

A framework for integrating molecular information in a stochastic genetic-epidemiological model for Marek's disease resistance in poultry

M. NATH*

Central Avian Research Institute, Izatnagar, 243 122, India

*Corresponding author: Dr.M.Nath@gmail.com

Marek's disease (MD), caused by a herpesvirus, is a very infectious, lymphoproliferative and chronic disease of poultry. The main control strategy for MD is vaccination. Breeding for improved MD resistance poultry stock is possible since MD resistance has been associated with MHC haplotypes, QTL and candidate genes. However, integration of host genetics vis-à-vis other control strategies and utilisation of molecular information for MD in practical breeding programmes is still a challenge due to absence of specific genetic-epidemiological model for MD. Hence, objectives of the present study were to develop a genetic-epidemiological model for MD infection in poultry and assess the impact of genetic and vaccination strategies on overall MD dynamics. A compartmental model considering susceptible, exposed, cytolytic phase 1, latent, cytolytic phase 2 and proliferative phases of MD infection was developed and simulated stochastically in a population of 10,000 birds for 500 days. The results showed that the basic reproductive ratio and percent of the population infected in an MD epidemic were 5.8 & 80% and 0.6 & 20% for unvaccinated and vaccinated cases, respectively. An increased interval for latent to cytolytic 2 phase decreased MD-related mortality, while a decreased transmission coefficient decreased the major epidemic probability. The model outcomes correctly identify that whilst the proportion of infected individuals in a genetically resistant population may be high, the incidence of disease will still be rare, since infection may rarely cause obvious clinical cases of disease. It was concluded that the present model of MD would be a valuable tool for evaluation of different genetic and non-genetic strategies for controlling MD in poultry populations. Particularly in the post-genomic era, as possible genetic markers or genes in disease pathogenesis are identified, it may become more straightforward to integrate genetic information into the model.

Keywords: Marek's disease; mathematical model; genetics; disease resistance

Introduction

Marek's disease (MD), caused by a herpesvirus, Marek's disease virus (MDV), is a very infectious, lymphoproliferative, chronic and economically important disease of poultry. The main control strategy for MD is vaccination. However breeding for improved MD resistance stock is an attractive option since MD resistance in host has been associated with MHC haplotypes (Briles *et al.*, 1983), QTLs (Vallejo *et al.*, 1998) and candidate genes (Liu *et al.*, 2001). However, integration of host genetics vis-à-vis other control strategies and the utilisation of genes or gene markers for MD in practical breeding programmes is still a challenge. Currently, applications of genetic-epidemiological models for evaluation of disease control strategies are being explored (Bishop and MacKenzie, 2003). There is still no epidemiological model on MD currently available that explains the infection dynamics and therefore integration of genetic and non-genetic strategies to control MD has not been attempted. Hence, objectives of the present study were to develop a genetic-epidemiological model for MD

infection in poultry, identify parameters' spaces that describe the disease dynamics correctly and investigate impact of possible genetic and vaccination control strategies on overall disease dynamics.

Materials and methods

Infection process and epidemiological model. The transmission of infection by MDV may be described by so-called compartmental models (Anderson and May, 1992), in which individuals move from one state to another, defined according to the events that follow as a result of infection. A compartmental model considering different infective phases of MD within the host system, as described by Witter and Schat (2003), was considered. These are susceptible (S), exposed (E), cytolitic phase 1 (CI), latent (L), cytolitic phase 2 ($C2$) and proliferative (P). The transmission coefficient (β) denotes the rate at which infected individuals transmit infection to susceptible animals, and it is the expected number of new infections per infectious animal per susceptible animal per day. The infectivity of virus depends on virulence and shedding of virus by individuals in different phases. The recovery rate (γ) is the expected number of recoveries per infected animal per day. The mortality rate (μ_d) implies disease-dependent mortality, which is the expected proportion of individuals dying per day among infected individuals. Additionally, the model also considers disease-independent mortality (μ_i), which is the expected proportion of individuals dying per day due to disease-independent cause.

