Identifying critical parameters in the dynamics and control of microparasite infection using a stochastic epidemiological model

Identifying critical parameters in the dynamics and control of microparasite infection using a stochastic epidemiological model[1]

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ABSTRACT: A stochastic epidemic model is presented to study infection transmission dynamics, and hence epidemic severity and disease incidence, in a closed population. The aim was to understand the relative importance of various parameters that influence the dynamics of potential epidemics, particularly when the genetic mechanisms of resistance or tolerance to infection are considered. Simulations explored the effect of varying the transmission coefficient, latent period, recovery period, mortality rate, and the period of loss of immunity on overall epidemic outcomes. The critical parameters influencing the transmission of infection, and hence disease incidence, were the transmission coefficient, the latent period, and the recovery period; the period of loss of immunity had only trivial effects. Ideally, control strategies should decrease the transmission coefficient and/or increase the latent period and/or decrease the recovery period. By equating measured traits with disease transmission parameters, the model described in this paper can be used to identify which disease resistance genes or QTL will be truly effective in helping to develop disease-resistant livestock that suffer fewer epidemics and side-effects of infection. In particular, emphases should be placed on finding genes that decrease the transmission of infection, increase the latent period, or decrease the recovery period.

Key Words: Animal Health, Disease Resistance, Disease Transmission, Epidemiology, Genetics, Immunology

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Introduction

Animal health affects production economics, animal welfare, and food safety. Previously, disease control has been achieved by such strategies as chemotherapy, vaccination, sanitation, culling, and biosecurity. However, these approaches are not always effective. Besides, an increased and inappropriate use of chemicals or vaccines has often led to the evolution of resistant pathogens, with concerns expressed over the potential contamination of animal products. Therefore, alternative disease control measures are needed and an exploitation of genetic variation among hosts in resistance to infection may complement or sometimes replace existing strategies.

Genetic differences between animals in resistance to infection have been documented for all major domestic species and for many important diseases (Axford et al., 2000; Bishop et al., 2002). Currently, there is a large research effort worldwide attempting to exploit this genetic variation by gene discovery. However, it is not always obvious which genes or QTL will be most effective in controlling infection or disease and improving health. For example, studies by Vallejo et al. (1998) and Yonash et al. (1999) found 14 QTL associated with resistance to Marek's disease, for a total of nine traits describing the proliferation of tumors, survival, and viremia. A critical question for the implementation of breeding strategies is which of these QTL would be most effective in helping to control the disease.

This article addresses the traits or processes that are critical in controlling the transmission of infection, and hence improving flock or herd health, for microparasitic (e.g., bacterial or viral) infections. A stochastic epidemic modeling approach to describing microparasitic infections was demonstrated by MacKenzie and Bishop (2001), and, in the present article, the model is adapted to assess the relative importance of various genetic regulation strategies in controlling the transmission of infection, and hence the incidence of disease.

Material and Methods

Overview of Methodology

This article will explore the properties of epidemics in closed populations caused by microparasitic infections

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and will determine the processes or parameters that are critical in determining the severity of the epidemics. By relating these processes or parameters to measurable traits, we can then determine the types of QTL or genes that will have the greatest impact in disease control and improving herd health. To achieve this, our approach will be as follows. We will develop a stochastic model describing the transmission of infection and the severity of subsequent epidemics and apply it within a simple defined population. An important livestock disease will be identified for which parameter estimates are available from published literature, to give benchmark results. We will then explore the reasonable parameter space, as described below, for each parameter, simulating the consequences of altering each parameter in turn.

Population Structure

We considered a medium-sized population of intensively housed animals, such as pigs. The population comprised 1,000 individuals of the same age and physiological status. For simplicity, the population was considered to be completely homogenous, with equal mixing among individuals. The population was assumed to be closed, with no new introductions of animals during the epidemic period. There was no disease-independent mortality in the population. It was also assumed that, once an epidemic started, there was no external intervention (such as medication, vaccination, isolation) to check the progress of the epidemic and that the epidemic took its own course.

Infection Process and Parameter Definition

The transmission of infection during microparasitic epidemics may be described by so-called compartmental models (Anderson and May, 1992), in which animals move from one state to another, defined according to the events that follow as a result of infection. The phases of infection in the host can be broadly defined as follows.

First, a susceptible individual gets infected from an infected individual. The transmission coefficient (β) denotes the rate at which infected individuals transmit infection to susceptible animals, and is the expected number of new infections per infectious animal per susceptible animal per day. In the context of disease genetics, the parameter β depends upon the infectivity genotypes of infected animals and the susceptibility genotypes of susceptible animals. Therefore, for a constant infectivity, β is proportional to the susceptibility genotypes of animals. Conversely, for a constant susceptibility, β is proportional to the infectivity genotypes of the infected animals.

After infection, the latent period ensues, which is the period during which the individual is infected but noninfectious, and is not yet capable of transmitting the infection because the abundance of the infectious agent is low. The parameter σ is the inverse of the expected latent period.

The next phase is the infectious period when the abundance of pathogens is high and the individual is capable of infecting other susceptible individuals. After the infectious phase, host recovery may occur when the abundance of pathogens decreases to a low level or zero and antibody titers rise to a high level to prevent any further infection for a definite period. The recovery rate (γ) is the reciprocal of the infectious period and is the expected number of recoveries per infected animal per day. Infected individuals also may die as a result of infection. The mortality rate (ε) implies the disease-dependent mortality, which is the expected proportion of individuals dying per day among the infected individuals.

Finally, the immunity in the recovered individuals may not be life-long and may persist only for a period of time, after which they become susceptible again. The rate of loss of immunity (ω) is represented by the reciprocal of the expected period between the time of recovery and the time when recovered individuals again become susceptible. Here it is assumed that $\omega > 0$ for the present infection, so that immunity is not life-long. We will refer to this period as the *loss-of-immunity period*.

Epidemic Model

The stochastic epidemic model used in this paper was outlined by MacKenzie and Bishop (2001). In brief, a stochastic epidemic model simulates the epidemic process as a series of random events in time, with the probability of specific events defined by the parameters of the model. The possible event types for this model are as follows: a susceptible animal becomes latently infected, a latently infected animals becomes infectious, an infected animal recovers or dies as a result of infection, and an animal that has recovered loses immunity and becomes immunologically susceptible again.

In addition to event type, the model requires simulation of the inter-event time. For a population with I infected animals, S susceptible animals, L animals in the latent class, and R recovered animals; the inter-event time in an epidemic has a mean

$$1/(\beta c\mathrm{SI} + \sigma \mathrm{L} + \gamma \mathrm{I} + \varepsilon \mathrm{I} + \omega \mathrm{R}) \qquad [1]$$

where c is the contact rate between animals (assumed to be 1 in this paper), and other parameters are as defined above. The inter-event time may then be drawn from an exponential distribution as $\ln(r) \times$ (mean inter-event time), where r is a random number in [0, 1].

