals with the best phenotypes will have the worst EBV. This explains why the realised progress based on scenarios with 60 half sibs (although being considerable as a result of between family selection) is much less than predicted, even for a continuous trait. At the same time it underlines the importance of including the own performance alongside half sib information, both in selection and prediction.

The challenge then is to combine two sources of information with very different distributions – binary for own performance and continuous for half sib data. Often, the optimal selection strategy is to combine all available information in a selection

index and select on the index in a single round of selection. With a disease, however, which seriously affects the long-term (reproductive) health of animals or their suitability for sale as breeding animals, a first stage of selection is required to discard all diseased animals. In a second stage, selection would be within the healthy animals based on their half sibs (and other relatives). Two-stage selection theory is appropriate for this case. In the current study, we consider that diseased animals are still suitable for breeding and accordingly use a selection index in the simulation. The two-stage approach is then proposed to predict progress, because it can combine the two separate prediction methods.

Although predictions from the two-stage method are generally accurate, there are three cases where we observe a small deviation from simulations. Firstly, an overestimation of the response occurs with low numbers of half sibs, especially with low prevalence and intense selection. This can be attributed to the half sib prediction in formula (2), which in this case makes the same overestimation. Since in our method we also include own performance, the total prediction error is smaller. In contrast, an underestimation of the selection response occurs when the selected fraction is equal to the proportion of healthy animals. In this case the two-stage approach makes the error of completely ignoring the HS information, and in the first step discards certain diseased animals that, based on HS records, should be selected. The third discrepancy is an under-prediction that occurs at high disease prevalences and a selection fraction that, in addition to all healthy animals includes some diseased. Most of the errors in prediction occur at extreme values for the prevalence. Because of the non-linear relationship between liability and prevalence, these errors have a much smaller effect on the prevalence than the liability, and in practice these would not be of major concern.

In practice selection against a disease may be in a relatively low-challenge environment, for instance in a nucleus flock and progress in terms of reduced prevalence may be limited. Because of the non-linear relationship between liability and prevalence, the marginal improvements in prevalence predicted in the low prevalence environment will become larger in dirtier environments. In other words,

little observable progress in the nucleus may lead to great strides in commercial farms. This is a general effect that can be expected for many disease traits, where prevalence of disease is the important trait.

This study investigated the response to one round of selection on a binary trait. For normally distributed traits one would expect that similar genetic progress can be achieved over many generations, apart from a small effect due to a decrease in genetic variance, the so-called Bulmer effect (Bulmer, 1971). For a binary trait, this would be true for the liability, if prevalences are not too extreme, but reductions in prevalence would become smaller with observed prevalence becoming smaller (and less than 50%). In the field, it will become increasingly difficult to identify the more resistant animals among the unaffected, and, as shown in this study inclusion of large groups of relatives will be important. Depending on the specific pathogen and environment, exposure issues may become more important at low prevalences. While this is problematic in terms of obtaining phenotypes for selection, it is also an additional benefit of selection for disease resistance that has so far been ignored. Elucidation of the true long-term effects in both genetic terms, taking into account the Bulmer effect and observed prevalence, as well as epidemiological effects, requires a multi-generation simulation.

In practice, breeding programmes are aimed at improving a number of traits, not just resistance to one disease, as in this study. Nieuwhof and Bishop (2005a) considered selection for resistance to footrot in combination with either growth rate or growth rate and litter size, but ignored the binary character of the disease. Based on the current study we can conclude that their prediction of genetic progress was overestimated by about thirty percent (based on the genetic merit of the top 25% selected at a prevalence of 10%, -0.445 for a continuous trait, -0.318 for a binary trait). Assuming linearity, their estimate for the genetic progress in one round of selection of about a fifth of the original prevalence can be corrected with the same 30%. The expected reduction in prevalence of footrot when selection is on a multitrait selection index is then 14% of the original prevalence, with a value of £1.9 M annually if applied across the British sheep population.

3.4.1. Conclusions

The response to selection on a binary trait depends on a number of factors, including the prevalence, use of information on relatives, heritability and the selection intensity. For cases where own performance is combined with observations on half sibs, the proposed method of predicting of the response to selection using a two-stage approach generally gives a good prediction, with exceptions where the proportion of healthy animals is close to the selected fraction and with few half sibs. When the prevalence of the undesirable character is very low and selection intense, there will be over-predictions on the liability scale, but these over-predictions will be somewhat less when responses to selection are expressed in terms of changes in prevalence.

Considerable progress can be made in a selection programme for increased resistance of sheep to a disease, especially if own performance is combined with sib information. If the heritability of the underlying trait is 0.3, the genetic progress that can be achieved with single trait selection on a binary trait results in about halving the prevalence every round of selection, if the original prevalence is between 5 and 25%.

Chapter 4. Effects of variation in prevalence and exposure on the genetic response to selection on a binary trait

4.1. Introduction

In a selection programme, the genetic progress that can be achieved for a normally distributed trait depends directly on the accuracy of selection, genetic variation and selection intensity. In the previous chapter it was shown that for a binary trait – such as whether or not a sheep is affected by footrot – the original prevalence also has an effect on genetic progress.

In chapter 3 within each scenario the prevalence of the disease was kept constant. As outlined in general terms by Snowden (2006), in practice of course there is variation in prevalence between flocks or herds. In sheep, Wassink and Green (2001) report that prevalence of footrot in the worst affected month varies from less than 3% to over 20% depending on the flock. Østergaard and Grohn (1999) show that for a range of diseases in dairy cattle, incidence depends on parity and in the same species Heringstad *et al.* (2003) report variation in incidence of mastitis over time. One reason for a lower prevalence can be lack of exposure in a part of the population. Wassink *et al.* (2004), for instance, argue that prevalence of interdigital dermatitis (a disease related to footrot) can be reduced by limiting exposure to the disease-causing bacteria. For pigs, Rothschild (1989) argues that since clinical disease is very rare in breeding stock, scoring for expression of disease would not be very informative. The same conclusion does not necessarily apply to breeding stock of other species, such as sheep, which are kept in environments in which they are more widely exposed to disease agents, resulting in higher incidences of clinical and sub-clinical disease. In general, it can be expected that observed prevalences differ due to the environment (between and within flocks), exposure to the disease and a combination of these factors.

For prediction of the response to selection, variation in prevalence requires a different approach from variation in exposure. For a normally distributed trait, differences in levels between classes (e.g. flocks) are dealt with through fixed effects

in the model, and generally under the assumption that phenotypic variances are the same across classes. For a binary trait, however, the phenotypic variation and heritability depend on the prevalence. Lack of exposure will lead to misclassification of potentially susceptible animals as resistant, thereby limiting the opportunity to select against susceptible animals.

In this study, the effects of variation in prevalence and exposure on the response to selection on a binary trait will be investigated. The response will be predicted using standard techniques adjusted for the binary character of the trait. Simulation will be used to obtain realistic estimates of progress. Results will be compared to those for a scenario in which selection is on a binary trait in the absence of variation in prevalence and with full exposure.

4.2. Methods

4.2.1. Principles

Analysis of a binary trait in a threshold model has the advantage that adjustments can be made for fixed effects and heritabilities are independent of the prevalence (Cameron, 1997). This approach is based on the relationship between the heritability of a binary trait (h_{01}^2) and that of an underlying continuous trait or liability, assumed to have a standardised normal distribution (h_L^2). This relationship is approximated (Robertson and Lerner, 1949) by:

$$h_L^2 = p(1-p)z^2 h_{01}^2 \quad (1)$$

where p is the prevalence of the binary trait and z is the ordinate of the standardised normal distribution corresponding to p . The term $p(1-p)$ is the phenotypic variance of the binary trait. In case of variation in prevalence between fixed effect classes (e.g. flocks), in principle h_{01}^2 and p will vary in such a way that the same h_L^2 is estimated within each class. In practice, with animals having relatives in different flocks (and years) it will be difficult to apply flock specific heritabilities and breeding values would be estimated based on the h_{01}^2 at population level, i.e. using the population p .

4.2.2. Variation in prevalence at full exposure

Based on OP only, an animal j in flock i with observation $X=0$ or 1 (healthy or

affected) has its breeding value predicted as $EBV_{ij} = h_{01i}^2(X_{ij}-p_i)$. This EBV will rank healthy animals ($X_{ij}=0$) in flocks with the highest prevalence (lowest EBV_{ij}) as the best. If there are true differences in prevalence between flocks, not only p_i will vary by flock, but so will h_{01i}^2 as a function of p_i as described in (1) leading to a flock specific heritability h_{01i}^2 . A flock specific EBV (FBV_{ij}) can therefore be estimated as:

$$FBV_{ij} = h_{01i}^2(X_{ij}-p_i) = \{z_i^2 h_L^2 / [p_i(1-p_i)]\}(X_{ij}-p_i). \quad (2)$$

Therefore, when $X_{ij} = 0$ (i.e. the animal is healthy), $FBV_{ij} = -\{z_i^2 h_L^2 / (1-p_i)\}$, and when $X_{ij} = 1$ (diseased), $FBV_{ij} = \{z_i^2 h_L^2 / p_i\}$. Note that $-\{z_i^2 h_L^2 / (1-p_i)\} \leq \{z_i^2 h_L^2 / p_i\}$ for any value of z_i^2 , h_L^2 and p_i so that healthy animals will always have a negative flock specific EBV and rank better than affected animals. Because of characteristics of the normal distribution, the FBV for $X_{ij}=0$ decreases with increasing p_i for $p_i < 0.73$, regardless of h_L^2 . So that as long as the prevalence is less than 0.73 in anyone flock, the FBV, will identify healthy animals in the flocks with highest prevalence as the best, and there will be no difference in ranking on EBV and FBV. With p_i increasing beyond 0.73, the decrease in h_{01i}^2 becomes larger than the absolute increase in $(X_{ij}-p_i)$ so that $FBV_{ij} = h_{01i}^2(X_{ij}-p_i)$ increases to 0 and animals in flocks with these high prevalences would not be identified as the most resistant. This case is not relevant for endemic diseases that affect a small proportion of the population at any one time.

If this approach was extended to a breeding value based on n HS and the binary character of the trait taken into account, the FBV would be calculated as:

$$FBV_{ij} = \frac{\frac{1}{4} n h_{01i}^2}{1 + (n-1) \frac{1}{4} h_{01i}^2} (X_{ij} - p_i) \quad (3)$$

with X_{ij} the average over n HS, and assuming all HS are in the same flock i , showing that the flock specific estimated breeding value of an animal depends on h_{01i}^2 . This is in contrast to a threshold approach, which would be based on h_L^2 rather than h_{01i}^2 and put the same weight on each group of HS regardless of flock prevalence. As long as n is the same across HS groups, the threshold approach and an EBV based on a population wide prevalence would result in the same ranking of animals, and hence the same selection result.

The FBV for n HS using a flock specific heritability puts higher weights on HS groups from flocks with a prevalence closest to 0.5 (when h_{01i}^2 is at its maximum). The same HS groups will also have the lowest (i.e. best) values for $X_{ij}-p_i$, so that there are two mechanisms that favour animals from flocks with prevalences close to 0.5.

4.2.3. Variation in exposure

In case not all animals in a population are exposed to the disease agent, we need to consider two types of prevalence; the virtual prevalence which is defined as the prevalence of a disease if all animals are exposed to the disease agent (hence referred to as p) and the proportion of animals showing signs of the disease, the observed prevalence. If a proportion of e animals is exposed the observed prevalence is equal to ep . Below, it is assumed that the probability of exposure is the same for all animals in a flock and that exposure has no genetic component. An animal is deemed susceptible if it becomes infected upon exposure.

For incomplete exposure, $e < 1$, a proportion of $1 - ep$ animals will be healthy, either because they are exposed and resistant $e(1 - p)$ or because they are not exposed $(1 - e)$. Only the former contribute to selection for resistant animals and they contribute $e(1 - p)/(1 - ep)$ of animals selected. Therefore, assuming normality, the response to selection (ΔG_e) would be reduced to:

$$\Delta G_e = \frac{e(1 - p)}{1 - ep} \Delta G$$

with ΔG the response at full exposure. Compared with full exposure, both the accuracy of selection and the genetic standard deviation are reduced by the square root $\sqrt{e(1 - p)/(1 - ep)}$.

Since OP is a discontinuous trait, however, the approach described by Falconer and Mackay (1996) should be applied, in which the effective selection intensity depends solely on the proportion of candidates with the desirable phenotype (i.e. healthy) if there are sufficient healthy animals available for selection. If all healthy and some diseased animals are selected, the selection intensity is the weighted average of the

selection intensities in the two groups. OP selection on an incompletely exposed binary trait with heritability h_{01}^2 is then equivalent to selection on a fully exposed binary trait with heritability $h_{e01}^2 = e(1-p)h_{01}^2/(1-ep)$. The response to selection of all $1-ep$ healthy animal, expressed at liability level (genetic standard deviation of h_L) is:

$$\Delta G = \sqrt{\frac{e(1-p)}{1-ep}} i h_{01} h_L$$

with i depending on the observed prevalence ep .

It can be shown (Appendix 1) that for a group of n half sibs, with on average a proportion of e exposed, the accuracy of selection is:

$$\rho = \frac{1}{4} h_{01} \sqrt{\frac{e(1-p)n}{(1-ep) + e(1-p)(n-1) \frac{1}{4} h_{01}^2}} \quad (4)$$

This correlation contains the exposure e as well as the product of prevalence and exposure (i.e. the observed prevalence, ep) showing that the effect of partial exposure depends on the prevalence. If $e=1$ the formula reverts to the standard formula for accuracy of selection and is independent of p , except for the effect of p on h_{01}^2 as described in (1).

Figures 4.1a and 4.1b show how ρ depends on p and e at $h_L^2=0.3$ and a family size of 60 HS. It can be seen in 1a that ρ increases as e increases and is maximum when $e=1$, at which point the accuracy is the same for p and $1-p$. For $e<1$ and $ep<0.5$, there is always a lower accuracy for ep than for $1-ep$. Further, the highest accuracy is not at $ep=0.5$. At any given virtual prevalence (p), the relationship between exposure and correlation is almost linear for $e>0.1$, and at an exposure of only 0.3 still about 50% of accuracy is achieved if $p \leq 0.5$. Figure 4.1b shows that at a given exposure ρ increases to a maximum, and then decreases as the observed prevalence gets closer to exposure (i.e. almost all animals are susceptible). Figure 4.1b can be used in practice to ascertain the sensitivity of the accuracy to unknown exposure levels.

The response to selection on a group of HS in terms of prevalence, taking into account the binary character of a trait as described by Foulley (1992), is calculated by substituting the appropriate accuracy ρ according to formula (4) into:

$$R^{\pm} = \Phi\left\{\frac{\mu \pm i\rho h_L}{\sqrt{1-i(i-\eta)\rho^2 h_L^2}}\right\} - \Phi\{\mu\} \quad (5)$$

for the cases where selection is for increased (R^+) or decreased (R^-) prevalence. In this formula, $\Phi(\mu)$ is the cumulative distribution of the standardised normal distribution evaluated at the initial prevalence and η is the threshold for the standardised normal distribution corresponding to the fraction selected.

When both OP and HS information is used, a two-stage approach can be used to predict genetic progress, as described in chapter 3. In the first stage selection would be on the OP (healthy animals only) and in the second additional selection is based on HS information using (5). Calculations for the second stage not only need to use the accuracy that takes into account incomplete exposure, but also the correct reduction in variance as a result of first stage selection on a trait with incomplete exposure. In general, the proportional reduction is $i_1(i_1-x_1)\rho_1^2$, where i_1 is the selection intensity in the first stage (i.e. all 1-ep healthy animals), x_1 is the corresponding threshold for selection on a standard normal scale and ρ_1 is based on the incompletely exposed observations in the first stage.

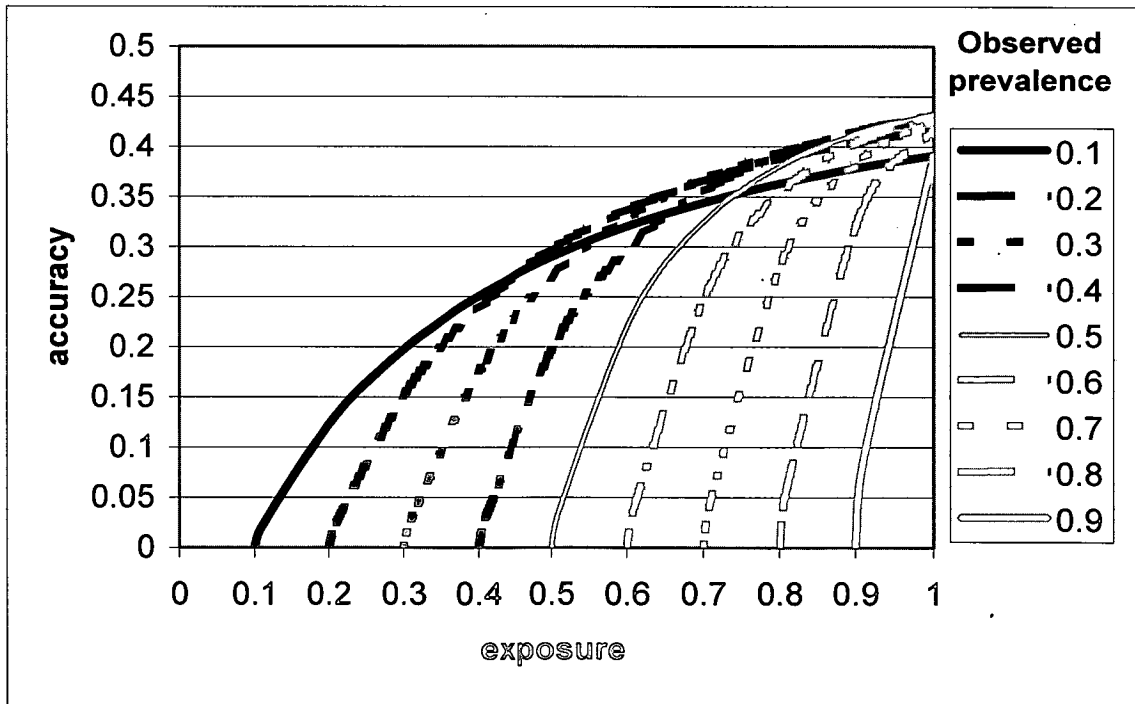


Figure 4.1a Accuracy of selection based on information from sibs, as a function of exposure, for different observed prevalences ($n=60$, $h_L^2=0.3$).

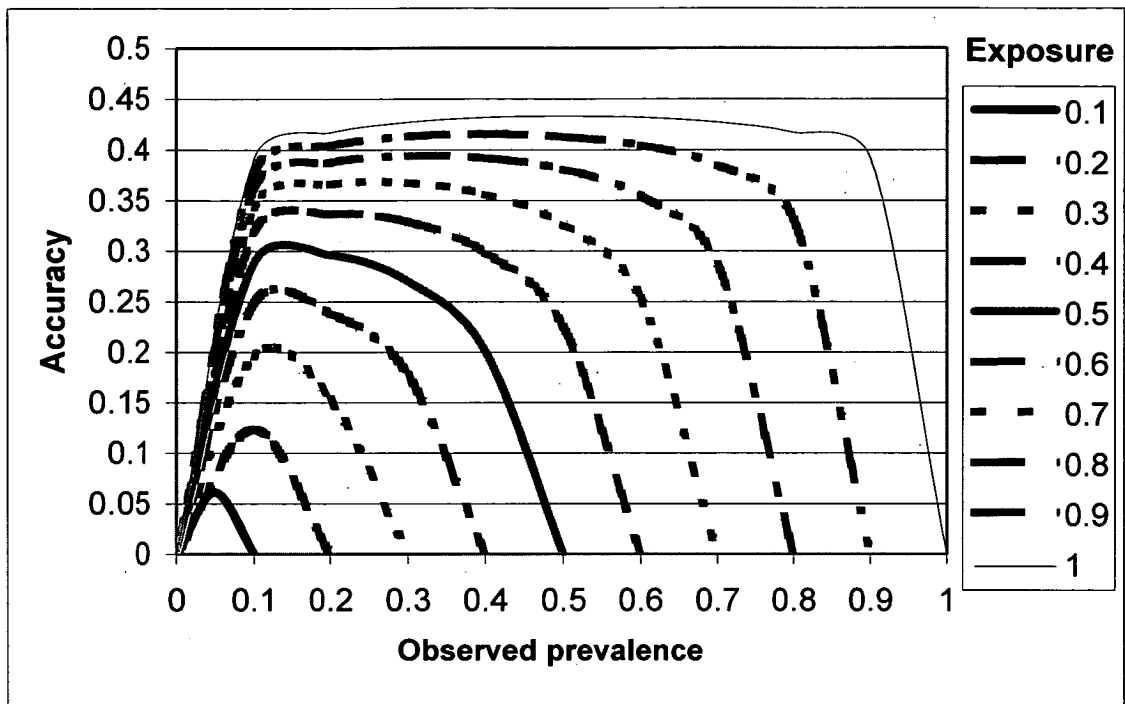


Figure 4.1b Accuracy of selection based on information from sibs, as a function of observed prevalences, for different exposure levels ($n=60$, $h_L^2=0.3$).

Simulation procedure

Response to selection in the standard scenario was estimated in simulated data as described in the previous chapter. In short, the population consisted of 6 flocks of 180 ewes each. Six reference sires (RS) were mated to 20 ewes in each of 3 flocks, and the remaining ewes were mated to stock sires (SS), with 30 ewes per stock sire. Litter size is 1. Selection candidates were all 180 lambs per flock. For offspring of RS, information from HS in the other flocks was included. For offspring of SS, HS information included 30 lambs born in the previous year.

An observed prevalence at population level of 0.10 was assumed and a heritability of the liability (h_L^2) of 0.30. Selection was on own performance, HS information (60 HS per family) or an index combining the two. Index weights in this case were based on standard selection index theory using the heritability for the binary trait (h_{01}^2) and based on observations pre-adjusted for the imposed fixed effects (i.e. these were not estimated from the data). Selected fractions of 10%, 25% and 50% were considered. Each scenario was replicated 1000 times.

The following comparisons were made, and an overview is given in Table 4.1:

1. Variation in prevalence due to the environment at full exposure

A scenario in which flock prevalence was 0.02, 0.04, 0.08, 0.12, 0.16 and 0.18 in the 6 flocks constituting the population was compared with the standard in which prevalence is 0.10 in all 6 flocks.

