*Proceedings of the World Congress on Genetics Applied to Livestock Production, 11.*535

Enhancing genetic disease control by selecting for lower host infectivity

S. Tsairidou[1], O. Anacleto[1], K. Raphaka[1], E. Sanchez-Molano[1], G. Banos[1, 2], J.A. Woolliams[1] & A. Doeschl-Wilson[1]

[1]The Roslin Institute and R(D)SVS, University of Edinburgh, EH25 9RG, Edinburgh, UK
Smaragda.Tsairidou@roslin.ed.ac.uk (Corresponding Author)
[2]Scotland's Rural College, Easter Bush Campus, Midlothian EH25 9RG, Edinburgh, UK

Summary

Infectious diseases have a huge impact on animal health, production and welfare. Animal breeding schemes exploit heritable variation in host susceptibility, however, increasing evidence suggests that there may be additional genetic variation in host infectivity, i.e. the ability of hosts to transmit infections. We combined quantitative genetics and epidemiology to investigate the potential for enhancing genetic disease control by utilising host infectivity.

A stochastic SIR (susceptible-infected-recovered) epidemiological model was used to simulate how disease dynamics are influenced by polygenic genetic variation in susceptibility and infectivity. Response to selection was calculated over 20 generations, exploring a variety of selection schemes differing in accuracy and intensity. Changes in epidemic risk and severity due to selection were compared between selection schemes considering only susceptibility, or combining susceptibility and infectivity. We explored how response to selection may be influenced by genetic correlations between susceptibility and infectivity, and finally, we present a case study for bovine tuberculosis, an infectious disease with global impact on cattle industry.

Our results demonstrate that genetic selection considering both susceptibility and infectivity significantly accelerates disease eradication when compared to selection for susceptibility alone. For example, with moderate genetic variance, selection only on susceptibility required 13 generations to reduce epidemic risk by 50%, while combined selection for both susceptibility and infectivity required only 7 generations. With a favourable genetic correlation between susceptibility and infectivity, progress in the selection scheme was marginally improved by adding infectivity in the breeding goal. However, with a negative genetic correlation, including both susceptibility and infectivity reduced the delay due to indirect correlated responses in infectivity by 6 generations. In conclusion, our results suggest that to develop efficient genetic disease control strategies in the short- and long-term, genetic effects for both susceptibility and infectivity should be considered.

Keywords: genetic gain, selection scheme, breeding objectives, breeding strategies, models

Introduction

The severity and spread of infectious diseases can be greatly influenced by host genetic heterogeneity (Keeling & Rohani, 2008; Doeschl-Wilson *et al.*, 2011). Heritable genetic variation in susceptibility, which may be defined as the propensity of becoming infected upon contact with an average infectious individual (Lipschutz-Powell *et al.*, 2012) is ubiquitous, and advances in genomics enabled selection schemes to target reduced susceptibility in

livestock (Bishop & Woolliams, 2014). Recently, awareness has emerged towards a second important host trait affecting disease prevalence in a population, namely the host infectivity, defined as an individual's ability to transmit infection (Lipschutz-Powell *et al.*, 2012; Anche *et al.*, 2014; Anacleto *et al.*, 2015). Highly infectious individuals generating disproportionally many new infections, i.e. super-spreaders, have been documented in several disease outbreaks (Lloyd-Smith *et al.*, 2005), and recent evidence suggests that infectivity and therefore super-spreading can be controlled by host genetics (Anacleto O. *et al.*, 2018).

Recent developments in inference methods, enable breeding values for host infectivity to be estimated in a fully quantitative model (Anacleto *et al.*, 2015), or single-gene models (Anche *et al.*, 2014; Biemans *et al.*, 2017). The aim of this study was to investigate the benefits from exploiting infectivity in genetic selection schemes. We used an SIR stochastic epidemiological model to simulate disease spread in animal populations undergoing selection for susceptibility and infectivity, and to assess the changes in epidemic risk and severity over generations due to selection. We also investigated how genetic correlations between susceptibility and infectivity may influence response to breeding schemes, and finally, we applied this methodology to bovine tuberculosis, an infectious disease with complex epidemiology, influenced by host genetics (O'Hare *et al.*, 2014; Tsairidou *et al.*, 2014; Banos *et al.*, 2017).