The next event type is determined by calculating the probability of a specific event in relation to all possible events. Thus, let Eq. [1] be RATE, then the probabilities that the next event is (i) the infection of an animal moving the newly infected animal to the latent class is $\beta c\mathrm{SI} \times$ RATE, (ii) the movement of a latent animal to the infectious class is $\sigma \mathrm{L} \times$ RATE, (iii) the recovery of an infected animal is $\gamma \mathrm{I} \times$ RATE, (iv) the death of an infected animal is $\varepsilon \mathrm{I} \times$ RATE, and (v) the loss of immu-

nity of a recovered animal is $\omega R \times$ RATE. Thus, the precise event can be determined by sampling from a random uniform distribution.

Implementing the Model and Capturing the Output

The model is implemented by introducing a single infected individual (the index case) into the farm. The inter-event time is calculated, the type of the first event is determined, and the epidemic commences. The epidemic continues until no infected animals remain at the end of the epidemic, or some predetermined criterion in terms of the severity or length of the epidemic has been exceeded. Outputs were captured and summary statistics derived as follows.

Probability of Epidemic. The probability that an epidemic will occur, given the presence of an infected individual, can be determined by the number of simulations that result in an epidemic. If the infected individual that was introduced in the population at the start of the epidemic recovers or dies without any secondary infections, then it is considered to be no epidemic. Otherwise, epidemics may be split into those that are major and those that are minor epidemics. Minor epidemics are those that die out without intervention (Bishop and MacKenzie, 2003). To distinguish unambiguously between major and minor epidemics, it may be necessary to let the simulations run for a very long time, and, for practical purposes, thresholds may be set to distinguish them. In these simulations, if more than 10% of individuals in the population became infected and the epidemic continued for more than 6 mo without intervention, the epidemic was deemed as being major. Otherwise, the epidemic was considered as minor. The choice of 10% of animals infected as the threshold was made on the grounds that epidemics that died out quickly generally resulted in fewer than 10% of the population becoming infected. However, our thresholds for major and minor epidemics are specific to the parameter space investigated and may not be appropriate for diseases with very high R_0 values (see below) or mortality rates.

Basic Reproductive Ratio. The basic reproductive ratio (R_0), is a dimensionless parameter that encapsulates the biological details of different transmission mechanisms. For microparasites, R_0 is the expected number of secondary infections produced by the introduction of an infected individual, during the course of its infectious period, into an otherwise completely susceptible population (Diekmann et al., 1990). In general, the probability of no epidemic (p) can be expressed as $1/(R_0 + 1)$ (Bishop and MacKenzie, 2003). Hence, R_0 was estimated as $(1/p) - 1.0$.

Epidemic Severity. Epidemic severity was defined in terms of the maximum proportion of animals infected during the epidemic (y_{max}) and the time of occurrence of y_{max}. The estimate of y_{max} was averaged for replications when a major epidemic occurred. Since the condition for determining a major epidemic was more than 10% of animals infected and a duration of 6 mo, simulations were stopped when they reached these thresholds. Therefore, summary parameters, such as the total proportion of animals that were infected and the duration of major epidemics, were not estimated.

Disease Case Study and Parameter Space Investigated

As a case study, we have considered transmissible gastroenteritis (**TGE**), a highly contagious enteric viral disease of swine. This disease is characterized by vomiting, severe diarrhea, and high mortality in pigs of less than 2 wk of age. Mortality is low in pigs over 5 wk of age, but considerable morbidity may occur as a result of infection. No specific treatment or effective vaccines are available for TGE. Estimates of parameters describing TGE have been published for growing pigs (Hone, 1994): the transmission coefficient (0.0007), latent period (2 d), recovery period (20 d), mortality rate (0.02), and days before loss of immunity (180 d).

In addition to the case study, the reasonable parameter space was investigated for each parameter, using the TGE parameters as benchmark values. The reasonable parameter space was defined by biological limits to each parameter as well as simulation outcomes. In this case, we wished to avoid outcomes in which R_0 exceeded 10, as diseases that are this infectious are probably best dealt with by nongenetic means. The aim was to examine the changes in epidemic pattern by introducing variation in one parameter, keeping other parameters constant. The specific parameter combinations were as follows: transmission coefficients (β), where it takes the value of 0.00001, 0.00005, 0.0001, 0.0005, 0.0007, or 0.001; six latent periods (1, 2, 7, 15, 30, and 180 d); six recovery periods (1, 2, 5, 10, 20, and 30 d); six mortality rates (0.00, 0.02, 0.05, 0.10, 0.20, and 0.30); and six values for the loss-of-immunity period (7, 15, 30, 60, 120, and 180 d). A total of 5,000 replicates were run for each combination of parameters.

Results

Case Study

The probabilities of no epidemic, a minor epidemic, and a major epidemic of TGE—obtained from 5,000 replicates—were 0.17, 0.01, and 0.82, respectively. A summary of other parameters is presented in Table 1. The high probability of a major epidemic means that, without any intervention, there is high chance that TGE will spread in more than 10% of animals in the population and the epidemic will last for more than 6 mo. The definition of a major epidemic that was used overestimated the incidence of "true" major epidemics, which is expected to be $(R_0 - 1)/(R_0 + 1)$ (Bishop and Mackenzie, 2003). However, in most practical situations, the definition of a major epidemic as one in which more than 10% of individuals become infected and the epidemic duration is of more than 6 mo seems conservative.

Table 1. Probability of no/minor/major epidemic, basic reproductive ratio (R_0), maximum proportion of infected animals (y_{max}), and time of y_{max} ($y_{max}Time$) and their corresponding standard deviations for different transmission coefficients (β), with other parameters held constant, based on 5,000 replicates[a]

$\beta \times (10^{-5})$, $S^{-1}I^{-1}d^{-1}$ [b]	Probability of epidemic			R_0	Estimates	
	No epidemic	Minor epidemic	Major epidemic		y_{max}	$y_{max}Time$, d
1[c]	0.893	0.107	0.000	0.12	0.000	—
	(0.004)[d]	(0.004)	(0.000)	(0.01)	(0.000)	(—)
5[ef]	0.632	0.368	0.0002	0.58	0.021	125.9
	(0.006)	(0.006)	(0.0003)	(0.02)	(0.002)	(58.21)
10[f]	0.473	0.276	0.250	1.11	0.056	155.4
	(0.006)	(0.006)	(0.008)	(0.03)	(0.001)	(0.89)
50	0.197	0.026	0.777	4.08	0.512	33.7
	(0.002)	(0.001)	(0.003)	(0.06)	(0.0004)	(0.02)
70[g]	**0.169**	**0.012**	**0.819**	**4.92**	**0.578**	**26.4**
	(0.002)	**(0.003)**	**(0.002)**	**(0.06)**	**(0.0001)**	**(0.01)**
100	0.147	0.011	0.842	5.80	0.629	20.8
	(0.002)	(0.001)	(0.002)	(0.10)	(0.0004)	(0.01)

[a]Other parameters in the model are kept constant (latent period = 2 d; recovery period = 20 d; mortality rate = 2%/d; and loss-of-immunity period = 180 d).
[b]S indicates the number of susceptible individuals, and I indicates the number of infected individuals.
[c]No major epidemic was observed in 5,000 replicates and hence y_{max} is zero and no $y_{max}Time$ was recorded.
[d]The standard deviations were calculated from parameter estimates obtained from 5,000 potential epidemics, further replicated 20 times to obtain a sample of estimates, and are shown in parentheses under each estimate.
[e]Among 20 estimates of 5,000 replicates each, 2 estimates based on 5 cases and 11 estimates based on 9 cases of major epidemic. The estimates of standard deviations for y_{max} and $y_{max}Time$ reflect these small sampling sizes.
[f]The failure of a given row of probabilities to sum to 1.0 is attributable to rounding error.
[g]Boldface type values indicate the epidemic properties for transmissible gastroenteritis with benchmark parameters values.