2. Variation in virtual prevalence and exposure at population level, leading to the same observed prevalence

Virtual prevalences were assumed of 0.909, 0.5, 0.25, 0.167, 0.125, 0.111 and 0.1 at population level, which for the observed prevalence of 0.10 implied exposure levels of 11%, 20%, 40%, 60%, 80%, 90% and 100% respectively. Index weights were based on the observed prevalence. All flocks had the same virtual prevalence and exposure level.

3. Variation in virtual prevalence and exposure at flock level

The same observed prevalence of 0.10 in each of the six flocks was created by combining virtual prevalences of 0.1, 0.2, 0.4, 0.6, 0.8 and 0.9 with exposure levels of 100, 50, 25, 16.7, 12.5 and 11.1% respectively. Expectations of genetic progress were calculated assuming full knowledge of exposure rates in each flock. For OP this means first selecting animals from the flock with highest exposure, then the next, until the required number of animals is selected. For HS formula (4) was used with flock specific values for e and p (so that $ep=0.1$) and the average accuracy over 6 flocks was applied. Alternatively, the expected response to selection was based on the assumption that $e=1$ (full exposure).

4. Variation in observed prevalence due to different exposure at flock level at the same virtual prevalence

It was assumed that the virtual prevalence in each flock was the same and equal to the highest observed prevalence (0.18), i.e. assuming all animals were exposed in this flock, and that exposure in the other flocks was less than 100%. In the first flock

the exposure is 11% (observed prevalence 0.02), in the second through sixth flock exposure is 22%, 44%, 67%, 89% and 100% respectively. Accuracies were calculated based on both flock specific and population wide parameters.

Table 4.1 Scenarios investigated.

Scenario	Virtual Prevalence [§]	Exposure [§]	Observed prevalence [§]
Standard	0.1	1	0.1
Increased prevalence	0.18	1	0.18
1. Variation in flock prevalence, constant exposure	0.02, 0.04, 0.08, 0.12, 0.16, 0.18	1	0.02, 0.04, 0.08, 0.12, 0.16, 0.18
2. Population-level variation in exposure, constant observed prevalence.			
A	0.909	0.11	0.1
B	0.5	0.2	0.1
C	0.25	0.4	0.1
D	0.167	0.6	0.1
E	0.125	0.8	0.1
F	0.111	0.9	0.1
3. Flock-level variation in prevalence and exposure, constant observed prevalence	0.1, 0.2, 0.4, 0.6, 0.8, 0.9	1, 0.5, 0.25, 0.167, 0.125, 0.111	0.1
4. Flock-level variation in exposure, constant virtual prevalence	0.18	0.11, 0.22, 0.44, 0.67, 0.89, 1	0.02, 0.04, 0.08, 0.12, 0.16, 0.18

[§] One value in a box applies to the entire population, 6 values in a box indicate the value for each of 6 flocks

4.3. Results

The response to selection in the standard scenario - a prevalence of 0.1 with 100% exposure across all 6 flocks - was the same as in chapter 3 and in line with the predicted value.

4.3.1. Variation in prevalence due to the environment at full exposure

The accuracy of selection is higher in the absence of variation in flock prevalence (Table 4.2), and in the case of variation higher when weightings are based on population-wide parameters rather than flock specific. This confirms the validity of threshold approach, which weights observations equally regardless of prevalence.

Table 4.2 Accuracy of selection (*s.e.*) obtained from simulation, when flock prevalences differ due to environmental factors based on population or flock specific weights, at full exposure.

Information source	Accuracy	
	Flock prevalences	Population weights Flock specific weights
OP		
0.1	0.317 (0.030)	0.317 (0.030)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18	0.307 (0.030)	0.292 (0.031)
60HS		
0.1	0.371 (0.064)	0.371 (0.064)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18	0.350 (0.062)	0.339 (0.062)
OP 60HS		
0.1	0.462 (0.050)	0.462 (0.050)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18	0.438 (0.050)	0.422 (0.050)

In contrast, differences in flock prevalences due to environmental factors have a positive effect on the response to selection based on OP (Table 4.3), and this is directly related to the prevalence of the most severely affected flock(s). Within the variation considered, a higher prevalence allows for more stringent selection and a

higher accuracy, and high prevalence flocks do indeed supply all the selected animals (not shown).

If HS information is used, variation in flock prevalence has a negative effect on the response to selection. As with the accuracy, responses to selection are slightly lower if flock-prevalence-specific index weights are used rather than population-wide parameters. Flock-specific weightings apparently put too much emphasis on animals from high prevalence flocks.

Table 4.3 *Simulated response to selection (s.e.) on liability scale if flock prevalences differ due to environmental factors*

Information source	Selected fraction		
	10%	25%	50%
OP			
0.1	-0.057 (0.065)	-0.057 (0.053)	-0.057 (0.048)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18	-0.092 (0.102)	-0.090 (0.073)	-0.077 (0.055)
60HS			
0.1	-0.313 (0.116)	-0.247 (0.079)	-0.164 (0.060)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18	-0.293 (0.116)	-0.224 (0.077)	-0.156 (0.058)
OP 60HS			
0.1	-0.346 (0.112)	-0.278 (0.074)	-0.195 (0.057)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18	-0.333 (0.109)	-0.255 (0.074)	-0.184 (0.055)

4.3.2. *Variation in virtual prevalence and exposure at population level, leading to the same observed prevalence*

Table 4.4 and Figure 4.2 show that the response to selection tends to decrease with lower exposure. At full or high exposure and with intense selection, the predictions overestimate the simulated results by up to 20%, which is in line with earlier results with full exposure (chapter 3), and is attributed to relationships among selection candidates and the non-linear relationship between h_L^2 and h_{01}^2 . The simulations, however, show hardly any effect of exposure provided it is 40% or higher. At medium and low exposure, the predictions are very well in line with the simulations.

Table 4.4 Response to selection on the liability scale if observed prevalence is 0.1, but virtual prevalence is higher and exposure is lower than 100% (no differences among flocks). Shown are expected (*exp*) and simulated responses (*sim*) (*s.e.*)

Information source	Virtual prevalence	Exposure	Selected fraction					
			10%		25%		50%	
OP			exp	Sim	exp	sim	Exp	sim
	0.909	11%	-0.006	-0.003 (0.0077)	-0.006	-0.005 (0.063)	-0.006	-0.005 (0.058)
	0.500	20%	-0.019	-0.026 (0.0075)	-0.019	-0.026 (0.061)	-0.019	-0.028 (0.058)
	0.250	40%	-0.034	-0.042 (0.0072)	-0.034	-0.041 (0.060)	-0.034	-0.043 (0.055)
	0.167	60%	-0.044	-0.049 (0.0069)	-0.044	-0.052 (0.059)	-0.044	-0.052 (0.054)
	0.125	80%	-0.052	-0.054 (0.0070)	-0.052	-0.056 (0.058)	-0.052	-0.056 (0.053)
	0.111	90%	-0.055	-0.059 (0.068)	-0.055	-0.058 (0.055)	-0.055	-0.057 (0.051)
	0.100	100%	-0.059	-0.057 (0.068)	-0.059	-0.057 (0.057)	-0.059	-0.057 (0.052)
60HS								
	0.909	11%	-0.061	-0.057 (0.156)	-0.044	-0.040 (0.101)	-0.028	-0.025 (0.073)
	0.500	20%	-0.237	-0.214 (0.146)	-0.171	-0.163 (0.099)	-0.108	-0.106 (0.075)
	0.250	40%	-0.322	-0.285 (0.139)	-0.234	-0.217 (0.094)	-0.147	-0.141 (0.072)
	0.167	60%	-0.351	-0.306 (0.127)	-0.254	-0.237 (0.088)	-0.160	-0.155 (0.068)
	0.125	80%	-0.366	-0.309 (0.128)	-0.265	-0.240 (0.087)	-0.167	-0.160 (0.066)
	0.111	90%	-0.372	-0.306 (0.124)	-0.269	-0.244 (0.085)	-0.169	-0.163 (0.066)
	0.100	100%	-0.376	-0.313 (0.127)	-0.272	-0.247 (0.091)	-0.171	-0.164 (0.067)
OP 60HS								
	0.909	11%	-0.064	-0.063 (0.158)	-0.064	-0.046 (0.102)	-0.047	-0.030 (0.072)
	0.500	20%	-0.247	-0.237 (0.144)	-0.181	-0.182 (0.098)	-0.114	-0.121 (0.074)
	0.250	40%	-0.350	-0.312 (0.136)	-0.259	-0.244 (0.091)	-0.168	-0.164 (0.070)
	0.167	60%	-0.388	-0.337 (0.122)	-0.290	-0.265 (0.085)	-0.191	-0.182 (0.065)
	0.125	80%	-0.408	-0.337 (0.125)	-0.307	-0.270 (0.084)	-0.206	-0.189 (0.063)
	0.111	90%	-0.414	-0.337 (0.120)	-0.313	-0.273 (0.082)	-0.211	-0.192 (0.063)
	0.100	100%	-0.420	-0.346 (0.121)	-0.318	-0.278 (0.086)	-0.216	-0.195 (0.063)

These results indicate that in practice exposure levels of less than 100% do not affect the response to selection much at a given observed prevalence, unless exposure is extremely low, i.e. less than 40%. However, these results do assume that the exposure rate is the same in all flocks.

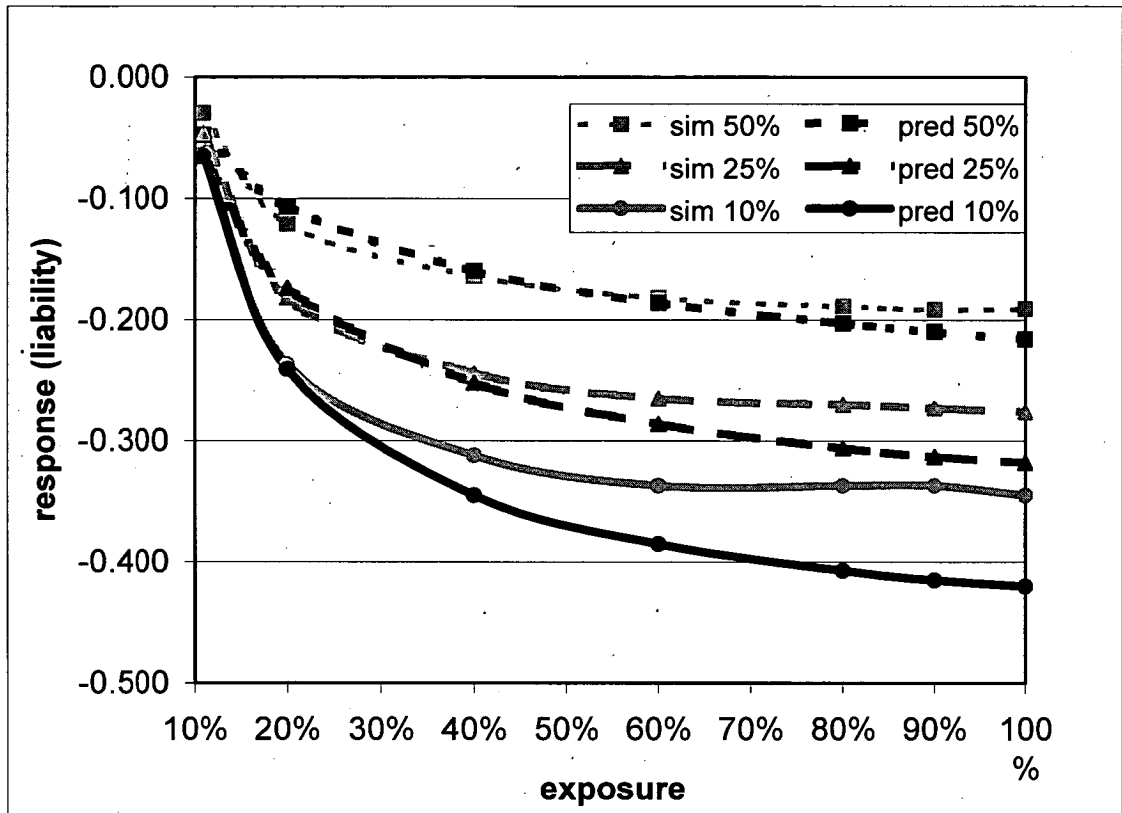


Figure 4.2 Simulated and predicted response to selection for OP 60HS, as a function of exposure and selection intensity, for an observed prevalence=0.1

4.3.3. Variation in virtual prevalence and exposure at flock level

Results for the scenario in which flock exposure levels vary in a way that offsets the variation among flocks in prevalence are presented in Table 4.5. Comparing these responses with those for a prevalence of 0.1 in Table 4.3 shows that significant reductions occur in expected genetic progress, even when HS are included. If results are compared with a scenario with incomplete exposure, but no variation across flocks, like the case of 40% or 60% exposure in Table 4.4, a sizeable reduction in response can be seen. Where HS are involved, this is true for both theoretical expectations and simulations. Therefore, these results indicate that between-flock

variation in exposure has an impact on genetic gain over and above that due to incomplete exposure, alone.

Table 4.5 *Expected and realised response (s.e.) to selection if between-flock variation in both virtual prevalence and exposure result in equal observed prevalences among 6 flocks (expectations based on full knowledge of exposure and population parameters, weightings in simulation based on observed prevalence).*

Information source	Selected fraction					
	10%		25%		50%	
	exp	sim	exp	sim	exp	sim
OP	-0.058	-0.030 (0.071)	-0.051	-0.029 (0.060)	-0.038	-0.028 (0.055)
60HS	-0.228	-0.218 (0.148)	-0.165	-0.160 (0.102)	-0.104	-0.100 (0.072)
OP60HS	-0.246	-0.244 (0.149)	-0.182	-0.180 (0.100)	-0.119	-0.117 (0.070)

4.3.4. Variation in observed prevalence due to different exposure at flock level, at the same virtual prevalence

Table 4.6 shows response to selection for the scenarios where flock prevalences differ as a result of exposure, while the virtual prevalence is the same for all 6 flocks. As in Table 4.3 and as expected, a variation in flock prevalence has a positive effect on the response to selection for OP, but not if HS are included. Selection of the top 10% on OP is from the flock with the highest prevalence, and since exposure is 100% in this flock, hardly any loss is observed compared to the scenario with 100% exposure throughout. With less intensive selection, animals are selected from flocks with lower exposures and the response to selection is lower, but it is still higher than in a scenario with equal (0.1) prevalence in all flocks.

Table 4.6 *Response to selection (s.e.) if the observed prevalences in each of 6 flocks vary as a result of differences in exposure at the same virtual prevalence of 0.18, compared to the standard scenario (prevalence of 0.1, full exposure) and a scenario with full exposure and a prevalence of 0.18. Expectations based on population parameters.*

Information source		Selected fraction					
Observed flock p		10%		25%		50%	
		exp	Sim	exp	sim	Exp	Sim
OP							
0.1		-0.059	-0.057 (0.068)	-0.059	-0.057 (0.056)	-0.059	-0.057 (0.052)
0.18		-0.096	-0.096 (0.064)	-0.096	-0.096 (0.054)	-0.096	-0.095 (0.050)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18		-0.096	-0.092 (0.103)	-0.089	-0.088 (0.071)	-0.069	-0.071 (0.058)
60HS							
0.1		-0.376	-0.313 (0.123)	-0.272	-0.247 (0.086)	-0.171	-0.164 (0.066)
0.18		-0.398	-0.341 (0.121)	-0.288	-0.264 (0.088)	-0.181	-0.173 (0.067)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18		-0.322	-0.276 (0.128)	-0.234	-0.214 (0.091)	-0.147	-0.142 (0.068)
OP60HS							
0.1		-0.420	-0.346 (0.119)	-0.318	-0.278 (0.081)	-0.216	-0.195 (0.062)
0.18		-0.450	-0.394 (0.112)	-0.344	-0.313 (0.081)	-0.235	-0.218 (0.061)
0.02, 0.04, 0.08, 0.12, 0.16, 0.18		-0.355	-0.316 (0.117)	-0.266	-0.246 (0.085)	-0.177	-0.169 (0.064)

For OP the responses realised in the simulation are very close to the predicted responses. With the inclusion of HS, exposure levels of less than 100% have a small negative effect on the response to selection, compared to both equal observed prevalences (0.1) across flocks and environmental variation in prevalence (Table 4.3). The differences are small, and increase with less intensive selection (i.e. selection in flocks with lower exposure levels). Selection on an index combining OP and HS is superior to either OP or HS, but the selection response is reduced when there is variation in exposure among flocks. It can be concluded that in practice, ignoring variation in virtual prevalence and exposure may therefore lead to only a minor overestimation of genetic progress.

4.4. Discussion

While in the previous chapter the effects of a binary distribution of a trait on the expected response to selection were quantified for scenarios with highly standardised conditions, in this chapter the emphasis was on the effects of variation in prevalence and exposure. Variation in observed prevalence among populations or flocks was considered to be caused by variation in environmental factors or in exposure, or a combination of the two. Theoretical predictions were developed and tested in stochastic simulations.

Differences within or between flocks in prevalence have a positive effect when only OP is used in selection, because the healthy animals in the flocks with highest prevalence are correctly identified as the most resistant. At the other extreme, it also increases the ability to identify the most susceptible animals (the affected animals in flocks with the lowest prevalence), so there will be a positive effect at any prevalence, except in the special case when the number of healthy animals is the same as the number of animals to be selected. It could be expected that this would no longer be the case when HS information is used. It appears, however, that in the scenarios investigated, flock prevalence remains an important determining factor for selection. The selection candidates with the greatest number of healthy sibs in flocks with a high prevalence are selected preferentially. When estimating breeding values

from groups of HS, using flock-prevalence based weighting factors apparently put too much weight on animals in high prevalence flocks, and genetic progress was reduced slightly as a result. This shows that the threshold model, which puts equal emphasis on all HS groups of the same size, is not just a convenient way to deal with different prevalences and heterogeneity of variance across flocks, but does indeed lead to better selection decisions than flock specific weightings.

In this study, the health status of an animal was considered as a function of its phenotype if exposed and its probability of exposure, so that an animal could be diseased only if it had a susceptible phenotype and was exposed to infection. In practice, one might think of a situation in which animals are more or less susceptible, with the more susceptible animals becoming affected at low pathogen levels, and the more resistant only at higher pathogen challenges. The scenarios with differences in prevalence among flocks do in fact model the interaction between phenotype and exposure insofar as animals that are more susceptible become diseased at lower exposure rates than less-susceptible animals. In terms of the threshold model; in this study the prevalence was determined by the threshold (at population or flock level) and the liability for each individual. While the latter reflects the resistance of an animal at a phenotypic level, the threshold is determined by the environment and one factor would be the magnitude of the pathogen challenge. A higher pathogen challenge then corresponds with a shift of the threshold to the left, so that a group of animals with certain liabilities will become affected. Thus, conclusions drawn from these scenarios should also apply to more general situations, in which animals in different flocks (or other classes) differ in their degree of resistance, depending on pathogen challenge and environmental factors.

Incomplete exposure of animals to a pathogen will result in incorrect classification of susceptible animals as resistant. For the scenarios investigated this has, however, only a limited effect on the accuracy of selection and the selection response. Predictions of genetic progress, based on the assumption that both exposure and prevalence at full exposure are known exactly, closely follow the simulated results. In practice only the observed prevalence (the product of exposure and prevalence at

full exposure) will be known. Depending on general knowledge of the particular disease and flocks, it may be possible to make more or less correct assumptions of exposure and prevalence. The various scenarios show, however, that predictions – and selection responses - are not very sensitive to these assumptions as long as exposure is above 40% and similar across flocks.

Another important assumption was that the heritability of resistance was known exactly. Unless it can be estimated in a deliberately exposed population, estimation of the heritability will be affected by the same issue of exposure. If the heritability was estimated in an incompletely exposed population but under the assumption of full exposure, the heritability would be estimated by dividing the realised genetic variance ($e^2\sigma_g^2$) by the observed phenotypic variance ($ep(1-ep)$) giving the estimated heritability ($\hat{h}_{01}^2$) as

$$\hat{h}_{01}^2 = \frac{e - ep}{1 - ep} h_{01}^2 \text{ which is less than the true } h_{01}^2 \text{ for any } e \text{ less than } 1. \text{ This estimate}$$

then automatically leads to a lower estimate for the expected genetic progress, counteracting any overestimations that would result from assuming too high an exposure in the prediction.

It was assumed that, within flock, exposure was completely random, i.e. not related to either certain families or genetic merit of animals. If this assumption does not hold, for instance due to common environments of relatives (e.g. maternal and litter effects for full sibs) this is expected to lead to a reduction of the potential genetic gain. The observation that simulated responses to selection fell short of predicted responses, suggests that this did indeed happen in this simulation. As simulated, environmental effects differed across flocks, but because most HS families were restricted to 1 flock (and at the most 3), an association between family and environment was created. This was most extreme in the scenario where flock exposure varied, but resulted in the same observed prevalence. Due to low exposure, the most resistant HS groups in flocks with a high virtual prevalence could no longer be identified as such and genetic progress was much lower. This is a special case, which may occur in practice if farmers maintain the disease in their flocks at a

similar level through different management practices; enhancement of animals' resistance or limiting exposure.

The prevalence observed in the field is the product of the exposure and the prevalence at full exposure (termed virtual exposure in this study). At a given observed prevalence, the accuracy of selection will increase with increasing exposure and hence lower virtual prevalence, but this effect is relatively small if exposure is over 0.2. Note that the observed prevalence also serves as a lower limit for the exposure when prevalence is 1, and that while very high prevalences are detrimental for genetic progress (due to a lack of variation) prevalences of 0.7 give good results for any exposure over 0.4.

Similarly, the observed prevalence serves as a lower limit for the virtual prevalence (when exposure is complete) so that an assessment can be made of whether the virtual prevalence will be too small to allow for any meaningful genetic progress. This supports the assertion of Rothschild (1998) that, in the case of pigs bred and selected under high health status nucleus conditions, there is not a great opportunity to make genetic progress for disease resistance. Biosecurity is generally much higher in pig breeding populations than in sheep, and for sheep the results of this study would apply only to endemic diseases. Certain scenarios require the use for breeding of animals that were at some stage diseased, depending on the nature of the disease this may or may not be realistic.