Material and methods

A population of 10,000 half-sib individuals was generated assuming different levels of polygenic genetic variation in susceptibility and infectivity, and the individuals were randomly distributed into 100 groups (e.g. herds) of same size. Susceptibility (g_i) and infectivity (f_i) trait values were calculated for each individual as $\log(g_i) = \mu_g + A_{gi} + e_{gi}$ and $\log(f_i) = \mu_f + A_{fi} + e_{fi}$, where μ_g and μ_f are the population means for the log-transformed susceptibility and infectivity respectively, A_{gi} and A_{fi} are offspring true breeding values (TBVs), and, e_{gi} and e_{fi} are environmental effects. This formulation results in log-normally distributed traits, which particularly for infectivity, accommodates the existence of super-spreaders (Anacleto *et al.*, 2015). Sire and dam true breeding values (TBVs) for susceptibility and infectivity were sampled from multivariate normal distributions with mean zero and (co)variance matrix **G**, and individual TBVs (A_{gi} and A_{fi}) were calculated as functions of sire and dam TBVs and Mendelian sampling terms.

A stochastic epidemiological SIR model (Keeling & Rohani, 2008) and the Gillespie algorithm (Gillespie, 1977) were used to simulate epidemics, generated in each group by a randomly chosen initially infected individual (index case). Individual heterogeneity in susceptibility and infectivity were incorporated in the epidemiological model as outlined by Anacleto *et al.* (2015), where the time-dependent infection rate $\lambda_j(t)$ of individual j is defined as the product of the average effective contact rate β (the rate of contacts between susceptible and infected individuals resulting in infection), the individual susceptibility g_j, and the sum of the infectivity f_i of the infected individuals in the same group n at time t, i.e

$$\lambda_j(t) = g_j \beta \sum_{i=1}^{n(t)} f_i .$$

Response to selection on the sires for susceptibility (R_g) and infectivity (R_f) was calculated following the breeder's equation and assuming discrete generations. The means for susceptibility and infectivity after t generations of selection were calculated on the log-normal scale, and offspring genetic variances were calculated from sire and dam variances accounting for the reduction in variance due to selection (Falconer & Mackay, 1997).

This process was repeated over 20 generations of selection, where each generation was undergoing epidemics following the SIR model described above. The impact of selection on

epidemic characteristics was assessed by calculating (i) the proportion of epidemics where index cases generated new infections, i.e. epidemic risk, (ii) the proportion of infected animals in groups where epidemics occurred i.e. epidemic severity, and (iii) the duration of epidemics. Means and standard errors were obtained over 50 replicates.

Furthermore, a selection index was used to explore the impact of genetic correlations between susceptibility and infectivity on response to selection and epidemic characteristics. Response to selection in each trait was calculated as, where i is the selection intensity for the index, **b** is the vector of weights applied to the traits in the index, and **G** and **P** are the genetic and phenotypic (co)variance matrices (Cameron, 1997).

Results and discussion

Impact of selection on epidemic risk and severity

SIR curves of individual epidemics over generations showed that the number and severity of epidemics were reduced due to selection. This decline was stronger and quicker when both susceptibility and infectivity were considered in the selection scheme (Fig. 1).

Assuming 50% selection on the sires, genetic variances of 0.5, environmental variances of 2, effective contact rate β of 0.02, and selection accuracies of 0.7 for both susceptibility and infectivity, selection only on susceptibility required 13 generations to reduce the risk of epidemics by at least 50%, while selection considering both susceptibility and infectivity required 7 generations (Fig. 2). Furthermore, epidemic severity in groups where epidemics occurred was reduced more efficiently when both susceptibility and infectivity were considered in the selection scheme. Specifically, epidemic severity was reduced by at least 50% after 6 generations of selection only on susceptibility, but after 3 generations of combined selection (Fig. 2). After 5 generations of combined selection, less than 10% of epidemics lasted longer than a year, while 10 generations of selection on susceptibility alone were required for the same outcome. Interestingly, after 14 generations of combined selection there were no epidemics lasting more than a year, while with selection only on susceptibility there were always some remaining long epidemics.