Effects of Altering the Transmission Coefficient

The epidemic properties for TGE for benchmark parameters except for the transmission coefficient (β), which is varied, are presented in Table 1. As β decreases, the probability of a major epidemic reduces considerably, and with β less than 0.00005 there is practically no incidence of major epidemics. The estimates of R_0 also correspond proportionally to values of β. Because the parameter β varies proportionally with the host genotype for susceptibility, everything else held constant, it can be concluded that β is of immense importance for the genetic control of disease resistance. It signifies whether a susceptible individual exposed to infection will readily get the infection or whether it will resist the establishment of the infectious organisms inside its body. Further results indicating the effect of β with changes in other parameters are presented in later sections.

Effects of Altering the Latent Period

As a general summary, the estimated R_0 increases as the latent period decreases (Figure 1a). This indicates that the quicker the infected individual starts shedding the infection, the greater the chances of other animals becoming infected. Additionally, R_0 is more sensitive to changes in the latent period as β increases. For example, when β = 0.00005, the R_0 value reduces from 0.58 to 0.42 when the latent period increases from 2 to 7 d. However for the similar change in latent period, the R_0 value decreases from 5.80 to 3.74 when β = 0.001.

The estimate of y_{max} also increases with a decrease in the latent period, for fixed values of other parameters (Figure 2a). For β = 0.001, the maximum proportion of individuals affected is almost 69% when the latent period is 1 d. There is declining trend of the incidence of major epidemics when the latent period is increased. The time of y_{max} is also affected by the latent period (Figure 3a). It is observed that with an increase in the latent period there is also an increase in time of occurrence of y_{max}. Therefore, an increase in the latent period not only reduces the maximum proportion of individuals infected, but simultaneously it delays the time when y_{max} will occur.

The effect of latent period on the dynamics of epidemic is evident from Table 2. Although the changes in the epidemic pattern are not appreciable when β is low, with higher values of β the changes are more prominent. If the latent period is very long, there is a low chance of a major epidemic even with a high value of β. For example, with β values ranging from 0.0005 to 0.001, the estimates of R_0 are less than one when the latent period is as long as 180 d. Hence, infective organisms with long latent periods will seldom cause major epidemics in a population as modeled in this paper, even if they have high transmission coefficients.

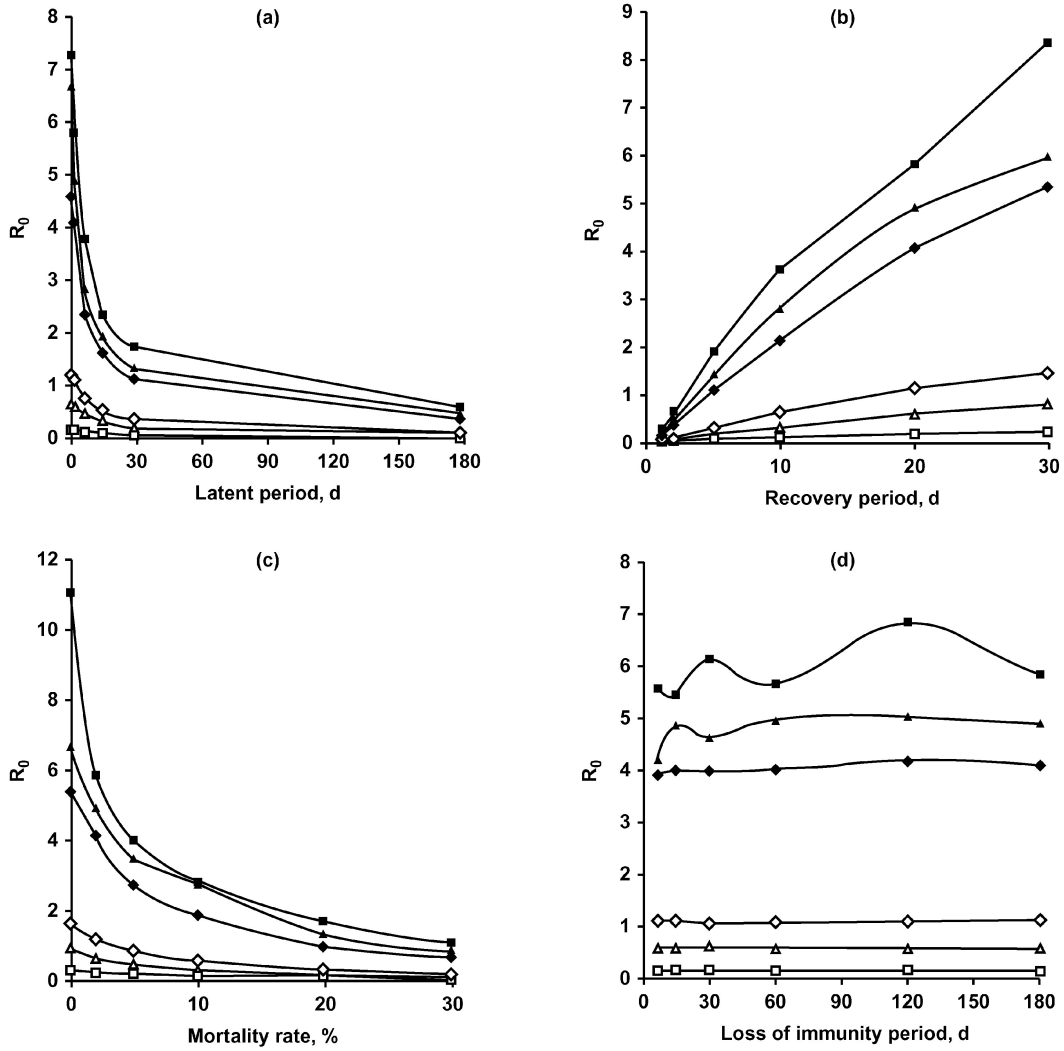

Figure 1. Comparison of estimates of the basic reproductive ratio (R_0) vs. different epidemiological parameters: (a) latent period, (b) recovery period, (c) mortality rate, and (d) loss-of-immunity period, for transmission coefficients ($\beta \times 10^{-5}$) of 1 (□), 5 (△), 10 (◇), 50 (◆), 70 (▲), and 100 (■).

Effects of Altering the Recovery Period

For fixed values of β, the estimated R_0 increases as the recovery period increases (Figure 1b). The variation in estimates of R_0 over a range of recovery periods is very low when β is low; however, the variation in R_0 is much greater for high values of β. For example, for a change of recovery period from 1 to 30 d, the change in R_0 is 0.31 when $\beta = 0.00005$, whereas the equivalent change in R_0 is 3.17 when $\beta = 0.001$. Hence, variation in the recovery period does not greatly influence R_0 if β is low. With high β values, changes in R_0 with changes in recovery period are more appreciable.