For practical breeding programmes these results indicate that incomplete exposure should not hamper achieving genetic progress. Provided sufficient numbers of relatives of selection candidates are included in the analysis, considerable progress is possible. Lack of exposure becomes a serious problem only when exposure is very low (less than 40%) or when it masks the fact that all or practically all animals in the population are fully susceptible to the disease. In many cases it will be possible to estimate exposure to the disease in a subset of the population, e.g. by tests for antibodies or, in the case of footrot, detailed hoof inspection and bacterial culture.

Where it was possible to quantify expectations of genetic progress, especially for variations in prevalence and exposure, these predictions showed trends similar to the simulation results but with typical overestimates of up to 20%. These overestimates were similar for the scenarios in chapter 3 in which absence of inter-flock variation in prevalence and exposure was assumed. Conversion of predicted and simulated selection results from the liability to the observed scale showed that overestimates on the liability scale are negligible in terms of the proportion of animals affected.

4.4.1. Conclusions

Variation in prevalence among flocks has a positive effect on genetic progress for OP, but is slightly negative if HS are included. Exposure of less than 100% has a negative effect on progress, but at population level the effect is limited if exposure is 40% or higher. With variation in exposure across flocks, selection will tend to be from those with highest observed prevalence (and also highest exposure) so that this is not a problem with intense selection. The highest risk with incomplete exposure is that it may hide undesirably high prevalences and lack of variation in resistance. Variation in exposure across groups of relatives may have a negative effect on the progress towards resistance, if it is not reflected in the observed prevalence.

Appendix 4.1 Derivation of the accuracy of selection for a group of incompletely exposed half sibs

In general, the accuracy of selection (ρ) is calculated based on the correlation between breeding value and its predictor from the observed data:

$$\rho = \frac{\sigma_{gp}}{\sqrt{\sigma_g^2 \sigma_p^2}}$$

with σ_{gp} the covariance between genotype and phenotype and σ_g^2 the genetic and σ_p^2 the phenotypic variation.

Each of these is calculated for n HS, of which e are exposed, in the following steps:

Genetic variance

The genetic variation σ_g^2 is not affected by exposure and on the liability scale is equal to $\sigma_g^2 = h_{01}^2 p(1-p)$, with p based on full exposure.

Covariance between genotype and phenotype

For $(1-e)$ unexposed HS the covariance between the phenotype and the genotype of the selection candidate on the liability scale is equal to 0. For e exposed HS it is $\frac{1}{4}h_{01}^2 p(1-p)$, so that across all HS $\sigma_{gp} = \frac{1}{4}h_{01}^2 ep(1-p)$

Phenotypic variance

As the incidence in a group of partially exposed unrelated animals is ep , the (binomial) variance is $ep(1-ep)$ rather than $p(1-p)$. When the population is subdivided into a family structure, the total variance is the sum of the between- and the within-family variance. The between-family variance for exposed animals is $\frac{1}{4}h_{01}^2 p(1-p)$ and since these animals make up a proportion e of the total family, between family variance is $\frac{1}{4}h_{01}^2 e^2 p(1-p)$. The within family variance is the phenotypic variance for a group n individuals, $ep(1-ep)/n$, minus the covariance between family members. As above, the latter is 0 for unexposed animals and $\frac{1}{4}h_{01}^2 e^2 p(1-p)/n$ for exposed animals. Summing the various parts gives the phenotypic variance (σ_p^2) as

$$\sigma_p^2 = \frac{ep(1-ep) - \frac{1}{4}h_{01}^2 e^2 p(1-p)}{n} + \frac{1}{4}h_{01}^2 e^2 p(1-p)$$

and the accuracy of selection is

$$\rho = \frac{\frac{1}{4}h_{01}^2 ep(1-p)}{\sqrt{p(1-p)h_{01}^2 \left\{ \frac{ep(1-ep) - \frac{1}{4}h_{01}^2 e^2 p(1-p)}{n} + \frac{1}{4}h_{01}^2 e^2 p(1-p) \right\}}}$$

which can be simplified to:

$$\rho = \frac{1}{4}h_{01} \sqrt{\frac{e(1-p)n}{(1-ep) + e(1-p)(n-1)\frac{1}{4}h_{01}^2}}$$

Note that the accuracy is different for p and $1-p$, unless $e = 0$ or $e=1$.

Chapter 5. The effect of footrot on weight gain in sheep

5.1. Introduction

Footrot is a highly contagious bacterial disease of sheep affecting the interdigital skin and surrounding soft and hard horn of a hoof, often resulting in severe lameness.

There are various options for control and treatment, and the most effective strategy appears to be prompt treatment of affected animals, which also reduces spread of the infection (Egerton, 2000; Green *et al.*, 2007). In Britain it is estimated that about 6% of adult ewes and 3% of lambs are affected at any time (Grogono-Thomas *et al.* 1998; Wassink and Green, 2001; Clements *et al.*, 2002) and the costs associated with the disease have been estimated at £24.4M annually for Great Britain or £1.32 per ewe and £0.15 per lamb (Chapter 2).

Infection of animals by a disease is expected to affect their general wellbeing and performance. For example, estimates of the reduction of live weight in lambs infected with internal parasites range from 6.2 to 23% (Coop *et al.*, 1985; Mackay *et al.*, 1998). Sheep scab leads to a 53% reduction in growth rate in lambs (Kirkwood, 1980) and a 10% loss in birth weight (Sargison *et al.*, 1995), while losses in lamb weaning weight due to Maedi-Visna have been estimated at 12% for the most severe cases (Pekelder, 1994). Based on results of Symons (1978) and Stewart *et al.* (1984) it can be estimated that ewes infected with footrot have a reduced lamb output of 18%. Marshall *et al.* (1991) investigated the long-term effect of footrot on the live weight of wethers that were 1.5 years old at the start of a 2 year trial. One group of animals that was left largely untreated over the study period showed a significant decrease in body weight at times of high footrot prevalence, but on average animals regained the lost weight in the following months. Any variation between animals in their response to footrot and the nature of this variation were not studied.

Genetic variation in resistance to footrot has been demonstrated (Raadsma *et al.*, 1994, Conington *et al.*, 2007), with the heritability depending on the definition of footrot (number of classes, observed or underlying scale) and reaching values up to 0.3. While Raadsma *et al.* (1994) showed an increased risk of footrot with heavier

live weights, they did not estimate the effect of footrot on live weight gain. Breeding objectives for most selection programmes for meat or multipurpose sheep breeds include higher growth rates, and it is important to know if higher weights achieved through selection will lead to higher susceptibility to footrot and consequently higher weight losses.

The current study aims to estimate the effect of footrot in lambs on their growth performance. Data on footrot severity and live weights are used from the experiment described by Raadsma *et al.* (1994) in which lambs were exposed to footrot and vaccinated 6 or 9 weeks later. A further aim is to separate effects of live weight on the risk of footrot from the effect of footrot on subsequent live weights. To this end, a number of extra traits are defined to describe footrot severity and the effects on growth. Genetic and phenotypic correlations between footrot severity and weight (gain) are estimated, allowing prediction of the effects of selection on increased weights on footrot and its consequences.

5.2. Material and Methods

5.2.1. Animals and treatments

A study was conducted over a four year period, as described in detail by Raadsma *et al.* (1994). Each year, two groups of about 200 Merino sheep were infected with footrot on two separate occasions followed by vaccination. All data from year 2, when the trial was interrupted by a dog attack that killed some sheep and required treatment of others, were eliminated, however. At the start of trial 1 when animals were about 10 months of age they were artificially infected for the first time, the second infection through exposure on pasture (start of trial 2) was about 33 weeks after the first and the two trials combined took 48 weeks (Table 5.1). Weights at, or close to, the start of each of these two trials and at 3-weekly intervals were recorded for up to 15 weeks after infection, although not all weights were taken on all animals (see Table 5.2). An overall footrot score was assigned to each animal at the same 3-weekly intervals on a 0 (no footrot) to 5 (severe footrot) scale and the number of feet affected was recorded. Data from animals that had footrot in week 27 (6 weeks prior to the second infection) were not considered for the second trial. Animals were

vaccinated with homologous strain vaccines 9 and 6 weeks post infection in each trial respectively, inducing a high degree of healing (Raadsma et al, 1994)

The total dataset comprised 1267 animals with complete records for the first trial (Table 5.2). Of these 1225 animals with a 27 week weight record were included in the analysis of the second trial (group size varying from 205 to 220 in trial 1 and 198 to 214 in trial 2).

Table 5.1 *Timeline of treatments and records over the two trials*

Reference	Time against Reference	Event	Records
challenge 1 ^a	-5 days	predisposition on wet mats	
challenge 1	0 days	infection through bandaging bandages removed, remain on wet mats	
challenge 1	+3 days		
challenge 1	+2 wk	1 st inspection and exit to pasture	footrot score, live weight
challenge 1	+3 wk	Inspection	footrot score, live weight
challenge 1	+6 wk	Inspection	footrot score, live weight
challenge 1	+9 wk	inspection + vaccination	footrot score, live weight
challenge 1	+12 wk	inspection + booster	footrot score, live weight
challenge 1	+15 wk	Inspection	footrot score, live weight
challenge 1	+27 wk	Inspection	footrot score, live weight
challenge 2 ^b	0 wk	predisposition with donor sheep	
challenge 2	+ 3 wk	first inspection	footrot score, live weight
challenge 2	+ 6 wk	inspection + vaccination	footrot score, live weight
challenge 2	+ 9 wk	inspection + booster	footrot score, live weight
challenge 2	+ 12 wk	Inspection	footrot score, live weight
challenge 2	+ 15 wk	Inspection	footrot score, live weight

^achallenge 1 occurred at 10 months of age

^bchallenge 2 occurred 33 weeks after challenge 1

Table 5.2 *Number of animals recorded and average footrot score, number of feet affected and average live weight over the two trials*

Time since start (weeks)	Number of records	Average footrot score	Average number of feet affected	Average live weight (kg)
2	1267	1.80	1.10	24.3
3	205	1.74	1.07	25.5
6	856	1.62	0.83	27.9
9	1267	1.48	0.70	28.9
12	1265	0.70	0.33	30.0
15	1265	0.24	0.10	31.7
27	1267	0.06	0.03	33.9
27 ^{\$}	1225	0	0	34.0
36	1225	2.18	2.12	35.8
39	1224	2.57	2.15	33.7
42	1224	1.81	1.47	33.1
45	1225	0.56	0.32	33.7
48	1225	0.54	0.38	34.6

^{\$} includes only those free of footrot for inclusion in trial 2

5.2.2. *Quantifying the Impact of Footrot on Weight Gain*

Initial inspections of the live weight data indicated that impacts of footrot on weight gain are transient. Therefore, additional traits have to be derived from the raw data to capture these transient effects. To enable this, a general framework for the effect of infection or disease on the live weight of an animal was developed as shown in Figure 5.1. In terms of effects on live weight, the first noticeable effect will be weight loss or reduced gain some time after the infection. This may coincide with the first observation of clinical signs of disease, precede them or follow later. If an animal recovers from the disease, the weight loss will reach a maximum and then decline and there may or may not be a permanent long-term effect on the animal's live weight.

Figure 5.1 shows a hypothetical profile for the change in footrot score that peaks at time $t=6$; a straight line depicts the weight gain of an unaffected animal, and a curve that of an affected animal that initially loses weight and then regains much of the weight loss through compensatory growth.

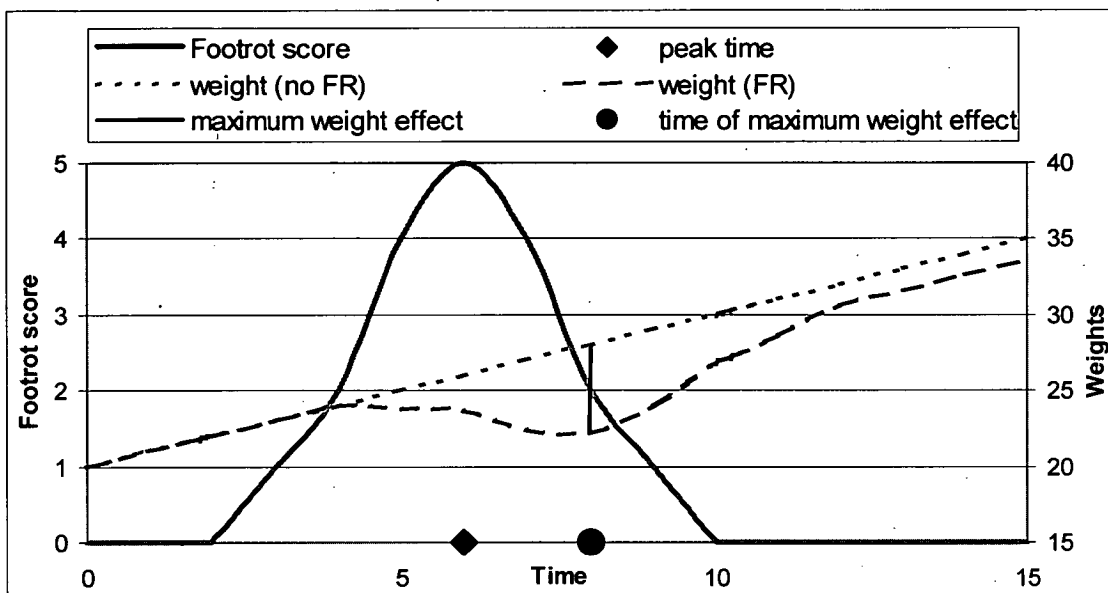


Figure 5.1 General framework for the development of footrot and weight following infection (footrot score on 0 to 5 scale, time after infection and weights in arbitrary units).

Based on this figure the following new traits can be defined:

Peak time ($tmfr$): the time between infection and the highest footrot score,

Maximum weight effect ($maxwte$): the biggest negative difference in weight of an infected animal compared to that expected from unaffected growth,

Time of maximum weight effect ($tmwe$): the time at which the maximum weight effect occurs since infection,

Time ($tmfr$) between maximum footrot and maximum weight loss.

5.2.3. Analysis

The effect of footrot on weight gain (or loss) can be estimated at two levels: a general estimate at population level and an individual animal estimate. The former can be estimated by comparing unaffected animals with affected animals, taking into

account severity of the disease (Marshall *et al.* 1991). The second method, which allows estimation of between animal variation, requires comparison of the actual growth curve of an affected animal with the unobserved curve predicted for that individual animal if had not been affected.

In line with Raadsma *et al.* (1994), animals were deemed unaffected if they did not have any overall footrot scores > 1 over a trial. Growth curves for unaffected animals in trial 1 were estimated using SAS GLM (SAS Institute Inc., 1989) fitting the model:

$$Y_{ijklmn} = flock_i + group_j + sex_k + rear\ type_l + dam\ age_m + b_1t + (b_2t^2) + (b_3t^3) + b_4day + b_5wtst + b_{6j}t.group_j + b_{7k}t.sex_k + e_{ijklmn}$$

With:

Y_{ijklmn} = live weight of animal n at time t since infection

$flock_i$ = effect of flock of origin ($i=1-4$)

$group_j$ = effect of treatment group ($j=1-6$)

sex_k = effect of sex (female, castrate)

$rear\ type_l$ = effect of rear type ($l= 1,2,3$)

$dam\ age_m$ = effect of age of dam ($m=2-9$)

day = day of birth within the calendar year

$wtst$ = start weight

t = time since infection, in weeks

$t.group_j$ = the interaction of $group$ with t

$t.sex_k$ = the interaction of sex with t

b_1, b_2, b_3 = linear, quadratic and cubic regression of weight on time since infection

b_4 = linear regression of weight on day of birth

b_5 = linear regression of weight on start weight

b_{6j}, b_{7k} = group or sex specific linear regressions of weight on time since infection

For trial 2 the same model was used, except that the sex by time interaction was not significant and was eliminated from the model. Note that for trial 1 the earliest available weight was two weeks after infection and this was considered the start

weight. In trial 2, the weight 6 weeks prior to the second infection (27 weeks after the first infection) was used as start weight.

For all animals, these regressions were then used to predict live weight at time t , using (i) the linear regression ($pwtl_i$) only, (ii) linear and quadratic terms ($pwtq_i$) and (iii) linear, quadratic and cubic ($pwtc_i$) terms:

$$pwtl_i = wtst + b_1t + b_5wtst + b_6t \cdot group_j + b_7kt \cdot sex_k$$

$$pwtq_i = wtst + b_1t + b_2t^2 + b_5wtst + b_6t \cdot group_j + b_7kt \cdot sex_k$$

$$pwtc_i = wtst + b_1t + b_2t^2 + b_3t^3 + b_5wtst + b_6t \cdot group_j + b_7kt \cdot sex_k$$

The same procedure was used for trial 2, but without the sex-specific regression of weight on time.

Deviations of actual from predicted weights, at various time points, were calculated for each animal, separately for the $pwtl$, $pwtq$ and $pwtc$ predictions. In affected animals, this deviation is expected to be negative (i.e. a reduction in weight gain). The maximum weight effect ($maxwte$) was the most negative deviation, and the time this occurred was the week of maximum weight effect ($tmwe$). In cases where the same maximum weight effect occurred more than once, the time of the maximum was the average of the occurrences when this maximum occurred. The variable $endwte$ was calculated as the weight deviation at the end of each trial, again separately for predictions based on linear, quadratic or cubic regressions.

The effect of footrot on these traits was then estimated with SAS GLM for all animals in each trial as:

$$Y_{ijklmn} = flock_i + group_j + sex_k + rear\ type_l + dam\ age_m + b_1day + b_2footrot + e_{ijklmn}$$

Where $Y_{ijklmn} = maxwte$ or $tmwe$ and $footrot$ = sum of footrot scores or maximum footrot score during the trial.

Regardless of the effects of footrot, $maxwte$ (and possibly $tmwe$) can be expected to have a genetic component, as it is a measure of growth compared to a group average. In this study we are interested in whether this genetic component is related to

measures of footrot resistance. Genetic analyses were done with an animal model using VCE 5.1 (Kovac and Groeneveld, 2003), generally with the model:

$$Y_{ijklmno} = flock_i + group_j + sex_k + rear\ type_l + dam\ age_m + b_1.day + b_2.wtst + b_3.footrot + animal_n + e_{ijklmno}$$

with variables defined as above and $animal_n$ is a random effect accounting for the direct genetic effect associated with animal n . The start weight effect accounts for the weight related risk of contracting footrot and was excluded from certain models in multivariate analyses of live weights. The footrot effect was not included when analysing footrot severity or in multivariate analyses with a footrot measure as one of the dependent traits. The pedigree contained 5815 animals.

5.3. Results

The average overall footrot score and live weights for animals deemed free of footrot ($maxFR < 2$) and also for affected animals are presented in Figure 5.2. The development over time confirms the basic framework in Figure 5.1. It can be seen that the impacts on live weight do appear to be transient, occurring after the time of maximum footrot severity.

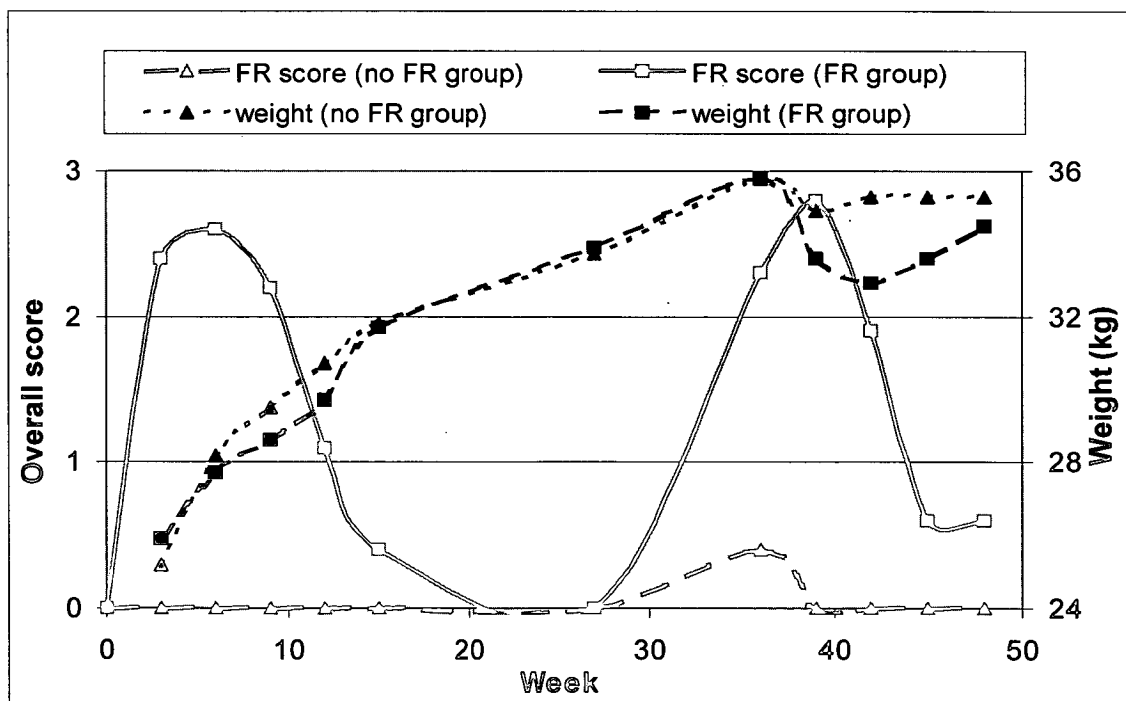


Figure 5.2 Average overall score and live weight for animals with a maximum footrot score < 2 (no FR group) and others (FR group)

Weights of animals were predicted using their weight at the start of the trial and growth curves estimated from the healthy animals. In trial 1, there were 435 healthy animals with a total of 2164 weight records, while only 84 animals, with 419 weights, were considered unaffected in trial 2. Linear, quadratic and cubic terms of the growth curves were significant in both trials.

5.3.1. Effect of footrot on live weight

Tables 5.3 summarise the parameters describing the impact of footrot. The traits shown are: *sumFR* the sum of all footrot scores over the trial, *maxFR* the maximum of the footrot scores over the trial, and other parameters are defined above. With regard to timing, it can be seen that peaks for footrot score and the maximum weight effect could occur at any time during the trials (from week 3 to 27 in trial 1 and week 3 to 15 in trial 2), but the average time of the maximum footrot score in both trials was between 6 and 8 weeks, with the maximum weight effect following later. In trial 1, depending on how the healthy growth was predicted, the maximum weight effect occurred 7 to 10 weeks after the highest footrot score (*twe_fr*), while in trial 2 on average the delay was only 2 to 3 weeks. There were some minor differences in the estimated effects using linear, quadratic or cubic terms in the prediction of healthy growth.

