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The interaction of host genetics and disease processes in chronic livestock disease: A simulation model of ovine footrot

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ABSTRACT

A stochastic, individual-based, simulation model of footrot in a flock of 200 ewes was developed that included flock demography, disease processes, host genetic variation for traits influencing infection and disease processes, and bacterial contamination of the environment. Sensitivity analyses were performed using ANOVA to examine the contribution of unknown parameters to outcome variation. The infection rate and bacterial death rate were the most significant factors determining the observed prevalence of footrot, as well as the heritability of resistance. The dominance of infection parameters in determining outcomes implies that observational data cannot be used to accurately estimate the strength of genetic control of underlying traits describing the infection process, i.e. resistance. Further work will allow us to address the potential for genetic selection to control ovine footrot.

1. Introduction

Footrot is an infectious bacterial disease of sheep in which infection is transmitted between animals via contaminated pasture (Beveridge, 1941). Clinical signs include lameness and foot lesions which start in the interdigital space and can progress to cause separation of the hoof horn from the sensitive dermis (Beveridge, 1941). The disease is common, with a prevalence of 8–10% in England (Kaler and Green, 2009), detrimental to production (Wassink et al., 2010) and reduces both animal health and welfare (Fitzpatrick et al., 2006). Footrot has been estimated to cost the GB sheep industry approximately £24.4 million per year in one study (Nieuwhof & Bishop, 2005) and £6 per ewe mated in another (Wassink et al., 2010) and in one survey sheep farmers rated it as the second highest threat to animal health and welfare, after only sheep scab (Morgan-Davies et al., 2006).

Field and experimental data suggest that susceptibility to footrot is partly under genetic control. A number of studies have estimated heritability of footrot severity and associated lameness, but only on data sets with short time scales or with limited observations (e.g. Skerman et al., 1988 (New Zealand); Raadsma et al., 1994 (Australia); Nieuwhof et al., 2008 (UK)). In New Zealand, there has been some success with breeding footrot resistance into Broomfield Corriedale sheep; selection for footrot resistance for 15 years resulted in greater resistance to clinical footrot than observed in other breeds when introduced to contaminated pasture in field trials (Skerman & Moorhouse, 1987). In Australia, selective breeding has also been successfully used to reduce the prevalence of footrot (Mitchell, 2001; Egerton et al., 2004). Hence it may be possible, in principle, to use breeding programmes to reduce disease prevalence or incidence in the UK (Conington et al., 2008). However, the climatic differences between Australia and New Zealand and the UK, where long, hot summers free from transmission do not occur (Green and George, 2008),

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could mean that breeding for resistance requires a different approach in the UK.

Heritability estimates can be made using pedigree and phenotype data, however true underlying heritabilities for traits describing resistance to infectious disease can be difficult to estimate from field data because the data are confounded by environmental factors, such as exposure rates, disease dynamics and diagnostic ability (Bishop and Woolliams, 2010). Heritability estimates made when disease prevalence is low often differ from estimates made when disease prevalence is high (Nieuwhof et al., 2008) because expression of genetic differences between hosts is exposure dependent. Further, when prevalence is very low there are often scale effects, i.e. very few observed infections, limiting the phenotypic variation seen between individuals and thus ability to identify genetic effects.

To fully understand endemic diseases such as footrot, and work towards long term solutions for control, genetics, epidemiology and their interaction must be considered in detail and simultaneously. Modelling has been used in a limited way to explore the potential for a reduction in footrot prevalence, particularly in the deterministic model of footrot produced by Nieuwhof et al. (2009). However, the complex nature of the disease has not yet been fully addressed in a simulation model.

In this study, a stochastic, individual-based, genetic-epidemiological model of footrot was developed that included sheep demography, individual host genetic effects and full flock life cycles. In this paper the model structure, assumptions and processes are presented, along with the results of a sensitivity analysis exploring the significance of variation in parameters whose values are unknown. The outcome of interest was the variation in disease patterns, not the mean value. This is important because it is variation between sheep that is the material observation for determining if genetic influences are important, and for selecting sheep for resistance.

2. Materials and methods

The model description follows the ODD (Overview, Design concepts, Details) protocol for describing individual- and agent-based models as defined by Grimm et al. (2006, 2010).

2.1. Purpose

The purpose of this model is to explore the interaction between host genetics and disease processes in footrot, by comparing the observable disease outcomes under a range of different conditions. It should allow comparisons of homogeneous and heterogeneous populations and the effects of population structure on the outcomes of different treatment and selection strategies. Criteria include the impact on short term disease prevalence or incidence and on the longer term population means for genetically controlled traits such as susceptibility.

Table 1
Information set at birth.

Field name	Description
IDNum	Unique individual ID number
YearOfBirth	Year in which sheep was born
Dam	Dam ID number
Sire	Sire ID number
Sex	0/1 (male/female)
Susceptibility (*Sus*)	Applied susceptibility phenotype (≥0)
TrueSus	True susceptibility phenotype (may be <0)
GTSus	Genetic term for susceptibility
Recoverability (*Rec*)	Applied recoverability phenotype (≥0)
TrueRec	True recoverability phenotype (may be <0)
GTRec	Genetic term for recoverability
Revertability (*Rev*)	Applied revertability phenotype (≥0)
TrueRev	True revertability phenotype (may be <0)
GTRev	Genetic term for revertability

2.2. Entities, state variables and scale

2.2.1. Population

The model population comprises sheep in three categories – ewes, lambs and rams. A base population of 200 ewes is simulated, with female lambs kept each year as replacements. The number of lambs born to each ewe is sampled from a Poisson distribution with mean 1.5 and a maximum number of lambs set at three. Data recorded for each ewe and lamb include genetic values which are set at birth and are dependent on parents' genotypes (Table 1), current status (e.g. disease state and age) and disease history. Animal phenotype and genotype definitions are given below. Rams do not participate in any disease events and only identification numbers and genetic information used to calculate genetic values for their lambs are recorded.

2.2.2. Host genetics

Within the population, sheep have unique genetic characteristics comprising three phenotypes – susceptibility, recoverability and revertability. Susceptibility governs the probability that a sheep will initially become infected, recoverability determines the length of time a sheep takes to recover from disease and revertability affects how quickly a sheep reverts to a susceptible state following a period of immunity.

All traits with a genetic component are assumed to be polygenic, i.e. affected by variants at many genes, and under partial genetic control. Under this situation, we may assume the central limit theorem, and sample animal genotypes from a normal distribution, the variance of which is a function of the trait variance and heritability.

For each trait the phenotype, P, for each sheep, i, may be defined as comprising the following components:

$$P_i = \mu + g_i + e_i \quad (1)$$

where μ is the trait mean in an unselected population, g_i is the genetic component (expressed as a deviation from 0) and e_i is the residual component (expressed as a deviation from 0), which is also assumed to be normally distributed.

The variance of P_i is the phenotypic variance of the input trait, denoted by σ_P^2 and the variance of g_i is $\sigma_A^2 = h^2\sigma_P^2$, where h^2 is the trait heritability. Assuming that g_i and e_i,