From Figure 2b, it can be observed that changes in the recovery period also influence the maximum proportion of infected animals in the population (y_{max}). In the range of β from 0.0005 to 0.001, increasing the recovery period from 5 to 20 d increases the y_{max} value by twofold or more. However, the time of occurrence of y_{max} is less influenced by the recovery period for moderate to high β values (Figure 3b). That means with a long recovery period the rate of spread of infection is much faster and more individuals are infected in an epidemic of a similar duration.

For a fixed value of β, the probability of no epidemic increases and the probability of major epidemics decreases with a decrease in the recovery period (Table 3). For intermediate to high transmission coefficients, the probability of minor epidemics is maximized for an intermediate recovery period. The probability of a major epidemic is almost nil for β values of 0.00005 or less, and it does not exceed 2% even if an animal takes as long as 30 d to recover from infection. However, for an infection with a moderate to high β, the recovery period plays an important part in removing the infection from the population. With a high β value of 0.001, the probability of a major epidemic reduces from 73 to 5% when the recovery period decreases from 10 to 5 d. Therefore, with increasing β values, there is a definite advantage in decreasing the recovery period.

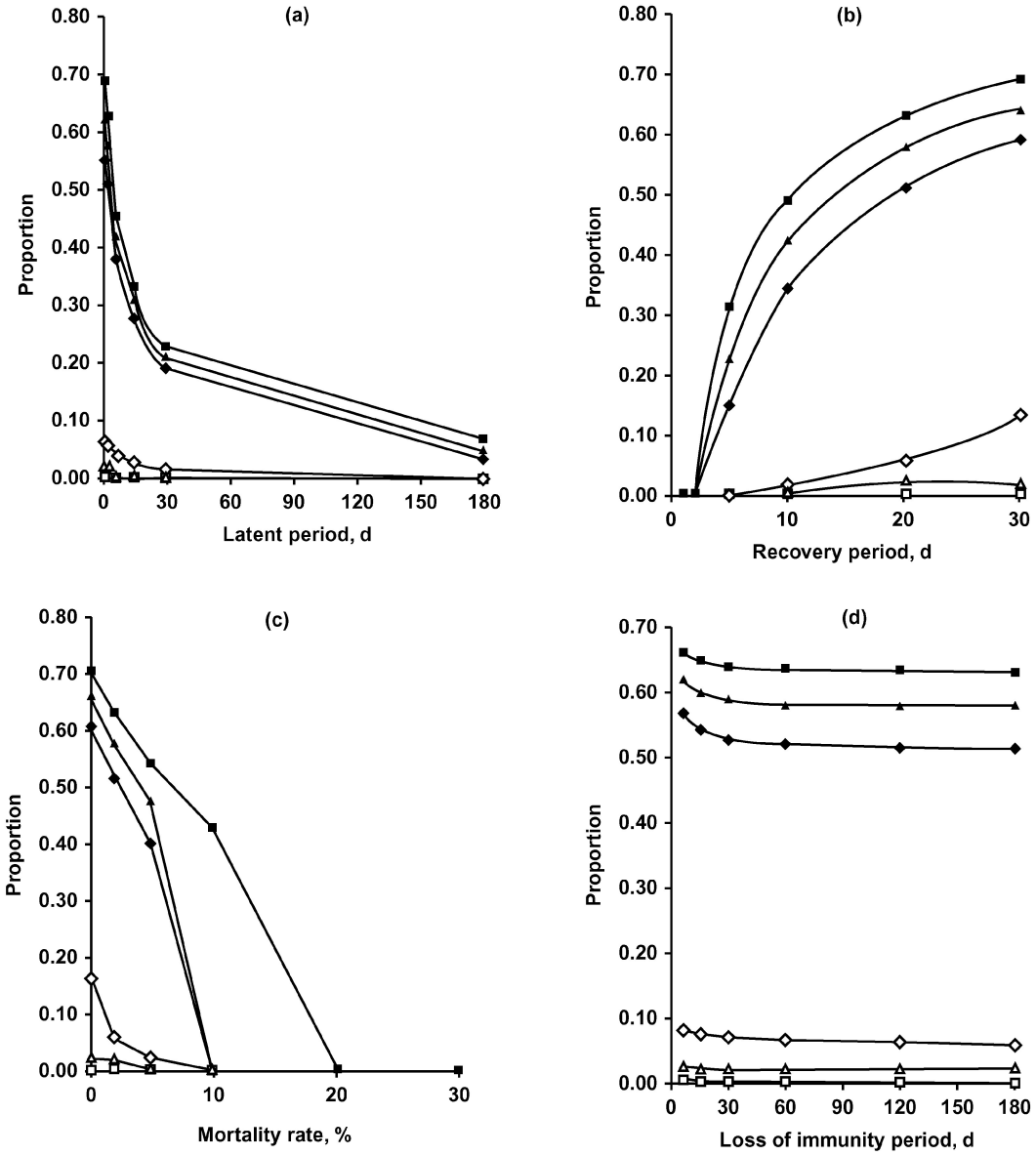

Figure 2. Comparison of estimates of maximum proportion of infected animals (y_{max}) vs. different epidemiological parameters: (a) latent period, (b) recovery period, (c) mortality rate, and (d) loss-of-immunity period, for transmission coefficients ($\beta \times 10^{-5}$) of 1 (□), 5 (△), 10 (◇), 50 (◆), 70 (▲), and 100 (■).

Effects of Altering the Mortality Rate

The estimates of R_0 decrease with an increase in mortality rate (Figure 1c). This happens because a high mortality rate leads to the elimination of the infected individuals from the population, thus preventing further spread of the infection. Hence, the concept of mortality can be considered equivalent to the concept of culling. Paradoxically, diseases with a mortality rate of more than 20% do not cause major epidemics as defined in this paper, even with high β values (Table 4), simply because the criteria of 6-mo duration and 10% infected are not reached. This phenomenon is similarly reflected in estimates of y_{max}. With a decrease in mortality rate, y_{max} increases in the range of intermediate to high values of β, although the time of y_{max} remains almost the same in this range (Figure 2c and 3c). The apparent inconsistency of 72 d as the time of y_{max} for $\beta = 0.0005$ and $\varepsilon = 0.30$ may be attributable to sampling variation since only 5 cases out of 5,000 replications actually showed a major epidemic for this parameter combination (Table 4).