Over the duration of trial 1, animals (both affected and not affected) gained an average of almost 10 kg and the average maximum weight effect (*maxwte*) was, as expected, negative (-1.8 to -3.3 kg), but by the end of the trial the effect on weight had almost completely disappeared. In trial 2, there was little weight gain (+0.6 kg) and the average maximum weight effect was larger (-4.1 to -4.7 kg). At the end of trial 2, which was much shorter, only a small weight loss remained, showing important compensatory growth.

The maximum weight effect is only moderately correlated with the weight at the end of each trial, whereas there is a much stronger correlation with the growth over the trial (adjusted for start weight) (Table 5.4).

Table 5.3 *Distributions of footrot and weights traits. Weights in kg and times in weeks*

Trait	Trial 1				Trial 2			
	Mean	SD	Min	Max	Mean	SD	Min	Max
<i>All animals (trial 1 N= 1267, trial 2 N=1225)</i>								
Gain	9.6	5.4	-6.0	28.0	0.6	3.7	-14.0	12.5
<i>FRmax</i>	2.1	1.5	0	5	3.0	1.0	0	5
<i>FRsum</i>	5.8	5.3	0	24	7.7	3.9	0	20
<i>Unaffected animals (trial 1 N= 435, trial 2 N=84)</i>								
Gain	9.6	5.4	-4.0	28.0	1.8	2.2	-4.9	6.3
<i>FRmax</i>	0.2	0.4	0	1	0.4	0.5	0	1
<i>FRsum</i>	0.3	0.6	0	3	0.6	0.7	0	2
<i>Affected animals (trial 1 N= 832, trial 2 N=1141)</i>								
Gain	9.6	5.4	-6.0	25.0	0.5	3.7	-14.0	12.5
<i>FRmax</i>	3.1	0.7	2	5	3.1	0.7	2	5
<i>FRsum</i>	8.7	4.5	2	24	8.2	3.5	2	20
<i>Maxwte</i> linear	-1.8	3.4	-14.5	12.1	-4.1	3.2	-16.0	5.7
<i>Maxwte</i> quadr.	-3.2	3.4	-17.0	9.5	-4.7	3.2	-16.9	5.0
<i>Maxwte</i> cubic	-3.3	3.4	-17.0	9.4	-4.7	3.2	-17.0	4.9
<i>Endwte</i> linear	-0.1	3.7	-12.9	14.6	-0.7	3.4	-12.6	12.3
<i>Endwte</i> quadr.	-0.4	3.7	-13.3	14.2	-0.7	3.4	-12.5	12.4
<i>Endwte</i> cubic	-0.5	3.7	-13.5	14.0	-1.0	3.4	-12.8	12.0
<i>Tmfr</i>	7.6	3.5	3	27	6.3	2.1	3	15
<i>Tmwe</i> linear	17.5	9.6	3	27	9.4	3.4	3	15
<i>Tmwe</i> quadr.	15.4	8.2	3	27	8.7	3.2	3	15
<i>Tmwe</i> cubic	15.0	8.3	3	27	8.7	3.4	3	15
<i>Twe_fr</i> linear	9.9	10.7	-21	24	3.0	3.8	-9	12
<i>Twe_fr</i> quadr.	7.8	9.4	-18	24	2.4	3.6	-9	12
<i>Twe_fr</i> cubic	7.4	9.5	-18	24	2.3	3.7	-9	12

Weight at the start of each trial has a clear effect on the size of the maximum weight effect, with a regression of 0.05 to 0.10 kg/kg of start weight on maximum weight

loss in trial 1 (depending on exact model) and about 0.15 in trial 2 ($P < 0.01$). Table 5.5 shows the effect of footrot on the size and time of the maximum weight effect in trial 1 and trial 2, estimated as a linear regression and depending on the order (linear, quadratic and cubic) used to predict healthy growth. Again there is little difference between estimates based on linear, quadratic or cubic predictions of healthy growth. Footrot, by either measure has a highly significant negative effect on live weight. For example in trial 1, an animal with a *SumFR* of 5.8 (the average) would lose about 0.5 to 0.6 kg compared to healthy growth. The effect of the maximum scores is slightly larger, ca. 0.6 to 0.8 kg loss at a maximum score of 2.1. The effects in trial 2 are much larger, both due to higher regression coefficients and higher average footrot scores, resulting in 1.7 kg weight loss at a sum of scores of 7.7, and 2.5 kg loss for a maximum score of 3.0. In trial 1, the effect of severity of footrot on the time the maximum weight effect (*tmwe*) occurs is also highly significant, with the effect occurring sooner for more severe footrot. There is no such effect in trial 2.

Table 5.4 *Residual correlations of the maximum weight effect (maxwte) with end weight or weight gain over each trial, using a linear prediction of healthy growth*

	Trial 1	Trial 2
End weight	0.62	0.31
Gain over trial	0.81 ^{\$}	0.62 ^{\$}

^{\$} gain and maximum weight effect adjusted for start weight

5.3.2. Genetic effects on weight loss

Univariate estimates of genetic variances and heritabilities for the various footrot and derived traits, based on models accounting for the standard fixed effects, start weight and sum of footrot scores for affected animals are in Table 5.6. In this model the genetic variance for each trait is adjusted to the same severity of footrot and the same growth potential (as approximated by the start weight). In trial 1, the heritability for the maximum weight effect is about 0.30 and higher than that of gain over the same period, which is 0.17. The heritability is smaller in trial 2, but the phenotypic variance is similar. The time of peak footrot or maximum weight loss and the length

of time between them have very small heritabilities, which also depend on the order of covariates used to estimate healthy growth.

Table 5.5 *Effects of footrot severity on weight and time of maximum weight effect ('regression') and level of significance in trial 1 and 2, depending on the order of the regression used in the prediction of healthy growth*

Trait	Order	Footrot trait	Trial 1		Trial 2	
			Regression ^{\$}	P	Regression ^{\$}	P
<i>Maxwte</i>	L	<i>SumFR</i>	-0.08	<0.001	-0.22	<0.001
	Q	<i>SumFR</i>	-0.11	<0.001	-0.22	<0.001
	C	<i>SumFR</i>	-0.11	<0.001	-0.22	<0.001
<i>Maxwte</i>	L	<i>MaxFR</i>	-0.30	<0.001	-0.80	<0.001
	Q	<i>MaxFR</i>	-0.39	<0.001	-0.83	<0.001
	C	<i>MaxFR</i>	-0.39	<0.001	-0.81	<0.001
<i>Tmwe</i>	L	<i>SumFR</i>	-0.20	<0.001	-0.01	0.59
	Q	<i>SumFR</i>	-0.18	<0.001	-0.01	0.72
	C	<i>SumFR</i>	-0.17	<0.001	-0.00	0.93
<i>Tmwe</i>	L	<i>MaxFR</i>	-0.57	<0.001	-0.15	0.14
	Q	<i>MaxFR</i>	-0.53	<0.001	-0.13	0.16
	C	<i>MaxFR</i>	-0.53	<0.001	-0.14	0.17

^{\$} linear regression units are kg/point for *maxwte* and *endwte*, weeks/point for *tmwe*

Table 5.7 shows the genetic and phenotypic correlations between the various variables defined from trial 1 data, including the sum of footrot scores and the maximum footrot score, as well as heritabilities for each variable. The model fitted was the same for all traits and excluded the start weight. Because the two footrot score variables were highly correlated and a model with both included would not converge, estimates in Table 5.7 are based on two separate multivariate analyses each excluding either footrot measure (estimates for parameters in both analyses were essentially the same). The estimates for the heritability of these traits were similar to those presented by Raadsma *et al.* (1994). Note that the heritabilities are

slightly different from those in Table 5.6 for the same trait; this is due to the differences in model and the multivariate analysis.

Table 5.6 Genetic variances and heritabilities for weight effects in affected animals ($n=832$ for trial, $n=1141$ for trial 2), depending on the order of the regression used in prediction of healthy growth. Models fitted included the standard fixed effects and start weight and sum of footrot scores as covariates, and for trial 2 also sum of footrot scores from trial 1

	Order	Trial 1		Trial 2	
		Genetic variance	h^2 (s.e.)	Genetic variance	h^2 (s.e.)
<i>Maxwte</i>	L	2.74	0.31 (0.07)	1.32	0.16 (0.05)
	Q	2.33	0.29 (0.06)	1.24	0.15 (0.05)
	C	2.21	0.27 (0.06)	1.26	0.15 (0.05)
<i>Tmwe</i>	L	6.45	0.11 (0.04)	1.05	0.10 (0.05)
	Q	1.31	0.03 (0.04)	1.65	0.18 (0.05)
	C	0.38	0.01 (0.03)	1.84	0.18 (0.05)
<i>Tmfr</i>		0.61	0.06 (0.04)	0.09	0.03 (0.04)
<i>Twe_fr</i>	L	8.64	0.12 (0.04)	0.57	0.04 (0.04)
	Q	2.77	0.05 (0.04)	1.41	0.11 (0.04)
	C	1.41	0.02 (0.04)	1.70	0.13 (0.04)

Footrot score and maximum weight effect have a negative genetic correlation indicating that selection for increased resistance to footrot would lead to a lower impact on weight in affected animals. The phenotypic correlation between *maxwte* and *tmwe* is quite negative, which is consistent with some animals recovering, while others continue to lose weight, but the genetic correlation is small and positive. There is a strong positive correlation between *maxwte* and *wtst* showing that at equal severity of footrot, larger animals cope better with the disease, and the negative correlation with *tmwe* suggests that the effects that do occur will happen sooner. Based on the negative correlation of *maxFR* and *tmfr* it appears that the sooner footrot reaches maximum severity, the less severe it is.

Table 5.7 Genetic parameters (standard errors) and phenotypic correlations for weight and footrot traits including start weight in trial 1. Heritabilities on, genetic correlations below and phenotypic correlations above diagonal

	<i>Maxwte</i>	<i>Tmwte</i>	<i>SumFR</i>	<i>MaxFR</i>	<i>Tmfr</i>	<i>Wtst</i>
	linear	linear				
<i>Maxwte</i>	0.29	-0.14	-0.14	-0.15	0.03	-0.08
linear	(0.05)					
<i>Tmwte</i>	-0.79	0.21	-0.16	-0.12	-0.03	-0.42
linear	(0.11)	(0.04)				
<i>SumFR</i>	-0.24	-0.21	0.18	n.c.	-0.16	0.09
	(0.15)	(0.15)	(0.04)			
<i>MaxFR</i>	-0.25	-0.15	n.c.	0.14	-0.44	0.06
	(0.14)	(0.12)		(0.03)		
<i>Tmfr</i>	0.11	-0.22	-0.57	-0.79	0.08	0.01
	(0.23)	(0.22)	(0.21)	(0.14)	(0.03)	
<i>Wtst</i>	0.67	-0.85	0.05	-0.13	0.32	0.25
	(0.13)	(0.09)	(0.16)	(0.11)	(0.26)	(0.05)

n.c. = no convergence

In alternative analyses (not shown) in which the start weight was included in the model as a covariate, or *maxwte* and *tmwte* were based on estimates of healthy growth including a cubic term, genetic and phenotypic correlations were very similar.

The equivalent estimates for trial 2 are in Table 5.8. Compared to trial 1 (Table 5.7), estimates of genetic correlations between weight loss and footrot are stronger, but there does not seem to be a correlation of footrot severity with timing of its peak. The genetic correlation between start weight and *maxwte* is much lower, indicating that at this stage, genes that affect growth have a much smaller effect on the reaction to footrot.

In contrast, the alternative analysis (not shown) that included start weight as a covariate in the model for the other five traits, shows similar genetic correlations, but

phenotypic correlations between footrot severity and weight loss are much stronger, confirming an important effect of footrot on weight loss. The phenotypic correlation between *tmwe* and *tmfr* of 0.89 after both have been adjusted for start weight, shows a strong dependency between timing of footrot and the maximum weight loss.

Phenotypic correlations (repeatabilities) across the two trials for weight loss and footrot scores were low (Table 5.9), as was the genetic correlation between *maxwte* in the two trials, although of opposite sign to the phenotypic correlation. In contrast the severity of footrot in the two trials has a highly positive genetic correlation, indicating environmental effects specific to each trial.

Table 5.8 Genetic parameters (standard errors) and phenotypic correlations for weight and footrot traits including start weight in trial 2. Heritabilities on, genetic correlations below and phenotypic correlations above diagonal

	<i>Maxwte</i> linear	<i>Tmwe</i> linear	<i>SumFR</i>	<i>MaxFR</i>	<i>Tmfr</i>	<i>Wtst</i>
<i>Maxwte</i> linear	0.15 (0.03)	0.09	-0.26	-0.25	-0.01	-0.21
<i>Tmwe</i> linear	-0.41 (0.14)	0.11 (0.02)	-0.02	-0.04	0.05	-0.17
<i>SumFR</i>	-0.46 (0.09)	0.16 (0.11)	0.24 (0.04)	0.78	0.21	0.02
<i>MaxFR</i>	-0.57 (0.11)	-0.13 (0.13)	0.89 (0.05)	0.13 (0.03)	0.01	0.00
<i>Tmfr</i>	-0.01 (0.18)	0.48 (0.15)	0.06 (0.22)	-0.26 (0.25)	0.05 (0.02)	-0.02
<i>Wtst</i>	0.23 (0.11)	-0.36 (0.08)	-0.13 (0.10)	-0.14 (0.13)	0.62 (0.15)	0.49 (0.04)

Table 5.9 *Phenotypic and genetic correlations between the same trait in the two trials, estimated in a model fitting start weight as a covariate*

Correlation	<i>Maxwte</i> linear	<i>Tmwe</i> linear	<i>SumFR</i>
Phenotypic	-0.19	0.09	0.07
Genetic (s.e.)	0.15 (0.03)	0.78 (0.03)	0.72 (0.03)

5.4. Discussion

This aim of this study was to estimate the effect of footrot on weight gain of affected animals, and to investigate the nature of the between-animal variation for this effect. A general theory was developed describing the relationship between disease and weight gain, and new traits were defined such as the maximum weight loss as a result of disease and the time after infection that this occurs.

The new trait of maximum weight effect was defined as the maximum weight loss of animals as a result of footrot. This trait required prediction of an animal's weight had it not been affected, which was achieved by applying the growth curve of unaffected animals in the same flock and taking into account various effects that may affect growth, such as sex and age. The accuracy of this prediction is difficult to assess, but is likely to be better in the first trial as it was based on many more animals.

The weight of an affected animal is determined by the animal's (unknown, but predicted) growth if it had remained healthy and the footrot effect, estimated as predicted growth – actual growth. Systematic errors may be introduced in the estimation of the footrot effect because healthy growth has an important genetic component, but is accounted for in the prediction by including an effect of start weight on growth. If the footrot effect for faster growing animals was still underestimated this would lead to a negative correlation between healthy growth and the footrot effect, but the actual genetic correlations between gain over the trial and weight loss are highly positive.

The estimation method for genetic parameters was based on the assumption of normal distributions. Some measures of footrot that violated this assumption (such as

a binary score of footrot/no footrot) were therefore excluded from the analyses. Skewness and kurtosis for *MaxFR* and *SumFR* were between -2 and +2 in both trials.

It was confirmed that a higher live weight is associated with an increased risk of footrot. Animals with average severity of footrot in the trial 1 and 2 are predicted to suffer weight losses of 0.5 and 2.5 kg live weight respectively, compared to uninfected animals. Animals subsequently regained most of the lost live weight later in the trials after they recovered from footrot. Weight loss, whether adjusted for the level of footrot or not, had a genetic component, with heritabilities of approximately 0.30 in trial 1 and 0.15 in trial 2. Although the two traits were similar in nature, the method of challenge, serogroup and virulence of challenge isolate and timing of challenge were different, and this may account for differences in relationship between weight gain and footrot.

For an average weight of animals around 30 kg, the weight loss estimated in this study is a much smaller percentage (2 to 8%) of live weight than found for other sheep diseases (Coop *et al.*, 1985; Mackay *et al.*, 1998; Kirkwood, 1980; Sargison *et al.*, 1995; Pekelder, 1994). The effect is similar to a 6.7% reduction in lamb output due to footrot in ewes estimated from results presented by Symons (1978) but much lower than the 30% found by Stewart *et al.* (1984). Costs of footrot to the British sheep industry estimated in Chapter 2 are based on extrapolating the average of results presented by Symons (1978) and Stewart *et al.* (1984) to a weight effect, i.e. an 18% reduction in growth. In Chapter 2 the total costs of footrot are estimated at £24.4M, of which only £1.5 M is due to reduced lamb growth so a reduction based on the current findings would have a little impact on the total. Both trials confirm findings by Marshall *et al.* (1991) that sheep eventually completely regain weight lost due to footrot, but in this experiment animals were treated by therapeutic vaccination rather than left untreated.

For the British meat sheep industry the main costs of footrot are suffered therefore in adult ewes at times of mating, lambing and lactation. In wool sheep, such as the Merino in this study, footrot will also impact negatively on fleece weight and fleece

quality, specifically staple strength, which is not recoverable (Symons, 1978; Stewart *et al.* 1984).

In general terms conclusions are similar for the two trials, which used the same animals, but there are differences in the size of the weight loss, the time frame and the heritability of weight loss and timing. While the trials differed in various aspects, including animal age, the method of infection and the time between infection and vaccination, it seems reasonable to assume that the previous infection affected the response of animals in the second trial. While the footrot scores across the two trials showed a high positive genetic correlation, this was not the case for the maximum weight effect. The animal's response to subsequent infections should not therefore be regarded as repeat measures of the same trait.

Selection for higher weights at a given age and consequent higher mature weights, as practised in most sheep breeding programmes, bears the risk, already established by Raadsma *et al.* (1994), that animals become more susceptible to footrot as a direct effect of weight. The current study shows that at a phenotypic level weight losses due to footrot also increase with severity, thus apparently compounding the negative effect of live weight on the animal's performance. In contrast, the first trial shows that at the genetic level animals with a high breeding value for growth lose less weight, which may be indicative of their (genetic) ability to better cope with the disease. The effect was smaller in Trial 2.

Alternatively, selection for increased resistance to footrot may lead to lower weights, if footrot scores are not adjusted for live weight. In theory a selection programme could include weight loss due to footrot in order to identify the more resilient animals i.e. those that do not lose weight while showing clinical signs of footrot. Estimation of weight loss is not practical, however, as it would require knowledge of the time of infection and frequent weighing. Selection on growth should to a large extent identify the same animals. The low repeatability of footrot scores across the two trials means that any selection programmes aiming to increase resistance to

footrot through selection of resistant animals under natural challenges would benefit from repeated scoring of the same animals and use of information on relatives.

Chapter 6. Genetic and phenotypic aspects of foot lesion scores in sheep of different breeds and ages

6.1. Introduction

Footrot is an endemic disease of sheep which costs the British sheep industry an estimated £24M annually (Chapter 2). The disease is caused by bacteria, *Dichelobacter nodosus*, that can survive outside sheep hooves for only a limited time (Egerton, 2000), with prevalences being higher under damper conditions.

Differences between breeds in resistance to footrot have been reported in Australia and the US. Emery *et al.* (1984) found that British breeds were more resistant than Merinos under a moderate challenge on pasture (as expressed in lower severity, rather than fewer feet affected), but not when cultures of *D. nodosus* were applied directly to each hoof. Burke and Parker (2007) found breed differences among various hair breeds, hair breed crosses and Dorset sheep in the number of locations on a hoof affected by footrot and odour but not footrot severity (or 'score') or consequential culling.

Comparing offspring from different Targhee rams, Bulgin *et al.* (1988) concluded that susceptibility to footrot is heritable, without presenting a heritability estimate. In a lamb population with a prevalence of footrot ranging from 1 to 34% in females and 31 to 57% in males, Skerman *et al.* (1988) calculated a heritability of 0.17 on the underlying scale for the binary trait (i.e. presence or absence of footrot) in Romney lambs of 8 to 9 months of age. In the same dataset, the heritability of 'overall score', an assessment of footrot severity on a continuous scale, was 0.14. The heritability estimated in an offspring-dam regression for the binary trait scored at about the same time was similar (0.12), suggesting that the trait in lambs of this age and ewes are genetically similar.

Raadsma *et al.* (1994) reported that in deliberately-infected Merino sheep of 10 to 21 months of age, the heritability for susceptibility to footrot can be as high as 0.3 when using the average of repeated measurements. The highest heritabilities were found if

footrot was analysed as a binary trait, i.e. presence or absence of footrot, or severe footrot, and using a threshold model. In the study of Raadsma *et al.* (1994), in which vaccination interventions were used, the repeatability of footrot scores was moderately high pre-vaccination (when prevalence was over 50%), but much lower post-vaccination (when prevalence was lower). The genetic correlation between successive cases of footrot after re-infection ranged from 0.14 to 0.95, with an average of 0.67, suggesting that some different genes are involved in response to subsequent cases of footrot.

The potential to decrease the prevalence of footrot in Great Britain through selective breeding depends on a number of factors, including the heritability of resistance to the prevailing strains and the effect of the British climate on the bacteria. It may also depend on breed of sheep and age. A practical breeding programme requires a measure that can be readily applied to large numbers of sheep on commercial farms. Because of the complexity of diagnosis of footrot, this study investigated lesion score as defined by Egerton and Roberts (1971) and applied by Raadsma *et al.* (1994). The effectiveness of a selection programme may be increased by repeated scoring of animals, which would be especially beneficial if the indicator traits were found to have a low repeatability. The aim of this study is to determine the heritability and repeatability of lesion scores in two breeds of sheep and at different ages, and to assess whether or not breeding for resistance to footrot is a promising option for British sheep breeders. The study follows a snapshot approach, in which all animals are measured simultaneously but little is known about the disease history of individual animals. This approach reflects the practical situation in the field and the conditions under which a commercial selection programme would operate.