Simulation strategy and model outputs. The epidemic model was simulated stochastically according to Bishop and MacKenzie (2003). 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 epidemic started with introduction of an infected individual. If this individual recovered or died without any secondary infections, then it was a case of 'no epidemic'. If more than 10% individuals of the population became infected, the epidemic was deemed as being major, otherwise, as minor. The model outputs also included the basic reproductive ratio (R_0), which 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). The R_0 was estimated as $(1/p) - 1$, where p is the probability of 'no epidemic' (Bishop and MacKenzie, 2003). Other model outputs include epidemic severity (defined as maximum proportion of animals infected during the epidemic, y_{max}) and the time of occurrence of y_{max} . The estimates of y_{max} and time of y_{max} was averaged over all major epidemic occurrences.

Parameters space and implementation of the model. A medium-sized, equally mixing, homogenous, closed population of 10,000 birds was assumed. Possible intervals between different phases are available in literature (Schat and Markowski-Grimsrud, 2000; Witter and Schat, 2003). The interval between (E, CI), (CI, L), ($L, C2$) and ($C2, P$) were considered as 7, 7, 21 and 21 days, respectively. The contact rate between individuals was 1.0 and disease-independent mortality was 0.0002 per day. Since specific values for other model parameters vary according to strain, dose and virulence of virus, route of infection, vaccination status, age and sex of birds, maternal antibody status, genetic resistance etc., these are not readily available. Different ranges of infectivity, γ and μ_d at $E, CI, L, C2$ and P were explored to identify parameter values that matched with MD epidemiology pattern. It was assumed that individuals at the latent phase do not cause new infection. Once probable parameter values of MD infection dynamics were determined, the model was further explored taking into account parameters within the reasonable space, since different genetic control strategies would change parameter values within realistic range. Stochastic simulation of 1000 replicates was carried out for 500 days and model outputs on different situations were recorded.

Results and discussion

The β of 0.00005 and γ (CI) of 0.1 resulted in an R_0 value for MD of 5.80 with probability of a

major epidemic greater than 0.84. In case of major epidemic, 44% of infected population recovered while 50% died due to MD (Figure 1a). The y_{max} was 0.49 and this occurred around 9th week of age. The MD-related mortality was less than 0.3% during the period of first 40-45 days, which is the marketing age of broiler in general. Witter and Schat (2003) observed that prior to use of major vaccines against MD, poultry flocks were 80-90% more vulnerable to MD outbreak and once MD occurs, mortality was around 25 to 30% and occasionally as high as 60% in layer flock. In unvaccinated broiler flock, carcass condemnation due to MD was around 1% and could reach 10% or higher. Considering pathological changes in birds at C2 for MD-related carcass condemnation, the model outputs showed that around 3% birds up to 45th day would fall into the category of condemned carcass. Hence the model outputs for unvaccinated poultry flock closely reflects outcomes observed in practical situations.

In case of β of 0.00005 with γ (CI) of 0.9, the observed R_0 value was 0.59 and probability of major epidemic was 0.19. The proportion of exposed individual was high (0.97), but there was no visible clinical sign of MD since most of the exposed individuals were immunologically able to remove the virus (0.84) and only a small proportion (<10%) died due to MD (Figure 1b). The y_{max} was 0.10, which occurred at 14th week of age. It was observed that after introduction of modern vaccine against MD, mortality has reduced to less than 5% in layer and carcass condemnation of 0.2% or more in broiler (Purchase, 1985). These characteristics of MD infections are visible in the model outputs. Results showed that less than 0.1% of vaccinated birds actually showed C2 phase infection and hence likely to be condemned as undesirable carcass.