The results give some insights into the disease dynamics and in turn may help in optimum disease management. For example, for diseases with low to almost no mortality, it is quite possible that the disease will become endemic in the population if the β value is low to moderate. In the case of diseases with high β values ($\beta = 0.001$) and low mortality ($\varepsilon = 0.02$), it is always advisable that the infected individuals are identified and removed from the population as soon as possible because the chance of the individual itself recovering

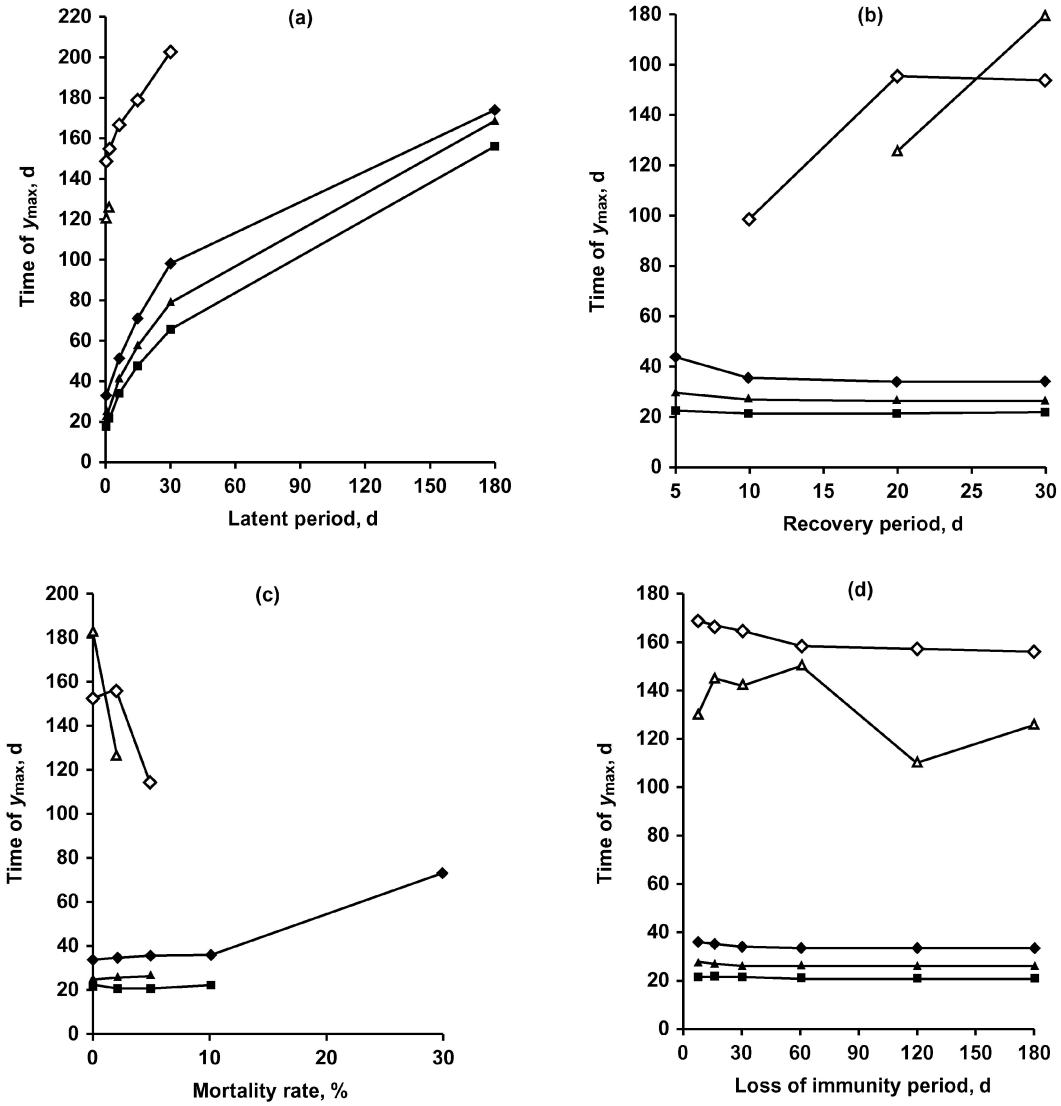

Figure 3. Comparison of estimates of time of occurrence of y_{max} vs. different epidemiological parameters: (a) latent period, (b) recovery period, (c) mortality rate, and (d) loss-of-immunity period, for transmission coefficients ($\beta \times 10^{-5}$) 5 (△), 10 (◇), 50 (◆), 70 (▲), and 100 (■). In all graphs, the absence of time of occurrence of y_{max} for a combination of parameter values indicates that no major epidemic was observed for that combination of parameters.

without infecting others (approximately 15%) is much lower than the probability that it will infect others and subsequently lead to more severe epidemics. If it is maintained in the herd, there is approximately an 84% possibility that it will infect more than 10% individuals in the population and the epidemic will last for more than 6 mo.

Effects of Altering the Loss-of-Immunity Period

With other parameters fixed, changes in the loss-of-immunity period do not make any appreciable changes in the epidemic pattern (Table 5), under the circumstances modeled in this paper. The estimates of R_0 remain almost the same even with a wide range in the loss-of-immunity period (from 7 to 180 d) within a given β value (Figure 1d). There is also little change in the estimates of y_{max} and the time of y_{max} when other parameters are constant (Figure 2d and 3d). Therefore, the loss-of-immunity period appears to be the least important parameter of those investigated, since it has little influence on disease dynamics in the short term.

Discussion

Biological Context

Discoveries of various genes or quantitative trait loci (**QTL**) associated with disease resistance clearly indicate the possibilities of developing animal strains that have enhanced genetic resistance to various diseases. However, allelic variation at different genes may influence the disease dynamics in different ways, and, therefore, the main objective of this paper was to understand

Table 2. Probability of no/minor/major epidemic for different transmission coefficients (β) and latent period ($1/\sigma$) keeping other parameters constant[a]

	Probability of epidemic		
$1/\sigma$, d	No epidemic	Minor epidemic	Major epidemic
$\beta = 1 \times 10^{-5}$			
1	0.89	0.11	0.00
2	0.89	0.11	0.00
7	0.92	0.08	0.00
15	0.94	0.06	0.00
30	0.96	0.04	0.00
180	0.99	0.01	0.00
$\beta = 5 \times 10^{-5}$			
1	0.61	0.39	0.00
2	0.63	0.37	0.00[b]
7	0.71	0.29	0.00
15	0.77	0.23	0.00
30	0.84	0.16	0.00
180	0.95	0.05	0.00
$\beta = 10 \times 10^{-5}$			
1[c]	0.46	0.28	0.27
2	0.47	0.28	0.25
7	0.57	0.25	0.18
15	0.66	0.23	0.11
30	0.75	0.21	0.04
180	0.92	0.08	0.00
$\beta = 50 \times 10^{-5}$			
1	0.18	0.03	0.79
2[c]	0.20	0.03	0.78
7	0.30	0.04	0.66
15[c]	0.39	0.06	0.56
30[c]	0.48	0.10	0.43
180	0.74	0.17	0.09
$\beta = 70 \times 10^{-5}$			
1	0.13	0.01	0.86
2	0.17	0.01	0.82
7	0.26	0.03	0.71
15	0.34	0.05	0.61
30[c]	0.44	0.07	0.50
180	0.69	0.16	0.15
$\beta = 100 \times 10^{-5}$			
1	0.12	0.01	0.87
2	0.15	0.01	0.84
7	0.21	0.02	0.77
15[c]	0.30	0.03	0.66
30	0.37	0.05	0.58
180[c]	0.64	0.13	0.22

[a]Other parameters in the model are kept constant (recovery period = 20 d; mortality rate = 2%/d; loss-of-immunity period = 180 d).
[b]One case among 5,000 replicates.
[c]The failure of a given row of probabilities to sum to 1.0 is attributable to rounding error.