6.2. Material and Methods

6.2.1. Animals

This study included two populations of sheep; Scottish Blackface (SBF) and mules, i.e. the female progeny of longwool breed sires and hill ewes. In 2005, Scottish Blackface ewes and their lambs in two commercially managed SAC flocks were scored for footrot. Details of the structure of these flocks are described in Conington

et al. (2006). In 2006, ewes in the same two flocks, as well as ewes in three commercial SBF flocks were scored, including 330 animals that had been scored as lambs in the previous year. All five flocks are members of the Scottish Blackface Sire Reference Scheme (<http://www.bfelite.co.uk/>) and genetic links exist among them. Six generations of pedigree were used in subsequent statistical analyses, as well as routinely-collected data on date of birth, farm, management group, sex, litter size and, for lambs, live weight at about 20 weeks.

The mules were from a population that had been created to investigate the effects of selection in purebred longwool rams on crossbred offspring. A total of 45 Blue Faced Leicester rams were crossed with 750 Scottish Blackface ewes and 750 Hardy Speckled Face over three years. The animals were kept on three farms in different parts of the country and recorded for maternal traits. In 2005, when they were first scored for footrot, they varied in age from 5 to 7 years, and they were scored again in 2006. Details on these flocks are given by Van Heelsum *et al.* (2006).

6.2.2. Scoring

The scoring system described by Egerton and Roberts (1971) was implemented as described in detail by Conington *et al.* (2008) and summarised in Table 6.1. Animals were inspected and awarded a score of 0 (healthy) to 4 (severe footrot) for each hoof, where a score of 1 may indicate scald or early stage footrot. Animals that appeared to be affected by footrot or any other disease at scoring were promptly treated with antibiotic spray and pared where required.

The SBF ewes were scored once in each year, between 26 July and 17 October in 2005 and 2006. Lambs were born in April, weaned in mid-August and were scored on 26 September or 18 November 2005. The mules were scored twice in both years, with the first score between 24 July and 14 September and the second between 13 September and 20 October, with 30 to 80 days between successive scores on the same animal. There were a total of four scorers, two of whom scored in both years. Generally, sheep in the same management group were scored on the same or two

consecutive days. On the occasions when scoring of a management group spanned a longer period of time, the group was split accordingly for the purpose of the analysis.

Table 6.1 *Scoring system used in this study, each hoof is scored individually (from Conington et al., 2008)*

Score	Definition
0	No lesions
1	Mild interdigital dermatitis ('scald') with some loss of hair. Slight to moderate inflammation confined to interdigital skin and may involve erosion of epithelium
2	More extensive interdigital dermatitis and necrotising inflammation of interdigital skin.
3	Severe interdigital dermatitis and under-running of the horn of the heel and sole
4	Severe interdigital dermatitis and under-running of the horn of the heel and sole and with under-running extending towards the walls of the hoof.

Various traits were derived from the hoof scores, which are explained in detail in Table 6.2 For mules, an additional set of traits was defined to include scores on the same sheep at different times (Table 6.2).

Table 6.3 gives an overview of the numbers of animals scored at various times. Amongst the mule ewes, there were 389 second scores following a first score of no footrot, comprising 319 ewes. A total of 7381 animals were in the SBF pedigree, and 8356 ewes were in the mule pedigree.

Table 6.2 *Foot lesion traits derived from raw scores*

Acronym	Trait description
<i>FS</i>	Foot lesions as a binary trait: <i>FS</i> = 1 if any hoof score >0
<i>FS24</i>	Severe foot lesions as a binary trait: <i>FS24</i> = 1 if any hoof scored in the range 2 to 4
<i>FSsum</i>	Sum of scores over 4 feet
<i>FSmax</i>	Maximum score over 4 feet
<i>Nft1</i>	Number of feet with score > 0 at time of scoring
<i>Nft2</i>	Number of feet with score > 1 at time of scoring
For mules only (<i>nFS</i> = number of times an animal was scored, range 1-4)	
<i>FSa</i>	Average <i>FS</i> over available scores (i.e. a value between 0 and 1)
<i>FSan</i>	<i>FSa</i> for animals with <i>nFS</i> > 1
<i>FS24a</i>	Average <i>FS24</i>
<i>FS24an</i>	<i>FS24a</i> for animals with <i>nFS</i> > 1
<i>Nfeet</i>	Average number of feet affected
<i>Nfeet24</i>	Average number of feet with a score in the range 2 to 4
<i>Nfeetn</i>	<i>Nfeet</i> for animals with <i>nFS</i> > 1
<i>Nfeet24n</i>	<i>Nfeet24</i> for animals with <i>nFS</i> > 1

Table 6.3 *Numbers of foot lesion score observations*

	2005		2006	
	Event 1	Event 2	Event 1	Event 2
Mule ewes ^{†‡}	686	529	398	229
Blackface ewes [§]	1353		2987	
Blackface lambs	1199		Not measured	

[†] 498 ewes were scored twice in 2005 and 217 were scored twice in 2006.

[‡] Across both years, 710 ewes had a first score and 537 a second score.

[§] 1071 ewes were scored twice

6.2.3. Statistical Analysis

For SBF, footrot score data were linked to performance and pedigree records held by MLC's Signet breeding services and each derived footrot trait on a ewe was analysed in three ways, based on different datasets:

- A. Repeated measures over time of the same trait on a ewe (1 or 2 observations per animal)
- B. Traits measured in 2005 and 2006 treated as separate traits
- C. Repeated measures of the same trait on each of the 4 hooves of a ewe and over time (4 or 8 observations per animal)

Further, scores on lamb were analysed as:

- D. Measures on lambs, one observation per animal

For mules, footrot traits were analysed as follows:

- E. Repeated measures over time of the same trait on an animal (up to 4 observations per animal)
- F. Each scoring event treated as a separate trait
- G. As F but with censored traits; second scores valid only if no footrot was observed at the first score within each year

Method G was used because second scores may be affected by earlier cases of footrot, especially when animals were treated for footrot after the first score.

After initial investigation with the generalised linear model procedure of SAS (1989), an appropriate statistical model was determined by stepwise elimination of non-significant interactions and main effects using ASReml (Gilmour *et al.*, 2002) with an animal model for all traits, as well as a sire model with logit link function for univariate analysis of binary traits. The results presented are based on the model that contains all significant ($P < 0.05$) main effects and interactions for that dataset.

Based on this analysis the standard model used for genetic analysis of SBF ewes (sets A, B and C) was:

$$Y_{ijklmn} = \text{group}_i + \text{scorer}_j + \text{group}_i.\text{scorer}_j + \text{age}_k + \text{lsr}_l + A_m + e_{ijklmn}$$

Where: Y_{ijklmn} = footrot trait measured on animal m, $group_i$ = management group within flock, $scorer_j$ = scorer ($j=1$ to 4), age_k = age at scoring in years, with 6, 7 and 8 years considered as one class, lsr_l = litter size reared by the ewe in the year of scoring, $l=0, 1, \geq 2$ and A_m = additive genetic effect of animal m or its sire

In some data sets additional effects were of significant size and included:

A: $group_i.age_k$, $group_j.lsr_l$ and $animal_env_m$

B in 2005 and 2005&2006: $group_i.age_k$, $group_i.lsr_l$ and $scorer_j.age_k$

C: $scorer_j.age_k$, $scorer_j.lsr_l$, $scorer_j.age_k.lsr_l$, $scorer_j.lsr_l.age_k$, $foot_o$ and $animal_env_m$

Where: $animal_env_m$ = permanent environmental (i.e. non-genetic) effect associated with animal m, $foot_o$ = permanent environmental effect of the foot.

Note that management group is different for each scoring event, so that no separate effect for scoring event is required.

For lambs (set D) the model was:

$$Y_{ijklm} = group_i + scorer_j + group_i.scorer_j + b_1.age + lsr_k + b_2.swt + A_l + e_{ijklm}$$

Where b_1 =regression of footrot on age (age in days), b_2 =regression of footrot on scan weight and swt=scan weight (weight at approximately 20 weeks of age)

For the mules the following models were used:

Dataset E:

$$Y_{ijklm} = \mu + year_i + group_j + scorer_k + scorer_k.group_j + animal_l + e_{ijklm}$$

Where: Y_{ijklm} = footrot trait measured on animal l, $year_i$ = year of birth, $group_j$ = management group within flock, $scorer_k$ = scorer and $animal_l$ = additive genetic effect of the animal.

And datasets F, G:

$$Y_{ijklmn} = \mu + year_i + group_j + scorer_k + scorer_k.group_j + score_m + animal_env_l + animal_l + e_{ijklmn}$$

Where: $score_m$ = scoring event ($m=1,2$ or $m=1-4$ depending on the dataset)

The analysis of the additional persistency scores was based on the model used for dataset E with an extra fixed effect for the number of scoring events the trait was based on.

In mules, for some of the multivariate analyses of traits scored at different points in time, parameter estimates approached the boundaries of the parameter space and did not converge. In these instances, genetic and residual variances were fixed at the values obtained from univariate analysis. Consequently, standard errors of heritabilities and genetic correlations could not be estimated.

6.3. Results

6.3.1. Data summary

Table 6.4 shows the distribution of the foot lesion scores in SBF. The averages for *FS* and *FS24* are the presumed prevalence of footrot and severe footrot respectively, bearing in mind that individual animal diagnoses of footrot were not made. More lambs than ewes were affected, and the infection in lambs appeared to be more severe in terms of scores and number of feet involved. There was very little difference in mean scores between the two years for ewes. Because foot lesion scores were skewed to the right, log transformed values of *FSsum* and *FSmax* were included in the analyses, but this had no noticeable effect on results and is not reported here.

The average prevalence of foot lesion scores in mules (i.e. *FS* > 0) was 51%, ranging from 27% in 2006 (1) to 64% in 2005 (2) (Table 6.5), and from 42% in one flock to 59% in another. The average raw score on a foot basis over the four events showed no significant differences between feet and ranged from 0.32 (SD 0.65) for the left hind foot to 0.34 (0.65) for the left front foot, and was only marginally higher for front feet (0.337) than rear feet (0.322).

Table 6.4 Mean, standard deviation (SD) and third quartile (Q3) for derived foot lesion score traits in SBF lambs and ewes§

Trait	Lambs 2005			Ewes 2005		Ewes 2006	
	Mean	SD	Q3	Mean	SD	Mean	SD
<i>FS</i> †	0.34	0.47	1	0.17	0.37	0.18	0.38
<i>FS24</i>	0.13	0.34	0	0.09	0.28	0.08	0.27
<i>Fssum</i>	0.81	1.47	1	0.45	1.20	0.45	1.18
<i>FSmax</i>	0.54	0.92	1	0.32	0.83	0.33	0.86
<i>Nft1</i>	0.55	0.92	1	0.26	0.67	0.26	0.66
<i>Nft2</i>	0.18	0.52	0	0.12	0.44	0.10	0.37

† acronyms are explained in table 6.2

§ for lambs all first quartiles and medians are 0; for ewes all first quartiles, medians and third quartiles are 0 in both years

Table 6.5 Mean (Mn), standard deviation (SD) and third quartile (Q3) for derived foot lesion score traits in mules at the different scoring events†

Trait	2005 (1)			2005 (2)			2006 (1)			2006 (2)		
	Mn	SD	Q3	Mn	SD	Q3	Mn	SD	Q3	Mn	SD	Q3
<i>FS</i>	0.51	0.50	1	0.64	0.48	1	0.27	0.44	1	0.59	0.49	1
<i>FS24</i>	0.16	0.37	0	0.16	0.36	0	0.10	0.30	0	0.17	0.38	0
<i>Fssum</i>	1.28	1.83	2	1.78	1.91	3	0.59	1.26	1	1.62	1.99	2
<i>FSmax</i>	0.82	1.08	1	0.94	0.82	1	0.41	0.80	1	0.81	0.83	1
<i>Nft1</i>	0.90	1.11	1	1.49	1.46	2	0.42	0.83	1	1.26	1.35	2
<i>Nft2</i>	0.21	0.54	0	0.23	0.65	0	0.13	0.45	0	0.32	0.82	0

† first quartile is equal to 0 for all traits at all events, median is 1 for Q3 > 0, and 0 otherwise

6.3.2. Heritability of foot lesion scores in ewes

Estimates of genetic parameters based on the assumption that subsequent foot lesion scores are expressions of the same trait are given in Table 6.6 for SBF ewes in the two consecutive years (dataset A) and also for mules for up to four scores in two years (dataset E). Estimates for the heritabilities of *FS* and *FS24* in a threshold sire model were low to moderate (i.e. less than 0.2), and all other traits showed a smaller

genetic component. In SBF the permanent (i.e. non-genetic) animal effect was close to 0, and the repeatability (i.e. the sum of the heritability and the permanent animal effect) ranged from 0.03 to 0.33. In mules, heritabilities ranged from 0.08 to 0.19, with the permanent environmental animal effect being slightly lower, resulting in repeatabilities ranging from 0.13 to 0.33.

Table 6.6 *Estimates of permanent animal effect and heritability (standard error) in datasets A (SBF) and E (mules), depending on model (threshold sire or animal)*

Trait	Model	SBF		Mules	
		c_{animal}^2	h^2	c_{animal}^2	h^2
<i>FS</i>	Threshold	0.04	0.19 (0.07)	0.10	0.12 (0.06)
	Animal	0.00	0.08 (0.02)	0.02	0.11 (0.06)
<i>FS24</i>	Threshold	0.07	0.26 (0.11)	0.14	0.19 (0.10)
	Animal	0.01	0.05 (0.02)	0.01	0.13 (0.07)
<i>FSsum</i>	Animal	0.03	0.06 (0.02)	0.09	0.11 (0.06)
<i>FSmax</i>	Animal	0.02	0.06 (0.02)	0.10	0.12 (0.06)
<i>Nft1</i>	Animal	0.00	0.09 (0.03)	0.06	0.08 (0.05)
<i>Nft2</i>	Animal	0.00	0.03 (0.02)	0.03	0.12 (0.06)

Based on datasets B and F, Table 6.7 shows that the heritability for *FS* was reasonably constant over various scoring events, varying from 0.10 to 0.26 in the two populations, but for *FS24* the range was much larger; 0 to 0.61. For the other traits heritabilities were low to moderate, although they did vary across time.

A trend emerged from close scrutiny of the SBF flocks analysed, showing a relationship between flock-level prevalence of lesions and heritability, whether estimated using an animal model or a sire threshold model. In 2006, in the two flocks with highest prevalence of lesions, average prevalence was 0.30 and in the three flocks with lowest prevalence it was 0.10. In these two groups, threshold model heritabilities for *FS* were estimated as 0.36 (0.14) and 0.06 (0.13) respectively, with similar differences for sire and animal models, while estimates for *FSsum* and *FSmax* were similar to each other and to estimates based on all five flocks.

Table 6.7 Heritabilities (standard errors) for ewe traits measured in SBF in 2005 and 2006 (dataset B) and successive scores in mules (dataset F). FS and FS24 based on threshold sire model, other traits from animal model

Trait	SBF 2005	SBF 2006	Mules 2005(1)	Mules 2005(2)	Mules 2006(1)	Mules 2006(2)
<i>FS</i>	0.26 (0.14)	0.21 (0.10)	0.10 (0.09)	0.26 (0.15)	0.20 (0.18)	0.13 (0.20)
<i>FS24</i>	0.61 (0.23)	0.25 (0.14)	0.09 (0.14)	0 (0)	0 (0)	0.59 (0.39)
<i>FSsum</i>	0.19 (0.06)	0.04 (0.03)	0.08 (0.08)	0.16 (0.11)	0 (0)	0 (0)
<i>FSmax</i>	0.16 (0.06)	0.05 (0.03)	0.07 (0.08)	0.17 (0.11)	0.09 (0.11)	0.08 (0.17)
<i>Nft1</i>	0.17 (0.06)	0.08 (0.03)	0.10 (0.08)	0.19 (0.11)	0.04 (0.09)	0.03 (0.15)
<i>Nft2</i>	0.14 (0.06)	0.01 (0.02)	0.09 (0.08)	0.16 (0.10)	0.10 (0.11)	0.09 (0.16)

Comparing analyses at the level of the hoof rather than an animal in SBF (dataset C), lower estimates of heritabilities were obtained than at the level of the animal.

However, permanent environmental animal effects were slightly higher (Table 6.8).

Table 6.8 Estimates of variance components on a per foot basis in SBF ewes (dataset C) and depending on model. Standard error of heritabilities in brackets

Trait	model	c_{foot}^2	c_{animal}^2	h^2
<i>FS</i>	threshold	0.07	0.24	0.09 (0.04)
	animal	0.02	0.15	0.04 (0.01)
<i>FS24</i>	threshold	0.07	0.24	0.08 (0.06)
	animal	0.01	0.11	0.01 (0.01)
Raw score	animal	0.01	0.08	0.02 (0.01)

6.3.3. Correlations between successive scores

Table 6.9 shows that the genetic correlations between the same trait in SBF in the two years are far from unity, albeit with large standard errors. The phenotypic correlations are close to 0 or negative.

Table 6.9 *Estimates from the animal model of correlations (standard errors) between SBF ewe traits measured in 2005 and 2006 (dataset B)*

Trait	r_p	r_g
<i>FS</i>	0.04 (0.03)	0.30 (0.36)
<i>FS24</i>	-0.17 (0.03)	0.28 (0.38)
<i>Fssum</i>	0.07 (0.03)	0.39 (0.46)
<i>Fsmax</i>	0.06 (0.03)	0.18 (0.43)
<i>Nft1</i>	0.08 (0.04)	0.46 (0.36)
<i>Nft2</i>	0.03 (0.03)	0.55 (1.03)

Multivariate analyses of *FS* in mules, using an animal model (Tables 6.10 and 6.11), revealed phenotypic correlations close to 0 and a large range of genetic correlations. There was no indication for a stronger genetic correlation between adjacent scores or that a first (or second) score in a year had a higher genetic correlation with the first (or second) score in the other year. Removal of animals affected (and treated) at the first scoring from the second scoring in the same year (dataset G) resulted in a large increase in the estimates of genetic correlations between 2005(2) and 2006(1), but an opposite effect was found for the correlation between 2005(1) and 2006(2).

6.3.4. Genetic analysis of persistency in mules

Estimates of the heritability for various traits that combine scores from successive observations in mules, shown in Table 6.12, were generally higher than heritability estimates based on only one score.

Table 6.10 *Multivariate analysis of FS in mules (dataset F) in an animal model. Heritabilities (s.e.) on, phenotypic above and genetic correlations below diagonal. Genetic variances were fixed at values from univariate analyses, on which heritabilities and their standard errors are based, standard errors for genetic correlations could not be estimated.*

	2005 (1)	2005 (2)	2006 (1)	2006 (2)
2005 (1)	0.09 (0.08)	0.06	0.13	0.14
2005 (2)	0.06	0.14 (0.10)	0.18	0.06
2006 (1)	0.06	0.43	0.13 (0.11)	0.22
2006 (2)	0.87	0.40	-0.10	0.05 (0.15)

Table 6.11 *Multivariate analysis of FS in mules excluding second scores where the first score was not 0 (dataset G). Heritabilities (s.e.) on, phenotypic above and genetic correlations below diagonal. Genetic variances were fixed at values from univariate analyses, on which heritabilities and their standard errors are based, standard errors for genetic correlations could not be estimated.*

	2005 (1)	2005 (2)	2006 (1)	2006 (2)
2005 (1)	0.09 (0.08)	-0.14	0.13	0.10
2005 (2)	-0.00	0.08 (0.08)	0.14	-0.11
2006 (1)	0.26	0.92	0.13 (0.11)	-0.41
2006 (2)	0.22	-0.02	-0.12	0.01 (0.01)

6.3.5. Footrot in SBF lambs

The risk of foot lesion scores of 1 or more increases with higher weight at scanning (around 20 weeks of age) and, to a lesser extent with lower age, indicating that faster growing animals are most at risk. In a model without the age effect, the relative risk of FS and FS24 increased at a rate of 0.12 and 0.08 per kg live weight, respectively ($P < 0.05$ in both cases). There was no effect of the size of the litter in which an animal was raised.

All heritability estimates for footrot traits in SBF lambs were 0. Residual correlations between lamb and ewe traits were estimated on the 330 animals with observations in both classes, and ranged from -0.08 to 0.01 .

Table 6.12 *Heritabilities and standard errors (s.e.) for traits describing average scores over time in mules*

Trait	Heritability	s.e.
<i>Fsa</i>	0.13	0.09
<i>Fsan</i>	0.20	0.12
<i>FS24a</i>	0.19	0.10
<i>FS24an</i>	0.12	0.11
<i>Nfeet</i>	0.18	0.10
<i>Nfeet24</i>	0.17	0.10
<i>Nfeetn</i>	0.21	0.13
<i>Nfeet24n</i>	0.23	0.15

6.4. Discussion

In this study the heritability and repeatability of lesion scores in two populations of ewes and in lambs were investigated. While for the latter all estimates of heritability were 0, some medium heritabilities were found in ewes, especially when footrot or severe footrot was defined as a binary character and analysed using a threshold model, or when more than one measurement was taken on an animal. Repeatabilities were generally little higher than heritabilities, which is in line with low phenotypic correlations between successive scores on the same animal. As a result, heritabilities for traits increase if information from successive scores is combined.

Published estimates of the prevalence of footrot in ewes of about 6% (Grogono-Thomas *et al.* 1998; Wassink and Green, 2001; Clements *et al.*, 2002) are based on farmer surveys, and rely on farmers' opinions or observations of lame sheep, rather than clinical examinations of hooves from upturned animals, as reported in this study. The prevalence of severe lesions in this study (i.e. scores 2 to 4) ranged from 9 to 15% in SBF ewes and mules. Although these figures may not be directly

comparable, they are of a similar magnitude. Apart from differences in observation methods, there are effects of breeds and environments, including the time of year. In this study animals were all scored in summer and autumn when warm and damp conditions favour spread of footrot more than in other times of the year. The low repeatability of scores, even within the same year, highlights the high sensitivity to time and frequency of scoring for the identification of susceptible animals.

Although scorers were trained by the same person, the analysis found significant effects of the scorer and scorer by group effects for most traits as well as additional interactions of scorer (with litter size and age) for a number of traits. This means that any genetic improvement programme that includes foot scoring to predict genetic susceptibility to footrot should identify the scorer and attempt to use the same personnel across several flocks to avoid confounding with flock. It should be noted that the management group effect is confounded with the score date (with a group only scored on one or two successive days), so that the scorer by group effect may partly be a time effect. The repeatability of scorers has been investigated in a separate analysis (Conington *et al.*, 2008) showing high consistency between scorers and between subsequent scores by the same scorer on the same day.

