Impact of Genetic Diversity on the Prevalence and Dynamics of Infectious Disease in Livestock

A.Doeschl-Wilson[*†], R. Davidson[†], J. Conington[†], M.R. Hutchings[†], T. Roughsedge[†] and B. Villanueva[‡]

Introduction

There is substantial evidence that animals differ genetically in their response to infectious challenge, and the potential impact of host genetic heterogeneity on the dynamics and control of disease has long been recognized. Using stochastic epidemiological models, Springbett et al. (2003) demonstrated that populations with greater degree of genetic diversity in susceptibility to infection are less likely to suffer catastrophic epidemics, but more likely to suffer epidemics of lower severity. Their results imply that maintenance of genetic heterogeneity could be important for protecting populations from severe epidemics.

However, current understanding of the impact of genetic heterogeneity on disease patterns in the population is insufficient to fully grasp its importance for the design of breeding and management strategies. In the sparse number of studies that investigate the relevance of genetic diversity on disease dynamics, genetic heterogeneity is usually defined by a number of distinct subgroups conferring different levels of resistance to infectious challenge provided through direct contact between individuals. These assumptions ignore the fact that (i) genetic heterogeneity can occur in a number of traits affecting disease transmission apart from susceptibility, including the degree and duration of infectiousness or the duration of immunity, (ii) usually a great number of genes contribute to genetic variation implying that genetic variation is more appropriately expressed by continuous distributions rather than distinct subgroups, and (iii) many livestock diseases are transmitted by environmental contamination rather than direct transmission from animal to animal (e.g. mastitis in cattle, footrot in sheep).

In this study, a stochastic epidemiological model for bacterial infections transmitted through the environment has been developed to investigate the influence of genetic heterogeneity, represented through different traits and distributions of different shapes, on disease patterns. The model has been applied to footrot in sheep, an endemic bacterial disease of high importance to sheep production in the UK and many countries worldwide.

[*] The Roslin Institute and R(D)SVS, University of Edinburgh, Roslin, Midlothian EH25 9PS, UK
[†] Scottish Agricultural College, West Mains Road, Edinburgh EH9 3JG, UK
[‡] SGIT - INIA, Ministerio de Ciencia e Innovación, Carretera de la Coruña, 28040 Madrid, Spain

Material and methods

The epidemiological model. The model developed in this study is a stochastic representation of the deterministic compartmental SELDCRS model of Nieuwhof et al. (2009), where animals of a population of constant size (i.e. no birth and death) may progress through different disease states (susceptible (S), exposed (E), latent infected (L), diseased (D), asymptomatic carrier (C), recovered (R), susceptible (S)) over the time course of infection. The events in the stochastic model are the progression of an animal from one state to the next, shedding of bacteria of animals in categories D or C into the environment and the decay of bacteria in the environment. For each individual, an expected transition rate from one state to the next is defined as described below, as well as shedding rates for individuals in categories D and C. Environmental bacteria are assumed to decay at a constant rate. In the stochastic simulations, event k occurs with rate r_k, which is given by the sum of corresponding transition and shedding rates over all individuals in the category in question, or, if the event is bacterial decay, by the decay rate times bacterial load in the environment. Event times are sampled from an exponential distribution with parameter $R = \sum_k r_k$. The probability for a specific event k to occur is determined by its relative rate r_k/R.

Representation of genetic heterogeneity. It is assumed that animals can differ geneticially in their susceptibility to the infection (defined by the duration of time that an animal is expected to remain in category S after unit exposure), in their immune response expressed by the duration of time an animal remains in categories L, D or C, in the length of immune period, as well as in their shedding rates. For ease of interpretation, genetic diversity is considered for one trait at a time. The expected values for the trait for which genetic variation is assumed are sampled either from a normal distribution or a right skewed gamma distribution. The normal distribution represents the common assumption used in genetic analyses of disease data, in which susceptibility to a disease is considered as a normally distributed 'liability', whereas the skewed gamma distribution represents scenarios frequently observed in field studies, in which a relatively small proportion of the population has a disproportionately large contribution to the population's disease prevalence (e.g. Matthews et al. (2005)).

Stochastic simulations. Five thousand simulations were run for the model for each scenario (Table 1). The population means for the epidemiological parameters were taken from Nieuwhof et al. (2009). For the results shown below, a coefficient of variation of 0.6 in the normal distribution was assumed. To compare the influence of the shapes of the genetic heterogeneity distributions, the distribution parameters were standardized so that both types of distributions have the same expected mean and variance. To incorporate cases in which a significant proportion of individuals have extreme values, a gamma distribution was used with the same mode as the original gamma distribution but a wider tail ($\theta_2 = 10\theta_1$). Simulations started with the introduction of one latently infected individual into a susceptible population of 1000 animals, and modeled the course of infection over a period of 1 year, after which infection had either died out or converged to equilibrium prevalence (Figure 1).

Table 1: Parameter values of the stochastic simulations

Parameter	***Distribution / Values***
T(S)[α]	Normal: (μ,σ) =(6666.7, 4000), Gamma: (α,θ)=(2.69, 2478.68) or (1.17, 24786.8)
T(L)	Normal : (μ,σ) = (6.0, 0.6), Gamma: (α,θ) = (2.69, 2.228) or (1.17, 22.28)
T(C)	Normal : (μ,σ) = (1.0, 0.6), Gamma: (α,θ) = (2.69, 0.372) or (1.17, 3.72)
T(D)	Normal : (μ,σ) = (20.0, 12.0), Gamma: (α,θ) = (2.69, 7.436) or (1.17, 74.36)
T(R)	Normal : (μ,σ) = (30.0, 18.0), Gamma: (α,θ) = (2.69, 11.154) or (1.17, 111.54)
Shedding rate	Normal : (μ,σ) = (1.0, 0.6), Gamma: (α,θ) = (2.69, 0.372) or (1.17, 3.72)

[α] T(S) refers to the time (days) that an animal spends in category S. The same notation applies to other categories.