Table 3. Probability of no/minor/major epidemic for different transmission coefficients (β) and recovery period ($1/\gamma$) keeping other parameters constant[a]

	Probability of epidemic		
$1/\gamma$, d	No epidemic	Minor epidemic	Major epidemic
$\beta = 1 \times 10^{-5}$			
1	1.00	0.00[c]	0.00
2	0.99	0.01	0.00
5	0.97	0.03	0.00
10	0.94	0.06	0.00
20	0.89	0.11	0.00
30	0.86	0.14	0.00
$\beta = 5 \times 10^{-5}$			
1	0.98	0.02	0.00
2	0.96	0.04	0.00
5	0.87	0.13	0.00
10	0.76	0.24	0.00
20	0.63	0.37	0.00[b]
30	0.56	0.42	0.02
$\beta = 10 \times 10^{-5}$			
1	0.97	0.03	0.00
2	0.92	0.08	0.00
5	0.78	0.22	0.00
10	0.62	0.38	0.00[c]
20	0.47	0.28	0.25
30	0.41	0.17	0.42
$\beta = 50 \times 10^{-5}$			
1	0.88	0.12	0.00
2	0.74	0.26	0.00
5	0.48	0.51	0.01
10	0.32	0.38	0.30
20[e]	0.20	0.03	0.78
30	0.16	0.01	0.83
$\beta = 70 \times 10^{-5}$			
1	0.85	0.15	0.00
2	0.68	0.32	0.00
5	0.41	0.57	0.02
10	0.26	0.21	0.53
20	0.17	0.01	0.82
30	0.14	0.01	0.85
$\beta = 100 \times 10^{-5}$			
1	0.79	0.21	0.00
2	0.62	0.38	0.00
5	0.35	0.60	0.05
10	0.22	0.05	0.73
20	0.15	0.01	0.84
30	0.11	0.00[d]	0.89

[a]Other parameters in the model are kept constant (latent period = 2 d; mortality rate = 2%/d; loss-of-immunity period = 180 d).
[b]One case in 5,000 replicates.
[c]Fifteen cases in 5,000 replicates.
[d]Twenty cases in 5,000 replicates.
[e]The failure of a given row of probabilities to sum to 1.0 is attributable to rounding error.

the critical parameters influencing the transmission of infection and thus identify the potential significance of different QTL or candidate genes in terms of alleviating disease. The compartmental microparasitic epidemiological model that we have used is governed by the transmission coefficient (β) and such parameters as the latent period ($1/\sigma$), recovery period ($1/\gamma$), disease-dependent mortality rate (ε), and loss-of-immunity period ($1/\omega$). The challenge remains to relate these parameters to measured traits on the animal. Achieving this and then applying the model to specific diseases of interest will lead to practical suggestions in terms of developing strategies for choosing QTL or candidate genes for that specific disease or similar diseases.

The parameter β depends on the infectivity of infected animals, on the susceptibility to infection of uninfected

Table 4. Probability of no/minor/major epidemic for different transmission coefficients (β) and mortality rate (ε) keeping other parameters constant[a]

	Probability of epidemic		
ε	No epidemic	Minor epidemic	Major epidemic
$\beta = 1 \times 10^{-5}$			
0.00	0.86	0.14	0.00
0.02	0.89	0.11	0.00
0.05	0.93	0.07	0.00
0.10	0.95	0.05	0.00
0.20	0.98	0.02	0.00
0.30	0.98	0.02	0.00
$\beta = 5 \times 10^{-5}$			
0.00	0.53	0.43	0.04
0.02	0.63	0.37	0.00[b]
0.05	0.72	0.28	0.00
0.10	0.81	0.19	0.00
0.20	0.89	0.11	0.00
0.30	0.93	0.07	0.00
$\beta = 10 \times 10^{-5}$			
0.00	0.39	0.16	0.45
0.02	0.47	0.28	0.25
0.05	0.57	0.40	0.03
0.10	0.69	0.31	0.00
0.20	0.81	0.19	0.00
0.30	0.87	0.13	0.00
$\beta = 50 \times 10^{-5}$			
0.00	0.16	0.01	0.83
0.02[f]	0.20	0.03	0.78
0.05	0.27	0.60	0.13
0.10	0.36	0.64	0.00[c]
0.20	0.53	0.47	0.00
0.30	0.63	0.37	0.00[c]
$\beta = 70 \times 10^{-5}$			
0.00	0.13	0.01	0.86
0.02	0.17	0.01	0.82
0.05[f]	0.23	0.48	0.30
0.10[f]	0.32	0.69	0.00
0.20	0.45	0.55	0.00
0.30[f]	0.55	0.46	0.00
$\beta = 100 \times 10^{-5}$			
0.00[f]	0.08	0.00[e]	0.91
0.02	0.15	0.01	0.84
0.05	0.20	0.25	0.55
0.10	0.27	0.73	0.00[d]
0.20	0.39	0.61	0.00
0.30	0.50	0.50	0.00

[a]Other parameters in the model are kept constant (latent period = 2 d; recovery period = 20 d; loss-of-immunity period = 180 d).
[b]One case in 5,000 replicates.
[c]Five cases in 5,000 replicates.
[d]Ten cases in 5,000 replicates.
[e]Twenty cases in 5,000 replicates.
[f]The failure of a given row of probabilities to sum to 1.0 is attributable to rounding error.

Table 5. Probability of no/minor/major epidemic for different transmission coefficients (β) and loss of immunity ($1/\omega$) keeping other parameters constant[a]

	Probability of epidemic		
$1/\omega$, d	No epidemic	Minor epidemic	Major epidemic
$\beta = 1 \times 10^{-5}$			
7	0.89	0.11	0.00
15	0.89	0.11	0.00
30	0.89	0.11	0.00
60	0.89	0.11	0.00
120	0.89	0.11	0.00
180	0.89	0.11	0.00
$\beta = 5 \times 10^{-5}$			
7	0.64	0.36	0.00
15	0.63	0.37	0.00[b]
30	0.62	0.38	0.00[b]
60	0.63	0.37	0.00[b]
120	0.63	0.37	0.00[b]
180	0.63	0.37	0.00
$\beta = 10 \times 10^{-5}$			
7	0.48	0.26	0.26
15	0.48	0.26	0.26
30	0.49	0.26	0.25
60[d]	0.48	0.28	0.25
120[d]	0.48	0.27	0.26
180	0.47	0.28	0.25
$\beta = 50 \times 10^{-5}$			
7	0.20	0.02	0.78
15	0.20	0.02	0.78
30	0.20	0.03	0.77
60	0.20	0.02	0.78
120	0.19	0.02	0.79
180[d]	0.20	0.03	0.78
$\beta = 70 \times 10^{-5}$			
7	0.19	0.02	0.79
15[d]	0.17	0.02	0.82
30[d]	0.18	0.02	0.81
60[d]	0.17	0.02	0.82
120	0.17	0.02	0.81
180	0.17	0.01	0.82
$\beta = 100 \times 10^{-5}$			
7	0.15	0.01	0.84
15	0.16	0.01	0.83
30	0.14	0.01	0.85
60[d]	0.15	0.00[c]	0.84
120	0.13	0.01	0.86
180	0.15	0.01	0.84