From simulation studies, prediction accuracies for infectivity are expected to be lower than those accuracies for susceptibility (Anacleto *et al.*, 2015). Thus, we tested a range of accuracy values, but even when accuracy for infectivity was reduced to a lower value (e.g. 0.2), a significant reduction of disease severity was achieved through selection considering both susceptibility and infectivity. As might be expected, when the assumed genetic variances for susceptibility and infectivity were lower, differences between scenarios in reducing epidemic risk and severity were less pronounced.

Assuming a favourable genetic correlation of 0.5 between susceptibility and infectivity and zero environmental correlation, genetic variances of 0.5 for both traits and selection intensity of 0.5 for the index, selection only on susceptibility required 6 generations to reduce the risk of epidemics by 50% (Fig. 3), and 3 generations to reduce the proportion of infected individuals by 50%. Selection considering both susceptibility and infectivity with equal weights of 0.5 performed marginally better, requiring 5 generations to reduce the proportion of epidemics that occurred by 50% (Fig. 3), and 3 generations to reduce the proportion of infected individuals by 50%.

With a negative genetic correlation of -0.5 between susceptibility and infectivity progress was substantially delayed: selection only on susceptibility required 18 generations to reduce the proportion of epidemics by 50%. However, selection combining susceptibility and infectivity helped overcome this delay and required 12 generations (Fig. 3). These estimates of number of generations required are likely to be over-predictions, as a high selection accuracy was assumed, and the loss of variance due to selection was not accounted for.

Nevertheless, these results suggest that a breeding scheme directly selecting only for susceptibility and ignoring infectivity, could suffer a substantial loss in response to selection due to unfavourable correlated responses in infectivity.

Case study: bovine tuberculosis

A Susceptible-Latent-Infectious-Test sensitive (SLIT) epidemiological model was used to accommodate the complexity of bovine tuberculosis (bTB) transmission. In this model, susceptible individuals can become latent, i.e. infected but not infectious. Then individuals become infectious but are not yet detectable by the bTB diagnostic test. Finally, they become test-sensitive and can be identified and removed. An external source of infection was modelled, and detection of infected animals depended on the sensitivity of the diagnostic test (here assumed 60%) and the bTB testing intervals of 60 days routinely applied in UK herds.

The individual time dependent infection rate was defined as $\lambda_j(t) = \alpha + g_j \beta \sum_{i=1}^{I(t)+T(t)} f_i$, where I and T are the number of infectious and test-sensitive individuals at time t, α and β denote the average transmission coefficients accounting for the external source of infection (assumed constant) and cattle to cattle transmission, respectively.

Assuming 50% selection on the sires, an external source of infection of $5x10^{-05}$, genetic variance of 0.3 and accuracy of 0.5 for both susceptibility and infectivity, and no correlation between these traits, selection only on susceptibility required 9 generations to reduce the risk of an epidemic to emerge after introduction of an infected index case in a bTB free herd to 5% from a starting value of 29%, while combined selection required 5 generations (Fig. 4). Current bTB eradication strategies in the UK aim at achieving TB-free status for England by 2038. Recently published genetic evaluations for bTB susceptibility can complement the eradication strategy; however, based on these preliminary results using simulated data, considering infectivity alongside susceptibility to bTB, could accelerate disease eradication. Further modelling studies are required, to develop parameter values that faithfully reflect the true epidemic parameters and that will be based on existing bTB genetic evaluations (Raphaka K. *et al.*, personal communication; Banos *et al.*, 2017). Definition of appropriate bTB infectivity phenotypes will be crucial in this respect.