Lesion prevalence did not differ between feet, which is in line with conclusions from Parker *et al.* (1985) who found an apparently insignificant small difference in prevalence between front and rear hooves and Raadsma *et al.* (1992) who found no difference in prevalence of footrot among the four feet.

The estimate of the heritability of lesions scores in SBF lamb was 0, for all traits defined. To test whether or not this result was an artefact of the data structure, the heritability of weaning weight for the same lamb population was estimated. The resulting estimate of 0.35 does not support the suggestion that the footrot results may be an artefact the data structure. The zero heritability contrasts with results for footrot presented by Skerman *et al.* (1988) and Raadsma *et al.* (1994) who found low to medium heritabilities in lambs, although the lambs in these two studies were older, i.e. 8 to 10 months at the start of trial, than in the current study where they were an average of 5 months at time of scoring. If genetic variation in footrot is a function of

acquired immune responses to infection, it may be possible that lambs in this study were simply too young or had had insufficient exposure to footrot-causing bacteria for genetic differences between animals to be apparent.

Within the current study there was a trend for heritabilities for the binary trait *FS* to increase with increasing prevalence. Such an effect can be expected in a linear analysis, where variances depend on the mean, but it also existed in the threshold models. However, a simple biological reason may be hypothesised: certain genes that affect resistance to footrot, and hence the development of lesions, are possibly not expressed at low infection pressures, hence at a low prevalence. This, if correct, would also explain the difference in estimated heritabilities in lambs between the current study and that by Skerman *et al.* (1988) and Raadsma *et al.* (1994), in which animals were deliberately infected and the resulting prevalences were as high as 57% (Skerman *et al.*, 1988) and over 50% and 80% respectively in two trials pre-vaccination (calculated from data used in Raadsma *et al.* 1994).

Even in ewes where heritable variation in lesion scores was seen, low phenotypic and genetic correlations between subsequent scores were observed in this study, and similarly low correlations were also found by Raadsma *et al.* (1994). This may be the result of various factors including the strain of *D. nodosus* involved, the prevailing weather, prevalence of footrot and build up of acquired resistance in animals following successive challenges or as they age. Given this range of possible influences, it is encouraging that genetic correlations were positive, although it would be useful to have a better insight in the reasons for the low genetic correlations.

In this study we considered populations of ewes from two different genetic backgrounds. Although differences in heritability estimates for lesion scores were found across the breeds, these estimates do not differ greatly from each other or from previously published values for resistance to footrot. In SBF the heritability for foot lesions was estimated to be 0.19 and in mules 0.12, this is comparable to 0.16 and 0.31 estimated by Raadsma *et al.* (1994) in Merino lambs and 0.28 for Romney

(Skerman *et al.*, 1988, trait defined as footrot or scald), especially when taking into account the effect of prevalence. The respective figures for severe lesions are SBF 0.26, mules 0.19, Merino (1), 0.21, Merino (2) 0.16 and Romney 0.17 (footrot only). The heritabilities for the number of feet affected or severely affected in SBF (0.09, 0.03) and mules (0.08, 0.12) are close to estimates by Raadsma *et al.* (0.09 to 0.14).

From a practical perspective, this study shows that because certain footrot scores are estimated to have a medium heritability, it is possible to increase resistance to footrot in ewes through selective breeding. However, since the heritability of footrot in lambs is estimated to be 0, selection in lambs is not expected to lead to any progress, nor will selection in ewes lead to any direct genetic effect in lambs (but there may be an effect of more resistant ewes lowering the pathogen challenge faced by lambs).

Because of the classification of lesion scores in a limited number of classes and because at any one time most animals were healthy, traits scored on an animal-basis tended to be right-skewed. The number of feet affected (score>0) turned out to be normally distributed, but the number severely affected (score>1) had strong positive skewness and kurtosis, which would affect estimates for genetic parameters, although heritabilities for the two 'number of feet affected' traits were very similar. The threshold model was used for the binary traits to avoid this problem. *FSsum* and *FSmax* were log transformed to obtain theoretically more correct estimates for genetic parameters, but these turned out to be very similar to those estimated on the untransformed traits (which were presented for easier interpretation). Moreover, the results indicate that the foot scoring of sheep does not need to be comprehensive, with a simple binary trait indicating lesions (or not) or severe lesions (or not), depending on the breeding goal and prevalence, being at least as effective as scoring individual feet on a 0 to 4 scale. Importantly, because of the medium to low heritability and repeatability of the footrot score, the use of repeated observations on the same animal is recommended. It is a legal requirement (and wise management) to treat animals affected by footrot, or showing any signs of lameness, promptly. This will, however, affect the ability to score footrot on an equal basis for all animals, as recently treated animals will be protected by antibiotics and hoof treatments. Care

should therefore be taken that animals have a similar history of footrot within the season, and scoring may therefore best be undertaken at the earliest period of high prevalence within a season. Animals treated for footrot within a few weeks prior to scoring could be assigned a score reflecting their footrot status at treatment, rather than on the scoring day. Further, the between-flock comparisons in this study suggest that the heritability of resistance to footrot depends on the prevalence, with heritabilities being higher at higher prevalence. This means that selection will be more effective in those flocks with higher levels of footrot.

In practice, with differences in heritabilities depending on prevalence and time, as well as low repeatability, selection for resistance to footrot across flocks and within a commercial setting (i.e. with limited recording) may be complex. Therefore, the development of effective genetic markers for resistance to footrot would be very useful to the industry to complement conventional breeding.

Chapter 7. A genetic epidemiological model to describe resistance to an endemic bacterial disease in livestock: application to footrot in sheep

7.1. Introduction

Preventive measures and lost production due to endemic disease form an important part of the costs of production in many livestock production systems (Bennett and Ijpelaar, 2003) while they also affect animal welfare and marketability of breeding stock. It is well known that resistance to many diseases has a genetic component (Archibald and Bishop, 2006) and selection for disease resistance has long been considered a promising way to reduce disease prevalence (e.g. Axford *et al.*, 2000).

Selection for resistance to an infectious disease has the added benefit that it may reduce the pathogen burden, especially when the population under selection is the main reservoir of pathogens. This will lead to an additional reduction in prevalence, in addition to the direct genetic effect, as a result of reduced contamination from infectious animals, e.g. Bishop and Stear (2003).

The phenotype used in selection for disease resistance is often a score, which includes a class of healthy animals, and one or more classes of affected animals. In the case of endemic diseases the vast majority of animals at any one time may be classed as healthy, and this limits the opportunity for intense selection. In a threshold model, prevalences that are much lower than 50% also lead to low heritabilities on the observed scale. A successful selection programme can therefore be expected to decrease the subsequent response to selection through increased resistance and decreased pathogen burden.

Anderson and May (1991) describe the spread of a microparasitic (viral or bacterial) infection through a population of animals using a so-called SIR model, based on the rates at which susceptible (*S*) animals are infected (*I*) and then recover or are removed (*R*). A key parameter is R_0 which is the number of secondary infections

caused by an infected animal. One or more of these rates can be under genetic control, and affect R_0 . This model can be extended in various ways; for instance Bishop and MacKenzie (2003) described how a disease that is spread from animal to animal may or may not lead to an epidemic, and Nath *et al.* (2004) explored the consequences of selection to alter different model parameters. To make these models more applicable to typical livestock bacterial infections, Bishop *et al.* (2006) considered a disease in which the pathogen survives for some time, resulting in a source of infection present in the environment (E) from where it can infect susceptible animals. This was termed a SEIR model.

In the above models, the assumption is that recovered animals are no longer susceptible to the disease, and in a closed population without re-infection these models will therefore always lead to zero prevalence, either because there are no susceptible animals left or because the disease has died out. This outcome is inappropriate for typical endemic diseases, which often have a more or less stable prevalence over time. This stable prevalence, the endemic equilibrium, may be due to recovered animals losing their resistance and become susceptible again, or it may simply be a consequence of a continued introduction of new susceptible animals, e.g. offspring.

Building on the SEIR model (Bishop *et al.*, 2006), we introduce two new aspects to the model: (i) a period of latency (L) in which animals are infected but not yet infectious and (ii) loss of immunity so that recovered (R) animals can revert back to Susceptible. This creates a SELIRS model. Further, we consider the SELDIRS model in which animals can be diseased and infectious (D) or infectious but no longer clinically diseased (I). This model can be used to distinguish direct effects related to the number of diseased animals from indirect effects related to pathogen burden, by manipulating relative rates associated with D and I .

Footrot is an infectious disease of sheep caused by bacteria (*Dichelobacter nodosus*) that survive in soil for a limited time. The prevalence in adult sheep in Britain is around 6% (Chapter 2). Resistance to footrot has been shown to be heritable

(Skerman *et al.*, 1988; Raadsma *et al.*, 1994; Chapter 6), and selection for increased resistance is feasible.

The aim of this study is to develop a SELIRS epidemic model, in which pathogens survive in the environment for a limited time. The model will be applied to footrot in sheep and used to predict the changes in prevalence of footrot over time if selection is for resistance to the disease, accounting for the disease dynamics. The predicted progress in terms of reduction in prevalence will be compared with a model that ignores epidemiological effects.

7.2. Methods

7.2.1. Definition of epidemic models

Infectious and diseased animals are equivalent. Consider a population of N individuals, which, at time j , consists of S susceptible, L latently infected, I infected and R recovered animals. It is assumed that it is only category I animals that show clinical signs of disease and are infectious. Environmental contamination is quantified by the concept of an infectious dose; therefore at time j there are E infectious doses of the pathogen in the environment. Following Bishop *et al.*, (2006), and approximating the discrete process (e.g. daily steps) by a continuous one, the SELIRS model is defined by the following five differential equations:

$$dS/dt = -\xi ES + \lambda R \quad (1)$$

$$dE/dt = \phi I - \mu E - \omega NE \quad (2)$$

$$dL/dt = \xi ES - \nu L \quad (3)$$

$$dI/dt = \nu L - \gamma I \quad (4)$$

$$dR/dt = \gamma I - \lambda R \quad (5)$$

with ξ the rate at which susceptible animals become infected (latent) per infectious dose, λ the rate of loss of immunity, ν the rate at which latent animals show clinical signs and become infectious, ϕ the number of infectious doses shed per infected animal per day, μ the rate at which infectious doses die, ω the rate at which an animal physically removes infectious doses (e.g. by ingestion, adherence to the animal or squashing them) and γ the rate at which infected animals become immune. All rates are non-negative. An overview of symbols and their definitions is given in Table 7.1.

Two properties of this model are of importance, the notional reproductive rate (R') and the equilibrium prevalence. In standard epidemiological models the basic reproductive ratio, R_0 , is the number of infections caused by a single infected animal in a wholly susceptible population, during the course of its infectious period. The equivalent in the SELIRS model is the number of secondary infections due to a single infectious animal, for the time period over which the infectious material remains in the environment. Bishop *et al.* (2006) derived an expression for the notional reproductive rate in a SEIR model as:

$$R' = \frac{\phi \xi N}{\chi \gamma}, \quad (6)$$

where $\chi = \mu + \omega N$. Note that R' is defined for one infectious animal introduced to a fully susceptible population, so that $S=N$. The same expression may be used as an approximation to R' in an SELIRS model (Appendix 7.1), however it is not exact as the loss of immunity potentially increases the number of secondary infections in situations where the environmental contamination is long-lived and the period of immunity is short.

An equilibrium state will be reached when the number of animals in each state is the same from one day to the next, i.e. $dS/dt = dL/dt = dI/dt = dR/dt = 0$. It can be shown (Appendix 7.2) that the corresponding equilibrium number of infected animals (I^*) is:

$$I^* = \frac{\lambda \nu (N - \frac{\gamma \chi}{\xi \phi})}{\nu \lambda + \lambda \gamma + \nu \gamma} \quad (7)$$

Combined with (6), it follows that the equilibrium prevalence (p^*), i.e. I^*/N , is

$$p^* = \frac{\lambda \nu (1 - \frac{1}{R'})}{\nu \lambda + \lambda \gamma + \nu \gamma} \quad (8)$$

Hence, after rearrangement, R' may be defined as a function of the equilibrium prevalence as follows:

$$R' = \frac{1}{1 - (1 + \gamma/\nu + \gamma/\lambda)p^*}$$

Note that in equation (7) ϕ and ξ occur as the product $\xi\phi$ indicating that the rate of infection depends jointly on the number of infective units spread by infected animals and the number of units required for an animal to become infected. This means that there is no need for an exact definition of the infective dose.

Infectious and Diseased animals are distinguishable. In many instances animals may be infectious, even when no clinical signs of disease are apparent, a phenomenon in some circumstances referred to as ‘carrier status’. Defining clinical disease and infectious status as two separate but overlapping categories also allows greater flexibility in the exploration of the disease dynamics. This is achieved in the SELDIRS model, in which animals can be diseased and infectious (D) or infectious without showing clinical signs (I), with $N=S+L+D+I+R$. Equations (1) and (3) describing change in S and L remain the same, with the remaining equations being:

$$dE/dt = \phi(D+I) - \chi E \quad (9)$$

$$dD/dt = \nu L - \gamma D \quad (10)$$

$$dI/dt = \gamma D - \alpha I \quad (11)$$

$$dR/dt = \alpha I - \lambda R \quad (12)$$

The total time an animal is infectious is $1/\gamma + 1/\alpha$, rather than simply $1/\gamma$ as in the SELIRS model. Therefore, for purposes of model investigation, the pathogen burden in the population can be made independent of changes in γ if any reductions in the number of diseased animals (D) are compensated by an increase in the number of recovered but infectious animals (I), i.e. the total time that an animal is infectious ($1/\gamma + 1/\alpha$) is kept constant. The summary parameters in the SELDIRS model (see Appendix 7.3) are:

$$R' = \frac{\phi \xi N (1/\gamma + 1/\alpha)}{\chi} \quad (13)$$

$$p^* = \frac{\lambda \nu (1 - \frac{1}{R'})}{\nu \lambda + \lambda \gamma + \nu \gamma + \lambda \nu \gamma / \alpha} \quad (14)$$

Equation (14) can alternatively be written as:

$$p^* = \frac{\lambda v(1 - \frac{1}{R'})}{\lambda + v + v\lambda(\frac{1}{\gamma} + \frac{1}{\alpha})} \frac{1}{\gamma} \quad (15)$$

Table 7.1 Summary and definition of symbols used in epidemiological models.

Symbol	Definition
S	The number of susceptible animals
E	The number of infectious doses in the environment
L	The number of latently infected animals
I	The number of infectious animals
D	The number of animals diseased and infectious
N	The total number of host animals in the population
R	The number of recovered animals
v	The rate at which latently infected animals develop clinical signs
μ	The rate at which infectious doses (bacteria) die in the environment, other than by host animals
ω	The rate at which infectious doses (bacteria) are physically removed by each host animal in the population
χ	The total rate at which infectious doses (bacteria) are removed from the environment, calculated as $\mu + \omega N$
γ	The rate at which diseased and infectious animals stop showing clinical signs
λ	The rate at which recovered animals lose resistance and become susceptible
ξ	The rate at which susceptible animals become infected by 1 unit of infectious dose in the environment
ϕ	The rate at which an infectious animal sheds infectious doses in the environment
p	The prevalence of the disease as observed from clinical signs
α	The rate at which infectious animals that no longer show clinical signs of the disease stop being infectious
R'	The notional reproductive rate of the infectious disease

There are two differences between (14) and (8), the prevalence in the SELIRS model. First, if the assumption is invoked that the total infectious period is kept constant, then with decreasing $1/\gamma$ R' is constant in SELDIRS, but will decrease with decreasing $1/\gamma$ in SELIRS. Therefore, all other things being equal, the equilibrium prevalence in the SELIRS model will reduce if selection is for lower $1/\gamma$. There is an opposing effect of $\lambda v \gamma / \alpha$ in (14) which is non-negative for all values, leading to a lower prevalence in the SELDIRS model, at the same values for the other parameters. The balance of these effects depends on values for other parameters. The prevalence in (8) will be relatively insensitive to change in R' if it has a high value (i.e. not close to 1).

7.2.2. Predicting responses to selection

Improvement of resistance to disease by genetic selection in its simplest form, i.e. disregarding information from relatives, consists of selection of the healthy animals at one point of time. The expected response to selection on such a binary trait depends on the heritability of resistance and the prevalence. This can be calculated assuming a threshold model with an underlying normally distributed liability with heritability h_L^2 , which depends on the heritability of the binary trait (h_{01}^2) as: $h_L^2 = p(1-p)z^{-2}h_{01}^2$, where p is the prevalence of the binary trait and z is the ordinate of the standardised normal distribution corresponding to p (Robertson and Lerner, 1949).

For the case where the number of healthy animals available for breeding exceeds the number required for selection, and again disregarding information from relatives, the response to selection is calculated as if the selected proportion is equal to $1-p$, and on the underlying scale the response is $R_L = i h_L^2$ with i the selection intensity corresponding to $1-p$. Because of reductions in prevalence, the response to selection is not linear but decreases with increasing values of $1-p$.

In the context of the disease dynamics, selection for 'healthy' animals may be thought of as selection on one or more of the following:

- a. The recovery rate γ (i.e. infected animals recover quicker, e.g. due to an acquired immune response)
- b. The susceptibility of animals ξ (i.e. susceptible animals are more resistant to infection *per se*, requiring exposure to a greater number of infectious doses before becoming infected)
- c. The rate of shedding of bacteria ϕ (i.e. infectious animals spread fewer bacteria) - this is comparable to selection for reduced egg counts with nematode infections
- d. The rate at which immunity is lost λ (i.e. longer lasting immunity)
- e. The rate at which latently infected animals become infectious ν (i.e. longer latency, as seen in scrapie).

Note that ξ and ϕ occur only as products in R' and p^* , therefore their effects can be considered jointly in this model.

In the simplest analogy to the threshold model, one can think of the model parameters, particularly γ (i.e. recovery rate) or ξ (susceptibility) as being analogous to the liability, with heritable between-animal variation. This being the case, we can then assume that the liability and one or more of these parameters have the same distribution and heritability, and responses to selection can be calibrated between the threshold and SELIRS models. Note that because of (6) selection on ξ (or ϕ) is equivalent to selection on R' , given a constant γ .

The response to selection for a binary disease trait can now be estimated in two ways; based on the threshold model and on the SELDIRS model. The threshold model is fully described by the prevalence and heritability of resistance, but the SELDIRS model requires a great number of parameters. While estimates for most are available, prediction of the response to selection also requires knowledge of variation in the parameter under selection. One way to approach this is to require the threshold model and the SELDIRS model to give the same prediction for the response to one round of selection, denoted Δt and Δs respectively, under assumptions that should result in equivalence between the two models.

The predicted response to selection on the observed scale assuming a threshold model is: $\Delta t = \Phi(\tau \pm ih_L^2) - \Phi(\tau)$, with $\Phi(\tau)$ the cumulative standardised normal distribution evaluated at the initial prevalence, h_L^2 the heritability on the underlying scale and i the selection intensity corresponding with truncation selection of all healthy animals (Cameron, 1997).

We have seen in (15) that the prevalence according to the SELDIRS model (with $1/\gamma + 1/\alpha$ constant) is proportional to $1/\gamma$. In the threshold model response to selection on the observed scale is equal to the change in prevalence $p^*_1 - p^*_0$, with p^*_1 the prevalence predicted in the threshold model after one round of selection. For the epidemiological model to predict the same response to selection $ih^2\sigma_x = p^*_1 - p^*_0$, so that $\sigma_x = (p^*_1 - p^*_0)/ih^2$ (16) with σ_x the phenotypic standard deviation of the trait under selection.

The same standard deviation can now be used in the SELIRS models. Appendix 7.4 shows that the predicted response to selection for this model is independent of λ and v given R' , p_0 and h^2 .

If selection is on $1/R'$, or one of its animal-components other than γ , i.e. ξ or ϕ , and assuming that $1/R'$ is normally distributed, the phenotypic standard deviation σ_x that leads to the same response to one round of selection in the SELIRS model as the threshold model ($p^*_1 - p^*_0$) can be calculated (Appendix 7.5) as

$$\sigma_x = \frac{(v\lambda + \lambda\gamma + v\gamma)(p^*_1 - p^*_0)}{\lambda v i h^2} \quad (17)$$

7.2.3. Application to footrot

To apply the SELIRS model to footrot and predict likely effects of selection, parameters were chosen based on literature estimates of the length of time (in days) that each phase lasts, as shown in Table 7.2 Note that the required rates are the inverse of the length of time.

To investigate the consequences of a range of values for γ and R' , the p^* , λ and v were set at 0.08, 0.0333 and 0.1667 respectively, and γ varied from 0.025, 0.1, 0.2

and 0.3 so that corresponding values for R' were 1.18, 1.58, 2.91 and 18.08. Extreme values were investigated with $R'=20$, $\gamma=0.025$ and $p_0=0.5$.

Table 7.2 Published estimates of length of time (in days) of phases of the SELIRS model for footrot infection.

<i>Phase (parameter)</i>	<i>Length</i>	<i>Source</i>
<i>Trait definition</i>	<i>(days)</i>	
<i>Latency (ν)</i>		
Positive for <i>D. nodosus</i>	4	Egerton <i>et al.</i> , 1969
Positive for <i>D. nodosus</i>	5, 6	Roberts and Egerton, 1969
Signs of early footrot	8, 9	Egerton <i>et al.</i> , 1969
Typical signs of early footrot	7	Roberts and Egerton, 1969
Footrot observed in 13 out of 16 sheep	< 10	Egerton and Roberts, 1971
Footrot	10-14	Egerton, 2000
<i>Bacterial survival ($\chi=\mu+\omega N$)</i>		
Bacterial survival	≤ 14	Beveridge, 1941
Bacterial survival to the extent they are still infectious	≤ 7 days	Beveridge, 1941
Bacterial survival	< a few days	Laing and Egerton, 1981
Bacterial survival	≤ 4	West <i>et al.</i> , 2002
Required resting period of pasture to avoid infection	7	Egerton, 2000
<i>Duration of infection (γ)</i>		
Mean (may include re-infection)	190-208	Abbott and Egerton, 2003
Mean (may include re-infection)	21-77	Egerton <i>et al.</i> , 1983
With prompt treatment	1	
<i>Duration of immunity after recovery (λ)</i>		
Since start of treatment (and cured after 0-21 days)	26-31	Egerton <i>et al.</i> , 1969
Re-infection	< 63	Raadsma <i>et al.</i> , 1994

To investigate the predicted response to selection in the various models and depending on the main parameters, the equilibrium prevalence of footrot was calculated over 20 rounds of selection on $1/\gamma$ and $1/R'$ in the SELDIRS and SELIRS models, using discrete generations and a heritability of 0.3, and assuming a normal distribution for $1/\gamma$ and $1/R'$ with constant underlying variances and ignoring the Bulmer effect. With the initial prevalence set at 8%, the response to one round of selection using a threshold model was calculated to estimate σ_x according to (16) and (17). Then (14) and (8) were used to estimate R' given the other parameters. Changes in the parameter under selection ($1/\gamma$ or $1/R'$) that would result from selection of a random sample of healthy animals were calculated for each generation and the new value inserted in (14) or (8) as appropriate to obtain the equilibrium prevalence in the next generation.