[a]Other parameters in the model are kept constant (latent period = 2 d; recovery period = 20 d; mortality rate = 2%/d).
[b]Five cases in 5,000 replicates.
[c]Twenty-five cases in 5,000 replicates.
[d]The failure of a given row of probabilities to sum to 1.0 is attributable to rounding error.

animals, and in some cases on the proliferation of infection within the infected animals. Susceptibility may be related to both immune and nonimmune response genes that preclude infection or limit infection to the target organ. For example, some pigs are genetically resistant to infection with K88 (F4)-positive enterotoxigenic *Escherichia coli* strains because they lack the gene for the intestinal receptor for the K88 adhesin (Francis et al., 1998; Edfors-Lilja and Wallgren, 2000). Similarly, two alpha (1,2) fucosyltransferase genes (FUT1, FUT2) on porcine chromosome 6q11 have been identified and are closely linked to *E. coli* F18 receptor (ECF18R) loci (Meijerink et al., 1997). The absence of particular receptors in the host prevents the pathogens from getting to their target niche and thus helps in preventing estab-

lishment of the pathogens. An example of limiting the proliferation of microorganisms within the host system is the natural resistance associated macrophage protein 1 (*Nramp1*; now renamed *SLC11A1*, for Solute carrier family 11, member 1), an important candidate gene in disease genetics studies. It is associated with enhanced intracellular killing of bacteria by macrophages (Blackwell, 1996). It has been suggested that genetic differences in resistance to visceral infection by *Salmonella enteritidis* in chickens are at least partly due to genetic polymorphisms in the *Nramp1* region (Girard-Santosuosso et al., 2002). Genetic variation in β may also be due to genetic variation in infectivity and this has been clearly documented for nematode resistance in sheep, a macroparasitic infection. For example, genetic variation has been demonstrated for the total number of eggs shed per host per day and also the per capita fecundity of the parasites resident in the gut (Stear et al., 1997).

As the pathogen gains entry inside the susceptible host, it tries to escape from host immunity and multiply itself. During the latent period ($1/\sigma$), the number of infectious agents is low and the host is infected but incapable of transmitting the infection. Latency-related genes in microorganisms have been reported in the literature and although this is not related to host genotype, their impacts may still be used to illustrate the importance of the latent period. Several studies suggest that latency-related gene products play an important role in the latency or pathogenesis of BHV-1 (Jiang et al., 1998; Ciacci-Zannela et al., 1999; Inman et al., 2001).

When the pathogen enters into the host, the recognition, activation, and effector phases occur sequentially in the host immune system. Host genetics plays an important role in changing the recovery period ($1/\gamma$) through various immune-associated genes. For example, when foreign peptide (antigen) enters into the body, the primary immunological function of major histocompatibility complex molecules is to bind and present those antigenic peptides on the surfaces of cells for recognition by antigen-specific T cell receptors of lymphocytes, which eventually leads to triggering of immune response and destruction of pathogens. The associations of major histocompatibility complex alleles in various viral, bacterial, and macroparasite diseases in chickens, cattle, pigs and horses are well documented (Rothschild et al., 2000). The parameter recovery period in our epidemic model would depend in part on how quickly the effector phase can successfully remove the pathogens. Therefore, selection for genes that decrease recovery period would be advantageous because they would elicit an early immune response to eliminate the pathogens or to inhibit further multiplication of pathogens.

The mortality rate (ε) is not directly related with genetic control of the transmission of infection, as a desirable decrease in disease-dependent mortality potentially worsens epidemics, in terms of the number of animals infected. Rather, it may be considered equivalent to disease-dependent culling. The culling of infected animals removes the infected individuals from the population and reduces the further spread of the infection to other susceptible animals. The control of disease by immediate culling may be noted from the example of the foot and mouth disease epidemic in Great Britain. However, for welfare and economic reasons, increased disease-dependent culling cannot be considered as a selection objective. Clearly, decreased disease-dependent mortality is desirable from both welfare and economic perspectives, but it does not give the insurance of decreasing the likelihood of future epidemics in the herd nor does it decrease epidemic severity in terms of the number of animals infected.

Finally, once exposed to foreign antigens, the immune system provides protection to animals due to induction of specific immunity that protects against future infection, which is also controlled by the host genetic system. This is represented by the loss-of-immunity period ($1/\omega$) parameter in our model.

Interpretation of Results

Various stochastic epidemic models describing the dynamics of infectious diseases in animals are available (Bouma et al., 1995; Innocent et al., 1997; Stark et al., 2000). Most of these studies address issues related with population size, management practices, farm structure, movement of animals, and the like. Some of these models are also very simple in their structure, which may not be realistic for actual scenarios. Therefore, these models may not be directly applicable to the decision making process for genetic selection and the utilization of information on QTL or candidate genes. MacKenzie and Bishop (2001) demonstrated the use of genetic epidemiological models to quantify the impact of selection for resistance to infectious diseases in livestock populations. However, they only considered the effect of altering β in the context of the infection dynamics.

The model presented in this article allows simultaneous investigation of the effects of altering several parameters. In many circumstances, as described above, these parameters can be related to specific traits and QTL for specific diseases. Of the parameters investigated, the transmission rate β appears to be critical in determining the disease dynamics. For low β values, the effects of variation in other parameters, such as σ, γ, ε, and ω, on infection dynamics are small. The probability of a major epidemic is very low in diseases with low transmission coefficients and therefore should not generally be of prime concern, particularly for small- or medium-sized herds as demonstrated in the present model. Hence, if a disease is characterized by β as 0.00005 or less, then it can safely be said that there is no imminent danger of a major epidemic due to the particular disease even if it has very short latent period, short loss-of-immunity period, low disease-dependent culling, or a long recovery period. In other words, we should place particular importance on QTL or candi-

date genes that can reduce the value of β considerably. This is also justified when viewed with respect to other epidemiological parameters, such as R_0 and y_{max}. If there is no change in values of σ, γ, ε, and ω, then reducing β always has beneficial effects and would result in a reduction in the number of new infectious cases and in the maximum proportion of infected individuals in the population.

However, it can be noted that the changes in β over the defined parameter space do not always show uniform changes in major epidemic probabilities. Particularly, for the population structure modeled, the crucial range for β values seems to be from 0.00005 to 0.0005. For example, a twofold increase of β from 0.00005 to 0.00010 increases the probability of a major epidemic from 0.0002 to 0.25. On the other hand, for a similar twofold increase of β from 0.0005 to 0.0010, the major epidemic probability increases from 0.78 to 0.84. Therefore, the epidemic outcomes are very sensitive to changes in β in the range of 0.00005 to 0.0005.

If the disease is characterized by medium to high β values, or if the available QTL information cannot reduce the value of β to a desired level in the population, then we should give more attention to other parameters that we have described in the model, such as the latent period, recovery period, and disease-dependent mortality rate.

It has been observed that with a constant β value and the assumption of an infectious challenge on only one occasion, the loss-of-immunity period ($1/\omega$) is the least important parameter affecting the transmission of infection in the current epidemic. The changes in R_0, the probability of a major epidemic, and y_{max} are minimal with changes of ω, in the time scale investigated in this model. However, it must be pointed out that a long period of immunity will be beneficial in protecting against future epidemics.