Results and discussion

In almost all simulations, the infection in the population either dies out within a few weeks or reaches a peak prevalence after which it declines to small oscillations around an equilibrium. The probability of persistent footrot (given by the proportion of simulations converging to a non-zero prevalence) is 0.88 when no genetic diversity is assumed. Introduction of genetic heterogeneity generally increases the likelihood of footrot persistence (probabilities between 0.91 and 0.99). However, for populations with a significant proportion of resistant animals (represented by a long-tailed gamma distribution for parameter T(S)), the probability of persistent footrot decreases to 0.62. Also, normally distributed shedding rates decreases the probability slightly (p=0.83). Similarly, the severity of infection, defined by peak prevalence and the total proportion of animals infected during the entire simulated period, generally increases when genetic heterogeneity is assumed (average peak prevalence over all simulations is 0.60 for homogeneous populations and between 0.62 and 0.82 for heterogeneous populations; average total proportion of infected is 0.36 without genetic heterogeneity and between 0.38 and 0.60 with genetic heterogeneity). However, as for the probability of footrot persistence, footrot severity is considerably lower for populations in which a significant proportion of individuals has very low susceptibility (average peak prevalence is 0.33 and average proportion of infected individuals is 0.20).

Figure 1 shows the effect of genetic heterogeneity on the estimated time course in disease prevalence. There is relatively little difference in the prevalence patterns resulting from simulations of homogeneous populations and populations with normally or gamma distributed epidemiological parameter values, as long as the population does not contain a significant proportion of individuals with extreme values (i.e. gamma distribution (2) in Figure 1). Heterogeneities have the tendency to increase disease prevalence at all times. However, substantial differences in the prevalence patterns emerge if the population contains a significant amount of individuals with extreme values, as represented by gamma distribution (2) in Figure 1 (e.g. high resistance (graph A), prolonged period of infectiousness (graph B) or prolonged period of immunity (graph C). Surprisingly, strong variation in shedding rate has only a small effect on the prevalence patterns (graph D).

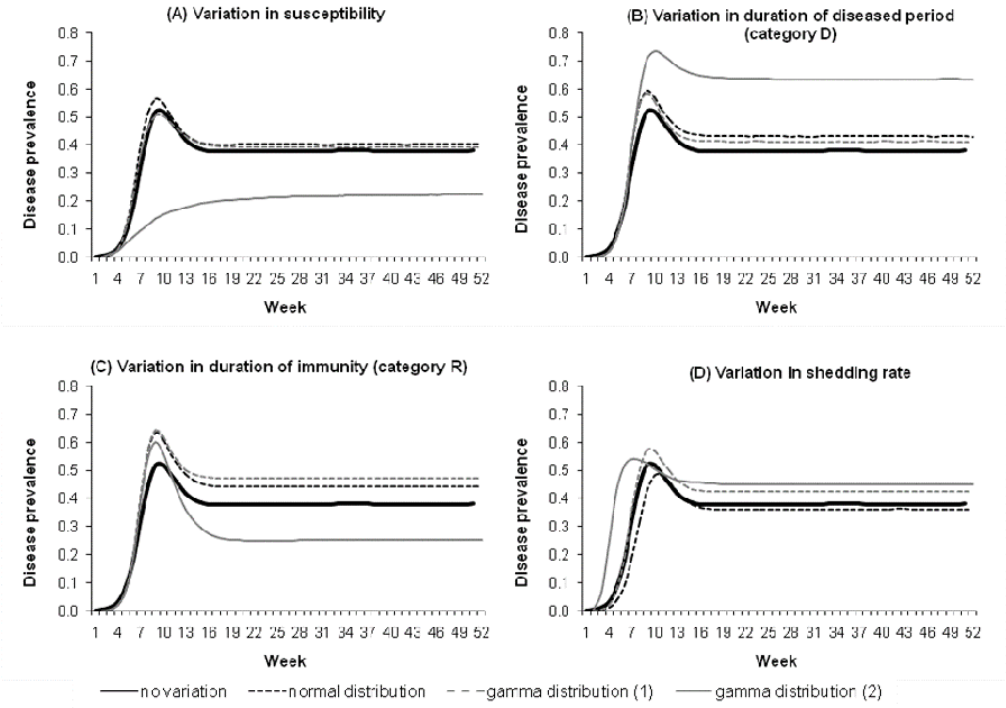

Figure 1: Impact of genetic heterogeneity in various epidemiological traits on disease prevalence over time. The estimated values are averages over 5000 simulations. The distributions' parameter values are given in Table 1; gamma distribution (1) and (2) refer to the first and second set of values, respectively.

Conclusion

The results of our genetic-epidemiological model for bacterial infections demonstrate that genetic diversity in different epidemiological characteristics tends to increase disease prevalence. The effects are relatively weak if the degree of heterogeneity is limited. However, disease prevalence decreases drastically if the population contains a substantial proportion of individuals with high resistance or immunity. The results of this study have strong implications for breeding and management strategies, which are currently being explored.

References

Springbett, A.J., MacKenzie, K., Woolliams, J.A. *et al.* (2003). *Genetics*, 165: 1465-1474.

Nieuwhof, G.J., Conington, J., and Bishop, S.C. (2009). Gen. Sel. Evol, 41 (1): 19

Matthews, L., Low, J.C., Gally, D.L. *et al*. (2006). *PNAS*, 103(3):547-552.