7.3. Results

7.3.1. *Predicted progress in the threshold, SELDIRS and SELIRS models*

Predicted responses to selection according to the SELDIRS model with selection on $1/\gamma$ (the time an animal is diseased and infectious) and the SELIRS model with selection on $1/R'$ are identical for values of $\gamma=0.2$ and $R'=2.91$ (Figure 7.1). Both responses are larger than the threshold model prediction after the first round (when they were fixed at the same value). This is the result of differences in the relationship between the trait under selection and prevalence which is close to linear for SELIRS and SELDIRS but not for the threshold model. As expected, the SELIRS model predicts a significant additional response from selection on $1/\gamma$ compared to the SELDIRS model, in which the total infection period is held constant. All graphs have a similar shape, showing diminishing returns at lower prevalences.

7.3.2. *Sensitivity of the predicted response to selection to γ and R'*

A value of R' of just greater than 1 leads to predicted prevalence of footrot quickly going to 0 (Figure 7.2). The reason is that R' drops below 1, so that the infection is not expected to be maintained in the population. In contrast, very high values of R' (such as 18) do not lead to a noticeable additional predicted response. With lower values for R' for footrot of about 1.5, an extra response of about 2 percentage points

can be expected in initial generations, but this difference decreases again in later generations.

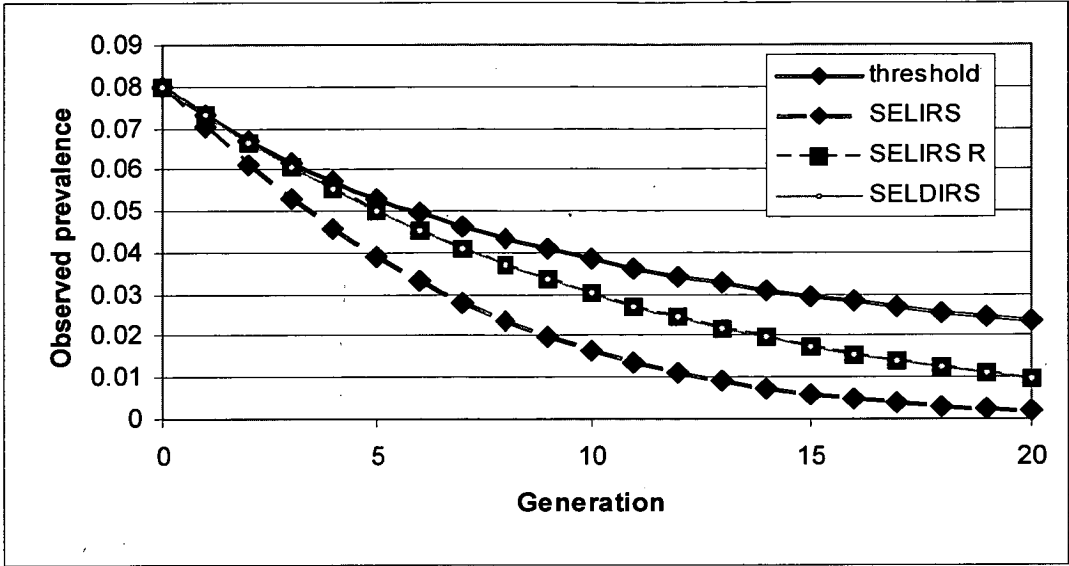


Figure 7.1 Predicted response to selection for resistance to footrot depending on model and whether the notional reproductive rate R' or the recovery rate γ is the trait under selection. $R'=2.91$, $\gamma=0.2$, $\lambda=0.0333$, $v=0.1667$, $p^*=0.08$ and $h^2=0.3$.

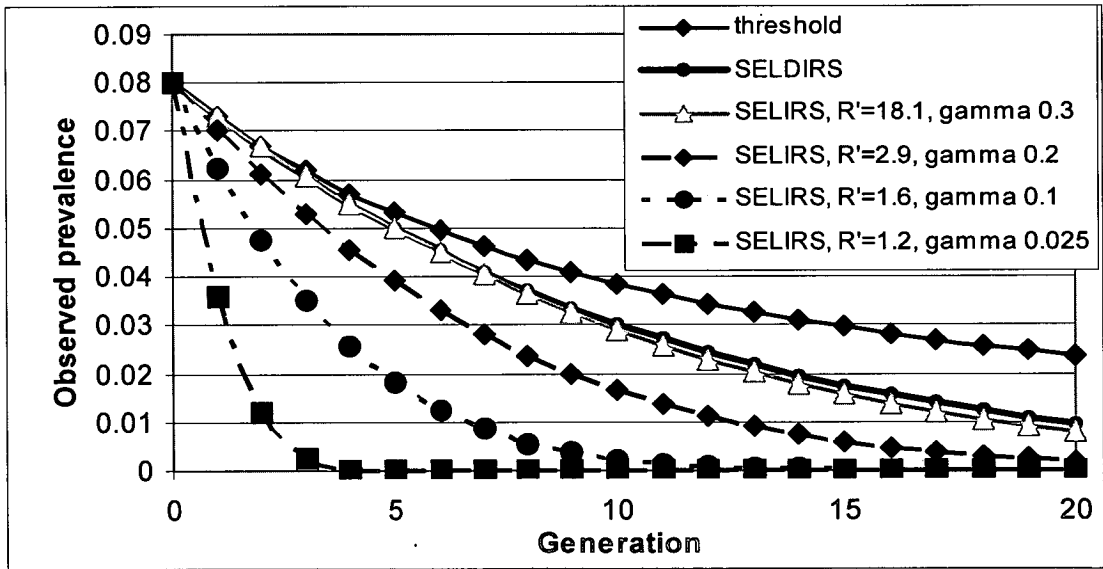


Figure 7.2 Predicted response to selection for resistance to footrot depending on the model used and the notional reproductive rate R' and the initial recovery rate γ . Selection is on γ , with $\lambda=0.0333$, $v=0.1667$, $p^*=0.08$ and $h^2=0.3$.

For more extreme cases, with R' and p^* large and γ small, a very different picture emerges with the SELIRS model actually predicting a lower response to selection for

larger γ in early generations than SELDIRS or selection on R' (Figure 7.3). This is because the variation in $1/\gamma$ is relatively small and changes have little effect on R' .

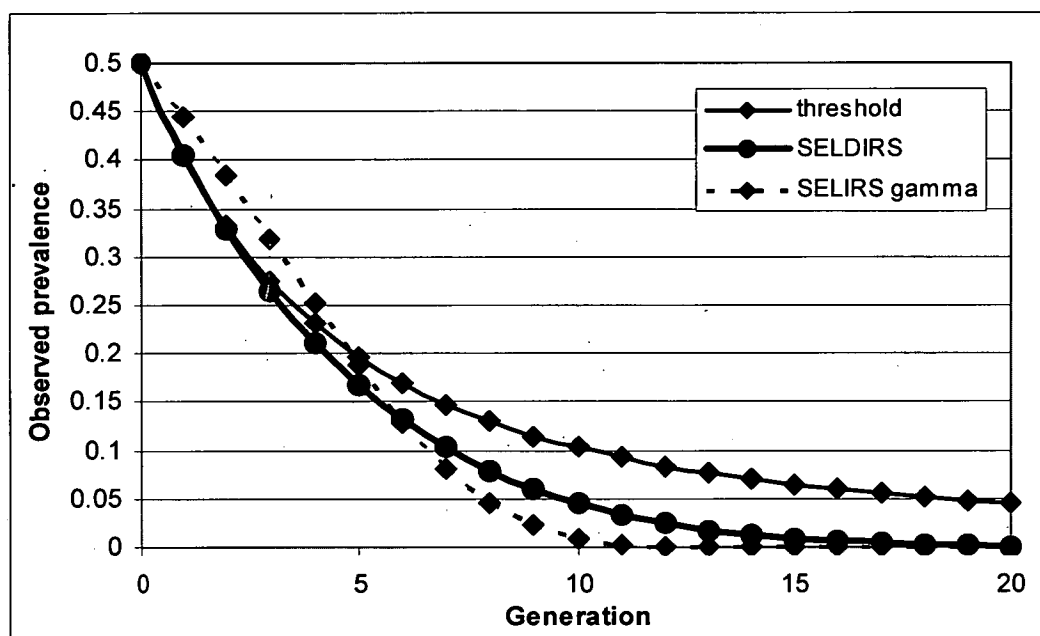


Figure 7.3 Predicted response to selection for resistance to footrot depending on the model and with selection on the recovery rate γ , initial values for the notional reproductive rate $R'=20$ and $\gamma=0.025$ and $\lambda=0.05$, $v=0.0625$, $p^*=0.5$ and $h^2=0.3$.

7.3.3. Sensitivity to v and λ

Additional calculations (results not shown) confirmed that the predicted response to selection on γ or R' does not depend on values of the rate at which latently affected animals become infectious (v) or the rate at which recovered animals lose immunity (λ), given γ , R' and p^* .

7.4. Discussion

A model was developed to predict the response to selection for resistance to an endemic bacterial disease, and this model was then applied to footrot in sheep. While the exact description of the epidemiological process requires a great number of parameters, many of which are poorly known, the prediction of relative responses to selection depends on only a few parameters. By using the threshold model to predict the response to one round of selection, and setting this as the standard, the only

epidemiological parameters required are the rate at which animals recover (γ) and the reproductive rate (R'), alongside the heritability of resistance to the disease.

It was shown that if the notional reproductive rate R' is under selection, changes in the prevalence are proportional to changes in $1/R'$. If selection is for larger γ (i.e. quicker recovery) the SELIRS model predicts a response that consists of the direct effect of animals recovering more quickly, plus an additional component arising from the resulting lower pathogen burden.

It seems counterintuitive that there is no such additional 'epidemiological' component from selection on R' , especially since selection on R' may in fact be on the susceptibility to infection as denoted by ξ , and which is a component of R' . The expectation might be that if fewer animals get infected, there should also be a reduction in pathogens. Formula (7) shows that the prevalence only depends on ξ through R' . An explanation is that a decrease in ξ only means that it takes longer for animals to get infected when facing the same challenge ($1/\xi$ days), but eventually they still become infected and shed the same number of bacteria. The advantage of a smaller ξ , i.e. larger $1/\xi$ is that it takes animals longer to complete the full SELIRS cycle, thereby reducing the number of animals that are diseased at any point in time.

In Raadsma *et al.* (1994) and in Chapter 6, the heritability for resistance to footrot was estimated based on the genetic variation within a population, rather than the response to selection. Therefore, these estimates are independent of possible effects of reduced pathogen burden in selected populations. This situation is comparable to the approach in the SELDIRS model if selection is on $1/\gamma$. If selection is on an element of R' other than γ , i.e. the rate at which animals become infected ξ , the longer cycle time for more resistant animals is fully expressed in unselected populations.

Little information is available on the value of the recovery rate γ , and one reason is that prompt treatment of affected animals means it is not fully expressed ($1/\gamma$ is censored). The prevalence without treatment could then be considerably higher and

R' larger. This scenario was investigated with an initial prevalence of 50%, and it was found that in early generations the expected additional effects are in fact negative, but the effect becomes positive later on. The reason for this negative effect, best understood by comparing (8) and (14) is that with increasing recovery rate in the SLEDIRS model animals spend increasing times in the I phase, i.e. they are no longer considered diseased but continue to spread bacteria. This slows down the whole cycle, with there being fewer susceptible animals compared to the SELIRS model, where recovered animals move directly to the phase of immunity. For our application to footrot this effect may be considered an artefact of the model, occurring only under extreme assumptions, rather than of biological importance, but it may be relevant for other diseases. Previously, MacKenzie and Bishop (1999) showed that in the SIR model applied to viral diseases, if R_0 is high then it may take many generations of selection before the expected number of animals infected during an epidemic is expected to decrease. This, also, is a scenario in which the epidemic model predicts a slower response to selection than the quantitative genetic model.

Knowledge of the traits that show genetic variation is clearly important. While the current results would suggest that this can be done by comparing the variation within a population with the response to selection, in practice this will be very difficult because it would require an unselected control or population with the same environmental conditions, but not affected by decreased shedding of bacteria by the selected animals. An alternative would be to estimate parameters directly from the length of time various stages last in selected and unselected populations following (deliberate) infection, comparable to the figures in Table 7.2.

In the absence of any estimates for the genetic variance of resistance to footrot, this study used the threshold model to standardise response to selection. Following the concept of an underlying normally distributed trait in the threshold model, normal distribution were assumed for $1/R'$ and $1/\gamma$. The inverse of the recovery rate $1/\gamma$ is a length of time, and it seems plausible that it has a positive skewness, with no negative values, and some animals taking extremely long to recover. A positive skewness looks likely for R' as well, especially for scenarios where mean R' is in the

critical range just above 1, with some animals potentially being extremely infectious. Positively skewed distributions for the inverse $1/\gamma$ and $1/R'$ would for instance occur if γ and R' were normally distributed. Under these scenarios, relative responses to selection can be recalculated with appropriately altered selection intensities. However, it should be remembered that a normally distributed liability in the threshold model is also an assumption that can be challenged.

It was shown that, under the prevailing assumptions, the reduction in prevalence at a given R' does not depend on the rate of loss of immunity λ and the rate of conversion of latently infected animals to infectious ν . This does not mean that these parameters are not important for the potential genetic progress; it means that once we know the response to one round of selection it is possible to predict further response without knowing the values of λ and ν .

In the current study a constant environment and a homogeneous population have been assumed. In practice environmental conditions will vary and this may affect survival of bacteria in the environment or the animals' phenotypes, while there may also be different classes of animals, e.g. adults and offspring with different phenotypes with regard to the disease. All these variations can be investigated based on the SELIRS equations, but may require running of a dynamic algorithm that calculates daily prevalence, rather than relying on equilibria. In rapidly changing environments the time to reach an equilibrium will become an important factor, with potentially no equilibrium being attained by the time prevalence is measured or selection decisions are made. In a stable environment, changes in parameters as a result of selection will lead to only small changes in the expected equilibria so that a new equilibrium can quickly be established.

Selection in this study was based on own performance and one observation per animal with disease resistance as the only breeding goal. In practice, information from relatives and repeated measurements will increase the response to selection. Assuming that resistance to footrot is not genetically correlated to any other traits under selection, selection on an index of traits will decrease the expected response to

selection for resistance. On the other hand, disease information on relatives will greatly improve the potential selection response rates for improved resistance. While all these considerations affect the magnitude of the response to selection, essentially by changing the ' h^2 ' term in the response equations, they do not alter the epidemiological effect of selection on $1/\gamma$ relative to the direct genetic effects as predicted by the SELDIRS model. Therefore, simple extrapolation is appropriate.

The models developed in this study are used to consider an endemic bacterial disease with bacteria being transmitted through the environment, where they can only survive for a limited period of time. The models can be applied to a variety of diseases and host species, where these conditions apply. The general trend of results is in fact similar to that seen for a different disease, ruminant gastro-intestinal parasitism, as shown by Bishop and Stear (1999). One difference is that these authors had better estimates of some traits, especially the rate at which animals spread infection, as this is captured in the faecal egg count trait.

In summary, this chapter has presented a novel epidemic model, and applied it to footrot in an attempt to explore likely responses to selection. A key parameter for the model, and also from a biological perspective, is the recovery rate. Given the long time that it takes animals to recover from the disease without human intervention, low values for the rate of recovery (γ) seem likely. If this is indeed the trait under selection when selecting for increased resistance, then the response to selection in terms of observed prevalence, including effects of reduced pathogen burden, could in the medium term be double that predicted by purely genetic models.

APPENDIX 7.1 Derivation of R' for the SELIRS model

The definition of R' is based on the introduction of 1 animal to a fully susceptible population, so that $S=N$. In the SEIR model 1 infected animal sheds ϕ infectious doses over $1/\gamma$ days, these doses survive for $1/\chi$ days infecting $N\xi$ daily so that $R' = \phi\xi N/\gamma\chi$. A more formal derivation is given in Bishop *et al.* (2006).

The extra L step in the SELIRS model does not affect this, as all latently infected animals will (sooner or later depending on ν) become diseased. For most parameter values, the loss of immunity (R animals reverting to S) does not affect the number of secondary infections, but extreme parameter values (long-lived environmental contamination combined with a short period of immunity) may lead to more secondary infections.

APPENDIX 7.2 Derivation of numbers of animals in various categories at the equilibrium in the SELIRS model

At the equilibrium (denoted by *) all derivatives, dI/dt etc are equal to 0, so that from (4) it follows that:

$$\gamma I^* = \nu L^* = \nu(N - S^* - I^* - R^*) \quad (7.2.1)$$

From (5) $R^* = \gamma I^* / \lambda$, and combining (3) and (4) gives $S^* = \gamma I^* / \xi E^*$, while from (2) $E^* = \phi I^* / \chi$, so that $S^* = \gamma \chi / \xi \phi$. Substituting into (7.2.1) then gives:

$$\gamma I^* = \nu(N - \gamma \chi / \xi \phi - I^* - \gamma I^* / \lambda)$$

Rearranging and solving for I^* yields:

$$\gamma I^* + \nu I^* + \gamma \nu I^* / \lambda = \nu(N - \gamma \chi / \xi \phi) \text{ or}$$

$$\gamma \lambda I^* + \nu \lambda I^* + \gamma \nu I^* = \nu \lambda(N - \gamma \chi / \xi \phi) \text{ so that}$$

$$I^* = \frac{\lambda \nu (N - \frac{\gamma \chi}{\xi \phi})}{\lambda \nu + \lambda \gamma + \nu \gamma} \quad (7)$$

APPENDIX 7.3. Summary parameters in the SELDIRS model

Following Appendix 7.1, R' for the SELDIRS model can be calculated from the product of number of infectious doses produced at rate ϕ by 1 infectious animal over the duration of the infection $(1/\gamma + 1/\alpha)$, the time these infections survive in the environment $(1/\chi)$ and the number of animals that will be infected at a rate of ξN , so that:

$$R' = \frac{\phi \xi N (1/\gamma + 1/\alpha)}{\chi}$$

As with the SELIRS model in Appendix 7.2, the equilibrium prevalence p^* can be calculated by setting all derivatives to 0. Combining (3) and (10) then gives $S^* = \gamma D^* / \xi E^*$, and from (9) and (11) it follows that

$$E^* = \frac{\phi(D^* + \frac{\gamma D^*}{\alpha})}{\chi}$$

so that:

$$S^* = \frac{\chi}{\xi \phi (\frac{1}{\gamma} + \frac{1}{\alpha})}$$

From (10), (11) and (12), $L^* = \gamma D^* / \nu$, $I^* = \gamma D^* / \alpha$ and $R^* = \gamma D^* / \lambda$. Substituting these values in $L + D + I + R = N - S$ and rearranging yields:

$$D^* = \frac{\lambda \nu \alpha N (1 - \frac{\chi}{\xi \phi (\frac{1}{\gamma} + \frac{1}{\alpha})})}{\nu \lambda \alpha + \lambda \gamma \alpha + \nu \gamma \alpha + \lambda \nu \gamma}$$

Therefore, from (14) the equilibrium prevalence is

$$p^* = \frac{\lambda \nu (1 - \frac{1}{R'})}{\nu \lambda + \lambda \gamma + \nu \gamma + \lambda \nu \gamma / \alpha}$$

APPENDIX 7.4 Derivation of the predicted response to selection on γ and demonstration that the rate of response in p^* depends linearly on λ and ν , given R' and p^* in the SELDIRS and SELIRS models.

SELDIRS model, i.e. R' is constant

$$\text{From (8) } p^* = \frac{1 - \frac{1}{R'}}{1 + \gamma\left(\frac{1}{\lambda} + \frac{1}{\nu}\right)}$$

$$\text{Therefore } \frac{1}{p^*} = \frac{1 + \gamma\left(\frac{1}{\lambda} + \frac{1}{\nu}\right)}{1 - \frac{1}{R'}}$$

Now consider the derivative $d(1/p^*)/d\gamma$. Solving this equation we obtain:

$$-\frac{1}{p^{*2}} dp^*/d\gamma = \frac{\frac{1}{\lambda} + \frac{1}{\nu}}{1 - \frac{1}{R'}}$$

Therefore:

$$dp^*/d\gamma = -\frac{\left(\frac{1}{\lambda} + \frac{1}{\nu}\right)p^{*2}}{1 - \frac{1}{R'}}$$

Thus, in the SLEDIRS model the predicted response in p^* to changes in γ is a linear function of $(1/\lambda + 1/\nu)$, and it also depends on R' and p^* but under the model assumptions it is independent of γ .