The latent period ($1/\sigma$) is important in influencing the disease dynamics pattern, which indicates that if the infectious organism takes more time to express its infectivity, this is advantageous in terms of disease control. The result reflects the fact that infective organisms with long latent periods are generally of lesser immediate concern, even if they have a moderate transmission coefficient. It is suggested that genetically increasing the latent period would also be a valid means of limiting future transmission of infection. A potential example is scrapie in sheep, where *PrP* alleles influence apparent host susceptibility. However, it is often argued using data from mice (Manson et al., 2000) and sheep (Gonzalez et al., 2002) that *PrP* alleles influence the incubation period (i.e., latency) rather than resistance to infection per se, and this argument is sometimes used to caution against selection on *PrP* genotype to limit the spread of infection. The results presented in this paper suggest that if it were not possible to alter transmission coefficient, then genetically increasing the latent period would also help in controlling future transmission of infection.

The recovery period ($1/\gamma$) is also important, as described above. It has been observed that a short recovery period can reduce the incidence of a major epidemic considerably. For instance, in the range of β from 0.0001 to 0.001, decreasing the recovery period from 20 to 10 d reduces the chance of major epidemic by approximately 10 to 50%. Hence, the QTL that decrease recovery period are also valuable for disease control.

The above conclusions have been drawn through a consideration of epidemic probabilities. However, broadly equivalent conclusions would also be drawn by considering the impact on other output parameters, such as the R_0 and y_{max} values. Decreasing the recovery period and increasing the latent period could decrease R_0 and y_{max} considerably and thus help in decreasing the incidence and severity of major epidemics. Similarly, increased disease-dependent culling would also decrease R_0 and y_{max}.

The present paper considers the utilization of the candidate genes or QTL to reduce the transmission of infection and hence the future incidence of disease. However, transmission of infection may not be the only factor determining the importance of a disease or the success of a control strategy. In practical situations, the application of a genetic strategy must be viewed in light of overall economic impact because disease management is one component of the overall production system. For example, in addition to the numbers of animals affected during an epidemic, the impact of infection in terms of the severity of illness, morbidity and the associated production loss will also affect the economics. The present model does not consider these factors or their economic consequences; however, the model could be used to provide inputs required for a detailed economic appraisal. This model potentially gives extensive information on the proportion of individuals expected to be exposed, to be infected, to recover, or to die during the epidemic and how these may be affected as a result of a disease control strategy. The next step may be to relate the time and state of the disease condition to the appropriate production parameters and analyze the economic impact. In other words, the information presented by our model could provide much of the necessary input into a full economic evaluation of various control strategies.

To summarize, apart from β, the parameters that should be of prime importance in designing genetic strategies for the development of disease-resistant stocks are σ and γ, and a decision-tree for evaluating these three parameters is shown in Figure 4. If we ignore disease-dependent culling in the context of genetic selection, then it is clear from the present study that both σ and γ are important from an epidemiological point of view. However, it is difficult to give precedence of one parameter over another. Rather, it seems that it would be more practical to consider each disease on a case-by-case basis in the light of available population information, epidemiological parameters, and genetic control strategies. For example, a number of QTL have

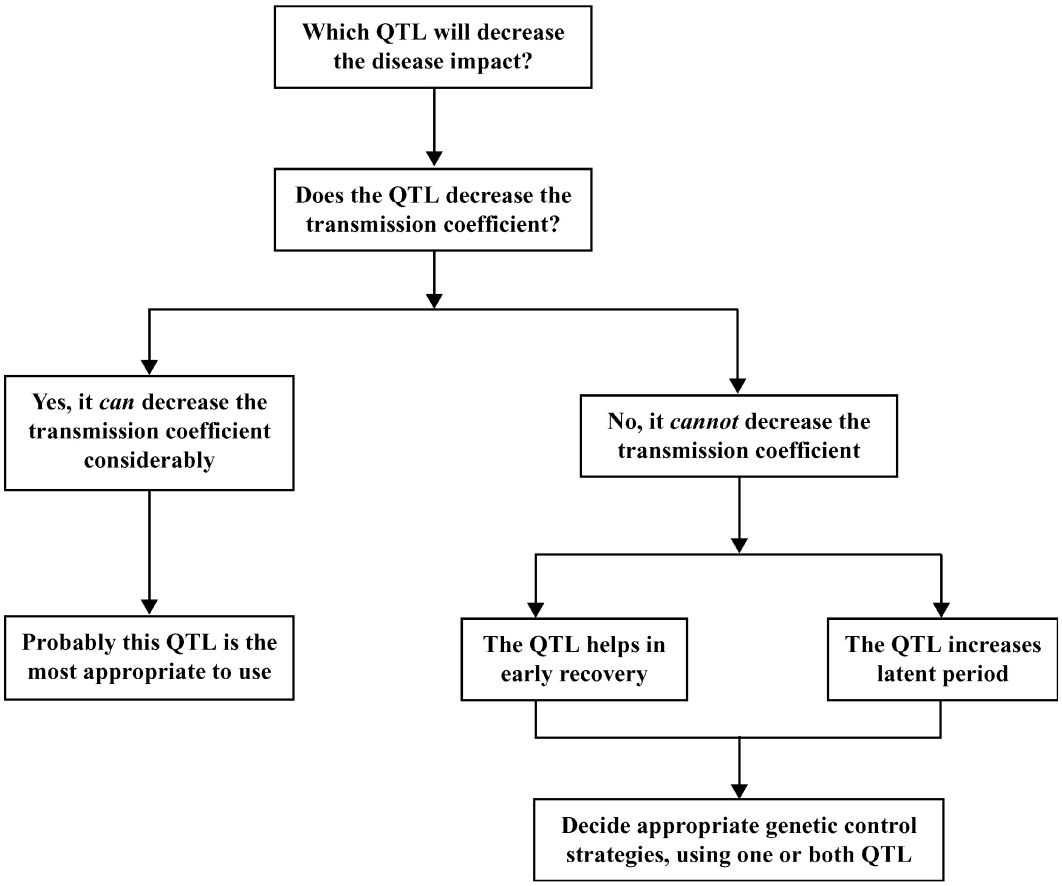

Figure 4. A decision-tree for utilizing quantitative trait loci (QTL) that influence the transmission of infection, the latent period, and the recovery rate.

been detected for Marek's disease resistance in poultry (Vallejo et al., 1998; Yonash et al., 1999). A challenge exists to critically evaluate the epidemiological implications of each of these QTL and determine which will have the greatest impact in helping to control the disease.

Implications

This paper identifies critical parameters controlling the transmission of microparasitic infections in domestic livestock using stochastic epidemic models. Critical parameters are the transmission coefficient, a function of both the host resistance to infection and the infectivity of infectious animals; the latent period; and the recovery period. Increasing resistance or the latent period, or decreasing the recovery period or the infectivity of infected animals, will all decrease the incidence of disease. These results are relevant to the development of strains of animals with enhanced resistance to specific infectious diseases. The utility of particular disease resistance quantitative trait loci or genes to control the transmission of infection can be determined by equating measured traits to model parameters and investigating their predicted impact on the dynamics of potential epidemics.

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