Implications

Genetic variation in infectivity has remained hidden due to the lack of methods that would allow to uncover it. Our results demonstrate that selection considering genetic variation in both susceptibility and infectivity can more efficiently reduce the risk and severity of epidemics compared to selection on susceptibility alone. Estimating infectivity is crucial particularly in the case of unfavourable correlations, which would not only delay progress in selection schemes using only susceptibility, but could also indirectly increase infectivity. Host infectivity creates new possibilities for genetic disease control, for example, identification and early removal of disease super-spreaders reduces the risk of infection for other animals in the herd and reduces environmental contamination. Utilising infectivity can not only accelerate response to selection, but it can render genetic disease control feasible for diseases where selection only on susceptibility would not be sufficient for disease eradication. Recently developed inference methods enable the detection of infectivity and the estimation of infectivity EBVs in polygenic models (Anacleto *et al.*, 2015). The next step is to estimate infectivity from epidemiological data.

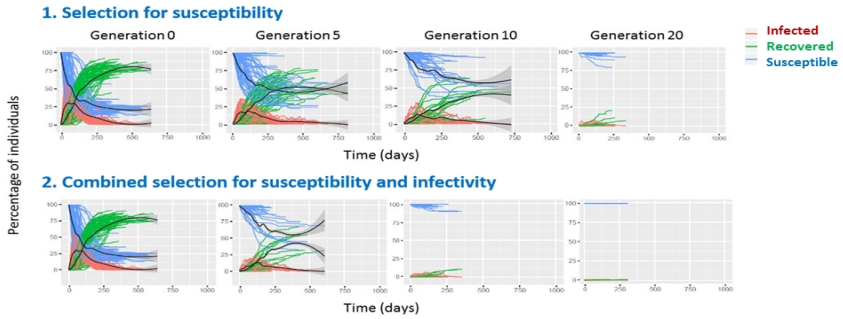

Figure 1. SIR profiles over generations of selection (a) only on susceptibility (upper row), and (b) on both susceptibility and infectivity (lower row), with selection accuracies of 0.7. The grey-shaded areas show the corresponding 95% C.I. for the fitted curve.

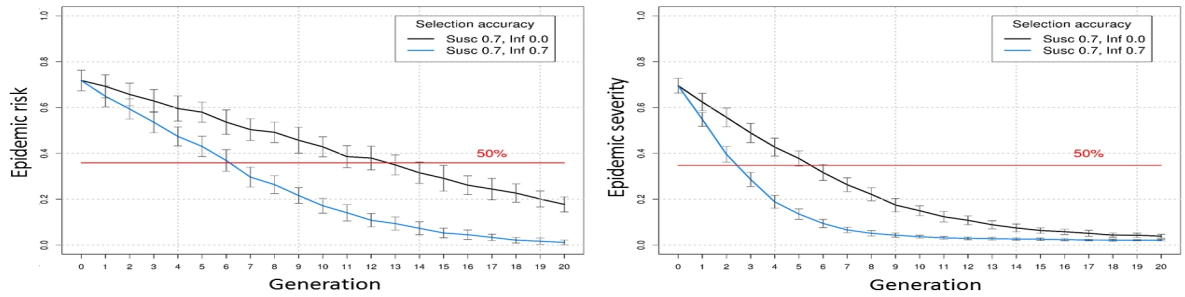

Figure 2. Epidemic risk and severity over generations of selection (a) only on susceptibility (black line), and (b) on both susceptibility and infectivity (blue line) with the traits assumed independent. Vertical bars represent standard deviations of the means across 50 replicates.