SELIRS model, i.e. R' depends on γ

Define a new parameter Q' so that $Q' = \frac{\varphi_{\xi N}}{\chi}$ and Q' is independent of γ . Since

$Q' = R'\gamma$ we have:

$$p^* = \frac{1 - \frac{\gamma}{Q'}}{1 + \gamma\left(\frac{1}{\lambda} + \frac{1}{\nu}\right)} \quad (7.4.1)$$

Equation (7.4.1) can be rearranged as

$$\frac{1}{p^*} \left(1 - \frac{\gamma}{Q'}\right) = 1 + \gamma \left(\frac{1}{\lambda} + \frac{1}{\nu}\right)$$

Solving the derivative $d(1/p^*)/d\gamma$ we obtain:

$$\frac{-1}{p^{*2}} \left(1 - \frac{\gamma}{Q'}\right) dp/d\gamma - \frac{1}{p^*} \frac{1}{Q'} = \frac{1}{\lambda} + \frac{1}{\nu}$$

Rearranging terms yields:

$$\left(1 - \frac{\gamma}{Q'}\right) dp/d\gamma = -\frac{p^*}{Q'} - \left(\frac{1}{\lambda} + \frac{1}{\nu}\right) p^{*2}, \text{ so that}$$

$$dp^*/d\gamma = \frac{-\frac{p^*}{Q'}}{1 - \frac{\gamma}{Q'}} - \frac{\left(\frac{1}{\lambda} + \frac{1}{\nu}\right) p^{*2}}{1 - \frac{\gamma}{Q'}} \text{ or}$$

$$dp^*/d\gamma = \frac{-p^*}{Q' - \gamma} - \frac{Q' \left(\frac{1}{\lambda} + \frac{1}{\nu}\right) p^{*2}}{Q' - \gamma}$$

There are two important differences from the derivative for p^* in the SELDIRS

model. Firstly, there is the extra element $\frac{-p^*}{Q' - \gamma}$, which is more important at low

values of Q' (i.e. low values of $\gamma R'$). Also, the second part of the equation includes γ , so that higher values of γ lead to higher rates of change.

APPENDIX 7.5 Calculation of the phenotypic standard deviation for $1/R'$

The predicted genetic response to one round of selection is:

$$ih^2\sigma_x = 1/R'_1 - 1/R'_0.$$

The difference in prevalence can also be calculated as $p_1 - p_0$, using (8):

$$\begin{aligned} p_1 - p_0 &= \frac{\lambda v(1 - \frac{1}{R'_1})}{v\lambda + \lambda\gamma + v\gamma} - \frac{\lambda v(1 - \frac{1}{R'_0})}{v\lambda + \lambda\gamma + v\gamma} \\ &= \frac{\lambda v(\frac{1}{R'_1} - \frac{1}{R'_0})}{v\lambda + \lambda\gamma + v\gamma} \\ &= \frac{\lambda v i h^2 \sigma_x}{v\lambda + \lambda\gamma + v\gamma} \end{aligned}$$

Rearranging gives:

$$\sigma_x = \frac{(v\lambda + \lambda\gamma + v\gamma)(p_1 - p_0)}{\lambda v i h^2} \quad (17)$$

Chapter 8. General discussion

8.1 Summary of results

The aim of this thesis was to identify opportunities for selection for increased resistance to infectious diseases in sheep and to explore the benefits and consequences of such selection for the British sheep industry.

Special emphasis was put on the calculation of costs and potential benefits and on those aspects of disease resistance that make it different from standard production traits, including the effect of prevalence of the disease and exposure to pathogens, epidemiological effects and the binary character of many disease traits.

Costs of sheep diseases

Chapter 2 showed that the most important sheep diseases, in terms of annual costs to the British sheep industry, are gastro-intestinal parasites, footrot, Chlamydial abortions (enzootic abortions of ewes) and Toxoplasmosis, with estimated annual costs of £84M, £24M, £20M and £12M respectively. Because in a breeding programme only small incremental improvements can be expected, the distinction was made between fixed costs such as preventive measures, which will be taken until a considerable reduction in disease incidence has been achieved, and variable costs, which are proportional to the prevalence such as treatment of affected animals and lost production. Variable costs associated with gastro-intestinal parasites, footrot, Chlamydial abortions and Toxoplasmosis were estimated at £84M, £12M, £1M and £9M respectively. These are similar to total costs, except for Chlamydial abortions where most costs are fixed (vaccination). For footrot, costs of preventive measures such as footbathing are of similar size to variable costs including lost growth, smaller litters and treatment costs. Based on these results, and the fact that a commercial service for selection against gastro-intestinal parasites already exists in Britain and elsewhere, the remainder of the thesis focused on footrot in sheep, though many results are applicable to other diseases and host species.

Predicting the response to selection on a binary trait

Footrot is generally scored on a 5 point scale (Egerton and Roberts, 1971), but with a typical prevalence under commercial conditions of less than 10%, the vast majority of scores would be 0 (healthy) and the small number of diseased animals subdivided among the remaining classes. In practice, this is similar to a binary trait considering healthy and affected animals. The response to selection on a binary trait based on own performance only can be predicted with a threshold model, assuming an underlying normally distributed trait and selection of a random sample of healthy animals if that is sufficient. If more animals are required, all healthy animals are selected supplemented with a random sample of diseased animals (Falconer and Mackay, 1996). Unless the required fraction of animals is close to the proportion of healthy animals, this system is inefficient, although inefficiencies decrease with incorporation of information from relatives. For example, Foulley (1992) considered the case where animals were selected on the disease status of their offspring. This proved much more accurate than mass selection, especially because his application considered dairy bulls, which are routinely progeny tested.

In the British sheep industry, progeny testing is less common, and animals are typically selected based on own performance and information on close relatives. An approach combining own performance with half sib observations for a binary trait (e.g. footrot) is therefore developed in Chapter 3. The approach uses the principle of two-stage selection, with selection of healthy animals on their own performance in the first stage. Depending on prevalence and required numbers, half sib performance is then used to select either additional animals among the diseased, or to select within the healthy animals selected in the first phase. Theoretical expectations generally agreed well with stochastic simulations using a selection index, except when the number of healthy animals was very close to the number required. In this case the two-stage selection procedure was essentially reduced to one stage, half sib information was ignored and the response to selection was underestimated. With a disease prevalence between 5 and 25% and a heritability on the underlying scale of 0.3 and other conditions as typical for British sheep breeding schemes, selection on

the disease trait alone and including half sib information on disease prevalence is predicted to halve the prevalence in every round.

The effect of prevalence and exposure on the selection response

In Chapter 4, effects of variations in the highly standardised circumstances of the model in Chapter 3 are investigated, including differences in prevalence among flocks and variation in exposure to the disease pathogen within and among flocks. Variation in prevalence, other than due to variation in exposure, can have a positive effect on the response to selection on own performance, because healthy animals in the most affected flock(s) can be considered most resistant and preferably be selected, therefore removing some of the random selection otherwise required. When half sib information was used, the predicted response to selection was slightly lower in case of variation in flock prevalence, but always higher than for own performance. Less than 100% exposure of animals to the pathogen had a negative effect on the response to selection, but with use of half sib information, and unless exposure was extremely low, progress was still predicted to be over 75% of that with full exposure, so that considerable genetic progress can still be made even with incomplete exposure.

The effect of footrot on live weight gain

The relationship between footrot and production was investigated with data from an Australian trial in which deliberately infected animals were weighed on a regular basis. While it had earlier been shown in the same trial that heavier animals tended to be more severely affected by footrot (Raadsma *et al.*, 1994), it was shown in Chapter 5 that animals with a higher genetic merit for growth coped better with the disease as they lost less weight than those with a low genetic merit for growth. Footrot score and maximum effects on live weight gain had a negative genetic correlation indicating that selection for increased resistance to footrot would lead to a lower impact on weight gain of affected animals.

Heritability and repeatability of footrot

In Chapter 6, the genetics control of footrot is investigated in British sheep and under British conditions. Data were analysed from animals that had been scored repeatedly for lesions by a team at SAC. Results were largely in line with those from Raadsma *et al.* (1994) and showed that in adult sheep lesion scores are heritable, with the h^2 typically around 0.2. A simple binary score turned out to be as effective as more complex traits which incorporated information on the severity of lesions. The repeatability of footrot lesions scores was low, i.e. not much higher than the heritability. This means that repeated measures or traits that combine a number of scores on the same animal over time will be much more effective than a single score per animal. An important finding was the absence of a genetic component for lesions scores in lambs. This implies that selection in lambs is predicted not to be effective and selection in ewes is predicted not to have an effect in terms of resistance of lambs to footrot.

These results were obtained under commercial conditions, mimicking the situation relevant to a commercial selection programme. Under highly controlled or standardised circumstances, e.g. with deliberate infection, or when each animal's history with regard to cases of footrot and treatments is known, the error variation would be expected to be lower. The heritability of resistance to footrot appeared to depend on the prevalence, with higher heritabilities at higher prevalences.

Epidemiological effects of selection for resistance

For infectious diseases where the host species is the main reservoir of the pathogen, such as footrot in sheep, the host may play an important role in maintaining and spreading the disease. Such effects have, for instance, been shown for gastrointestinal parasites where faecal egg counts are an indicator trait of how severely an animal is affected and additionally they quantify the contribution of an animal to further spread of the disease (e.g. Bishop and Stear, 1999). In Chapter 7 a model was developed that describes the various disease states that an animal can be in, with regard to footrot, and the rates at which an animal moves from one state to the next. It is shown that the speed at which animals recover and the rate at which animals

infect each other (the notional reproductive rate) are the most important traits determining the rate of progress in terms of reduced footrot prevalence. If selection of more resistant animals is in fact selection for faster recovery, there can be important additional benefits, as this will reduce the pathogen contamination from the host to the environment. If the initial notional reproductive rate is close to 1, a small increase in the recovery rate may be sufficient to lead to extinction of the disease. Until the parameters required to fully describe this model are estimated accurately exact quantification of effects remains problematic.

8.2 Can selection for disease resistance work?

The potential for selecting for disease resistance is often questioned due to factors such as temporary effects, incomplete exposure, difficulties in diagnosis and possible negative correlations with production traits. However, it must first be noticed that this is not special for disease resistance; even for a standard production trait such as growth rate, there will be issues about getting the correct weight (e.g. due to gut fill), there will be temporary effects affecting weights, e.g. because of sub-clinical disease and because animals do not grow at a constant rate, while there is an undesirable (positive) correlation between growth rate and fat contents (e.g. Safari and Fogarty, 2003). Considerable genetic progress in growth rates of sheep and other livestock has nevertheless been made (e.g. Amer *et al.*, 2007). So while factors like temporary effects, incomplete exposure, difficulties in diagnosis and possibly negative correlations with production traits affect selection for disease resistance, this does not in itself mean that genetic progress in this respect can not be achieved. The question is whether or not these factors are of sufficient size to seriously reduce the potential of selective breeding for disease resistance.

The analysis in this thesis has shown that, at least for circumstances investigated, lack of full exposure to the pathogen is not a major problem. In chapter 4 the accuracy of selection reduces with lower exposure, but because extensive use is made of relatives the reduction is less than 25%, unless exposure is very low. Chapter 6 uses footrot lesions as an indicator trait for footrot. Repeatabilities are low, confirming that diagnosis and ascertainment of an animal's resistance is far from

perfect, i.e. many susceptible animals are healthy at some point in time and would appear to be resistant. In spite of this, heritabilities are still sufficiently high to make genetic progress, even if based on a single observation per animal. The low repeatabilities mean that repeated scoring will be effective in increasing the accuracy. It was not possible to assess how good an indicator lesion score is for footrot, especially for the lowest lesion score, which may identify early stage footrot or scald. For the health of the animals this is not detrimental, however; in the 'worst' case animals would be unwittingly selected for resistance to scald rather than footrot. It is further noted that sheep populations were analysed over various flocks and years, so that it can be expected that different strains of *D. nodosus* were present on the affected farms. Again, this may have reduced the size of heritability estimates, but not to the extent that they become too low to be useful.

For practical applications in a breeding scheme, it is encouraging that Kaler and Green (2008) conclude that 'many farmers could not name all six lesions presented but probably could recognise the lesion in their flock', so that scoring can be done by breeders with only limited additional training, and farmers in general would recognise reductions in prevalence that are achieved.

The analysis of the Australian trial in Chapter 5 showed that the faster growing animals could in fact cope better with the disease, in terms of reduced weight losses. McLaren *et al.* (2008) also did not find important detrimental correlations between footrot resistance and production traits and conclude that no negative effect is expected from selection against footrot.

The only aspect of concerns remains the risk of co-evolution of the pathogen. This was not investigated in this thesis and therefore can not be fully addressed. It must be noted that a proposed selection programme, based on the results presented in this thesis, would use continued measurements of phenotypes, and if the pathogen co-evolved it would become apparent from the data, and automatically be incorporated in estimated breeding values. If the pathogen evolution leads to serious increases in prevalence in certain flocks, genetic evaluations will automatically identify

unaffected animals (and those with many unaffected relatives) in these flocks as the most resistant animals, thus immediately switching selection to those sheep that are resistant to the newly evolved pathogen. Such a reaction would not occur if selection were on genetic markers.

8.3 The importance of prevalence

The analysis in this thesis has shown a number of important effects of the prevalence on genetic aspects of footrot. As is well-known, the prevalence determines the phenotypic variance of a binary trait (which is $p(1-p)$, with p the prevalence). A prevalence-dependent variance can be a problem when various sub-populations (such as flocks) have different prevalences. The threshold model was developed to address this, and chapters 3 and 4 confirm that it is successful, given that the assumption holds of an underlying normally distributed trait which is independent of the prevalence. However, in Chapter 6 it was shown that the additive genetic variation in this underlying trait may in fact depend on the prevalence, with the heritability being higher in high prevalence flocks. Biologically this makes sense, as higher disease burdens (leading to higher prevalence) will allow more genes to be expressed or expressed to a greater extent, hence leading to larger genetic differences between animals. Selection at low prevalence may be even less effective than predicted in chapter 3 and 4, so that it may be advisable to use high prevalence flocks whenever possible, for instance commercial flocks with offspring from pedigree animals. It is advisable in across flock evaluations to include a procedure to correct for heterogeneity of variance, including heterogeneity of the heritability. Visscher and Hill (1992) considered this for dairy cattle with herd specific heritability estimates, but concluded that the sampling errors for within herd heritabilities would be too large to make a practical impact. For footrot in sheep it may be possible to use heritabilities (and sampling errors) appropriate for groups of flocks with a similar prevalence.

The theory behind the threshold model assumes a linear relationship between the cumulative normal distribution of the underlying trait and the observed prevalence. While this is generally a reasonable assumption, it becomes questionable at very low

(and very high) prevalences. As a consequence, a very large change in the underlying trait is required at a very low prevalence, to make an appreciable change in prevalence. This means that in intensively managed pedigree flocks – with generally lower levels of disease – the response to selection for resistance to footrot, while considerable on the underlying scale, may be disappointing in terms of prevalence. The same animals (and their offspring) will, however, do considerably better than unselected contemporaries in more extensively managed commercial flocks.

The observed prevalence is affected by the exposure of animals, and in principle this would especially be an issue if animals within the same contemporary group (flock and season) were not equally exposed. It is shown that, assuming that all animals within a contemporary group have equal risk of exposure and with the use of sufficient information on relatives this is not a problem, unless the exposure is extremely low. The number of recorded relatives required can realistically be achieved in typical breeding flocks.

8.4 Epidemiological effects

With all the complications that appear to affect selection for resistance to an infectious disease, it is important not to overlook the potential additional returns: those arising from a reduction in pathogen burden that benefits both selected and unselected contemporaries. The epidemiological model developed in this thesis in principle allows quantification of this effect, and based on plausible assumptions for the various parameters, it appears that these additional returns may be as large as the direct genetic effect. The model includes a great number of parameters, and selection of resistant animals will change the value of one or more of these; for example selection may lead to animals that are less likely to get infected or to animals that recover quicker once infected or both. There is uncertainty about the values of these parameters, and the main conclusion is therefore that the focus of further research in this area should be on establishing which parameter(s) is (are) under selection and estimate values for the recovery rate and the notional reproductive rate.

The same model can also be used to investigate the effects of selection in more complex (and realistic) situations, for instance where populations are a mixture of ewes which are selected for higher resistance and their lambs, in which direct genetic progress is not expected (since the genetic variance of footrot in lambs - and hence the genetic covariance with footrot in ewes - is zero). Temporary changes in the weather that affect survival of bacteria, and management practices that concentrate sheep and bacteria in a small area for a limited period of time (as in gathering for shearing or foot bathing) and thus facilitate the spread of the disease can easily be incorporated in the model. This may also help identify critical points for transmission of footrot and the most effective management practices to reduce prevalence of the disease.

Where it is difficult to model the effect of certain interventions aimed to reduce the incidence of footrot, other management actions or temporary environmental effects, it is possible to predict progress of the disease using a dynamic algorithm. This algorithm describes the number of animals in each of the phases in the SELIRS depending on the numbers on the previous day as determined by the various rates, or as determined by management or environment. For instance, moving the whole flock to clean pasture on day X can be modelled by setting $E=0$ on day X and then using the standard rates to predict day $X+1$. Likewise, gathering the flock in a small area can be modelled by assuming a higher value for the rate at which animals get infected for the time that the flock remains in this confined area.

The effects of selection on disease resistance on other traits in the next generation, be it as correlated response or in a multi-trait selection are straightforward and can be modelled using the genetic component of disease resistance, for instance in a selection index. The relative economic weight of disease resistance needs to reflect both the direct genetic and epidemiological benefits of disease resistance. The long-term response is more complicated, as the response to selection for disease resistance is not linear; and this would also affect the relative economic weight. The shape of trends for genetic and epidemiological responses as predicted in this thesis for univariate selection do apply for a multitrait situation, but they will generally take

longer to be achieved (there will be a positive effect of observations on a correlated trait),

Epidemiological effects complicate estimation of benefits of selection, as reduced pathogen burdens due to selection is compounded with environmental effects – an unselected control line can not be kept in the same environment or it would benefit from selection in the other line. This also complicates demonstration of the benefits of selection for resistance to footrot to the industry, as it requires grazing of more resistant and susceptible animals in separate fields in a number of replicates.

8.5 Practical recommendations

Commercial sheep in Britain are mainly crossbred. Although there are many variants, the standard system is based on commercial ewes that are crosses of longwool and hill breeds (such as mules). These ewes are mated to rams from terminal sire breeds to produce commercial lamb (Pollott and Stone, 2006). The apparent lack of additive genetic variance for resistance to footrot in lambs as estimated and reported in this thesis, means that the main benefits from selection will be in the crossbred commercial ewes and in the large populations of hill breeds. Very small benefits are predicted from selection in terminal sire breeds, as this will only affect pedigree flocks. Because of their great impact on commercial ewes, selection in longwool breeds would be the most effective, but in practice this may be difficult because of very small flock sizes (Pollott and Stone, 2006) and low uptake of performance recording.

In ruminants, schemes that have been successful (at least in uptake, if not always in results) in selection for disease resistance are those where collection of data is relatively easy and straightforward, such as scrapie genotypes in sheep and somatic cell counts in dairy cattle. In contrast, uptake of selection for resistance to gastrointestinal parasites in sheep has been very limited. The successes of pig and poultry breeders in incorporating resistance to diseases such as *E. coli* and Marek's disease respectively, seem due to effective selection in the nucleus and greater ability to market the benefits to their customers. Among these examples, footrot most

resembles gastro-intestinal parasites, although with lower costs and lower predicted benefits.

Within the constraints of the British sheep industry, and using quantitative genetic approaches only, the potentially most effective selection strategy for resistance to footrot would be to concentrate on longwool breeds and include footrot lesions scores of their crossbred offspring, as this would greatly increase the number of records and at a higher prevalence. The same recommendation applies to gastro-intestinal parasites, and the main effort – recording of purebred and crossbred pedigrees in one dataset – would be common to the two diseases.

A commercial test for resistance to footrot (based on a microsatellite marker within the MHC region, Escayg *et al.*, 1997) is available in New Zealand. The owners claim that it can distinguish between animals with different levels of resistance, so that under high infection pressure 7 to 19% of offspring of the most resistant rams will be affected by footrot against 22-83% among offspring of the most susceptible (Lottner, 2006). The limited number of scientific reports available, however, are not unequivocally supportive (Lottner, 2006; Abbott *et al.*, 2007). A project investigating the test in Britain as well as extending it to give a more comprehensive coverage of the MHC region is currently underway, but it seems unlikely that one simple marker test will eliminate, or even substantially reduce prevalence of footrot.

The best opportunity for resistance to endemic diseases such as footrot and gastro-intestinal parasites may therefore be their inclusion in genomic selection programmes (Meuwissen *et al.*, 2001). If such programmes were implemented in Britain, the potentially high economic (and animal welfare) benefits of resistance to disease justify their inclusion, while various estimates confirm that there is considerable genetic variation that can be exploited. Phenotypes to support such schemes would include repeated lesion scores on adult sheep of longwool and hill breeds, and preferably under high challenge. Scoring would need to be repeated after a few generations, among other reasons to verify that pathogens have not adapted to the resistance in the host.

Currently genomic selection schemes for livestock are most advanced in dairy cattle, where they use large (and well-recorded) paternal half sib families and take advantage of there being a very limited number of commercial breeds who also have small effective population sizes. One major advantage in dairy cattle is that genomic selection would dramatically reduce the generation interval, as it makes progeny testing redundant. This model can not be copied straight away to sheep.

Australian research in the area of sheep genomics is based on nucleus flocks of large size (thousands of animals) that are extensively recorded for other purposes. The additional costs of genomic selection are therefore limited (to genotyping rather than phenotyping), while progress can be made in a great number of traits (<http://www.sheepgenomics.com/>, <http://www.sheepcrc.org.au/>, Julius van der Werf personal communications, Ben Hayes personal communications). This example could be followed in the UK, and include footrot as one of many traits, through the creation of a nucleus flock of longwool sheep. This flock could be considerably smaller than in Australia, because of the smaller total population size for longwool breeds. The extent to which results would be applicable to other breeds will remain to be seen, but this should improve with denser coverage of the genome.

8.6 General conclusions

Footrot is a disease of economic importance showing additive genetic variability. Selection for resistance can be effective if based on simple binary scores, especially if animals are recorded repeatedly. Use of information on relatives will increase the accuracy of selection and greatly reduce the effects of incomplete exposure to the disease among animals and flocks. The response to such selection can be predicted with an approach developed specifically for binary traits, which also covers situations when exposure to infection is variable. Selection for resistance is expected also to result in animals that can better cope with the disease, in terms of reduced weight loss. A new epidemiological model predicts likely responses to selection, showing a considerable additional decrease in the prevalence of footrot compared to purely genetic predictions. It is concluded that in principle selection for increased

resistance to footrot can be expected to be successful in reducing costs of the disease to the British sheep industry. In practice, the best route to capitalise on this potential may be to include footrot in genome wide selection programmes based on extensively recorded nucleus flocks.

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