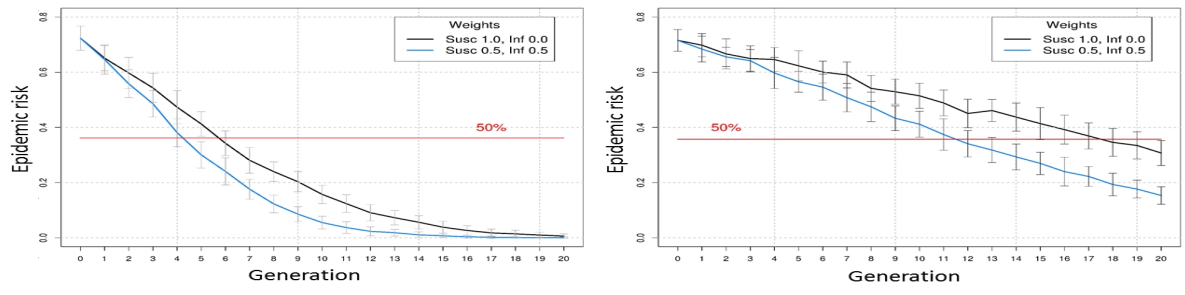

Figure 3. Impact on epidemic risk of positive genetic correlation cor_G=0.5 (left), and negative genetic correlation cor_G=-0.5 (right) between susceptibility and infectivity, with index selection (a) only on susceptibility by assuming in the index a weight of zero for infectivity (black line), and (b) on both susceptibility and infectivity with equal weights.

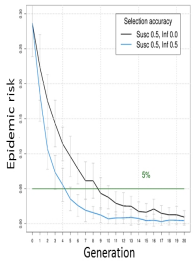

Figure 4. Reduction in the predicted risk of a bovine tuberculosis epidemic in a herd following introduction of an infected cow. Selection is (a) only on susceptibility (black line), and (b) on both susceptibility and infectivity (blue line). The traits are assumed independent.

List of References

Anacleto O, Garcia-Cortés LA, Lipschutz-Powell D, Woolliams JA, Doeschl-Wilson AB (2015). A Novel Statistical Model to Estimate Host Genetic Effects Affecting Disease Transmission. *Genetics* 201(3)**:** 871-884.

Anche M, Jong M, Bijma P (2014). On the definition and utilization of heritable variation among hosts in reproduction ratio R0 for infectious diseases. *Heredity* 113.

Banos G, Winters M, Mrode R, Mitchell AP, Bishop SC, Woolliams JA *et al* (2017). Genetic evaluation for bovine tuberculosis resistance in dairy cattle. *Journal of Dairy Science* 100(2)**:** 1272-1281.

Biemans F, de Jong MCM, Bijma P (2017). A model to estimate effects of SNPs on host susceptibility and infectivity for an endemic infectious disease. *Genet Sel Evol* 49(1)**:** 53.

Bishop SC, Woolliams JA (2014). Genomics and disease resistance studies in livestock. *Livestock Science* 166**:** 190-198.

Cameron ND (1997). *Selection indices and prediction of genetic merit in animal breeding*. Wallingford : CAB International: Wallingford.

Doeschl-Wilson AB, Davidson R, Conington J, Roughsedge T, Hutchings MR, Villanueva B (2011). Implications of Host Genetic Variation on the Risk and Prevalence of Infectious Diseases Transmitted Through the Environment. *Genetics* 188(3)**:** 683-693.

Falconer DS, Mackay TFC (1997). *Introduction to Quantitative Genetics.* . Longman.

Gillespie DT (1977). Exact stochastic simulation of coupled chemical reactions. *The Journal of Physical Chemistry* 81(25)**:** 2340-2361.

Keeling MJ, Rohani P (2008). *Modeling Infectious Diseases in Humans and Animals*. Princeton University Press.

Lipschutz-Powell D, Woolliams JA, Bijma P, Doeschl-Wilson AB (2012). Indirect Genetic Effects and the Spread of Infectious Disease: Are We Capturing the Full Heritable Variation Underlying Disease Prevalence? *PLoS ONE* 7(6)**:** e39551.

Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM (2005). Superspreading and the effect of individual variation on disease emergence. *Nature* 438(7066)**:** 355-359.

O'Hare A, Orton RJ, Bessell PR, Kao RR (2014). Estimating epidemiological parameters for bovine tuberculosis in British cattle using a Bayesian partial-likelihood approach. *Proceedings of the Royal Society B: Biological Sciences* 281(1783).

Tsairidou S, Woolliams JA, Allen AR, Skuce RA, McBride SH, Wright DM *et al* (2014). Genomic prediction for tuberculosis resistance in dairy cattle. *PLoS One* 9(5)**:**

e96728.