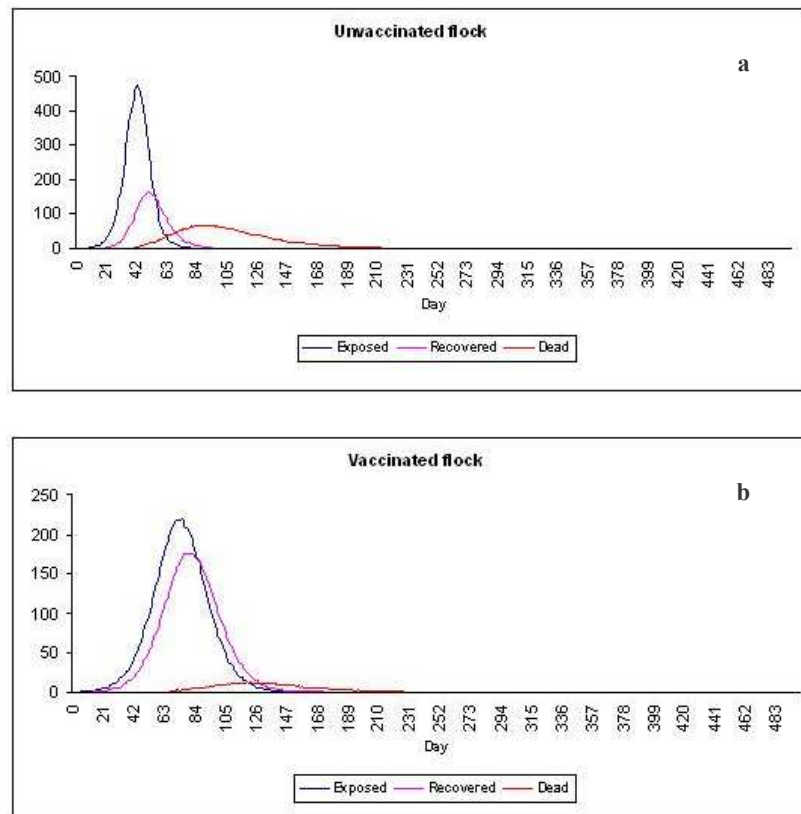


Figure 1. Model outputs for the number of exposed, recovered and dead birds due to epidemic of Marek's Disease during the period of 500 days in (a) unvaccinated and (b) vaccinated population of size 10,000

Considering the model outputs and its similarity with real MD infection dynamics, the γ values for E , $C1$, L , $C2$ and P were assigned as 0.01 0.1 0.001 0.0005 0.0001 for unvaccinated population and 0.01 0.9 0.001 0.0005 0.0001 for vaccinated population. This is also realistic and in agreement with general observations on MD infection in broiler populations, where vaccination is found to be 90% effective in controlling MD incidence.

In next step, simulations were performed to identify the change in disease scenarios under altered parameter space that might be possible under genetic selection where gene(s) products may contribute to change in parameter values at different phases of infection. The β was changed by 10-fold, upwards and downwards. The γ and μ_d at L , $C2$ and P phases were increased and decreased by ten-fold. The interval between L to $C2$ phases was considered as 180 and 500 days while in another case an additional increase in interval between E to C (60 days) along with L to $C2$ (500 days) was considered. During simulation under each case, all parameter values were fixed in ideal vaccinated or unvaccinated condition and only single parameter value in a given range was changed.

Increased μ_d and γ at later stages of disease was not beneficial since, due to the underlying nature of MD, infection was already established in the flock when these parameters expressed their beneficial effects. An increased interval for L to $C2$ phase decreased MD-related mortality and in case of unvaccinated flock, this decrease was to the tune of 17 to 25%. In case of increased interval for E to $C1$ and L to $C2$ phases simultaneously, proportion infected (y_{max}) and R_0 decreased and day of y_{max} increased. It is reported that infection in genetically resistant birds often remains latent in the lymphocytes and can last for lifetime of the bird (Witter *et al.*, 1971). Put another way, birds have the ability to enhance the interval for L to $C2$ long enough so that virus does not enter into $C2$ phase within its lifetime. The model outcomes correctly identify that proportion of infected individuals in a genetically resistant population may be higher but incidence of disease will be rare since infection may rarely cause overt disease. Among other parameters, as β was decreased by ten-fold, R_0 decreased by three-fold in vaccinated and unvaccinated populations. When β value was increased, it resulted in five- and nine-fold increases in R_0 value for above situations. Hence the impact of change of β is more in vaccinated population. In context of disease genetics, parameter β depends upon the infectivity genotypes of infected animals and the susceptibility genotypes of susceptible animals. It was evident that altering parameter β though genetic approaches would be an effective mean in reducing the impact of MD.

The proposed genetic-epidemiological model can be used along with the information generated from genomic approaches that identify genes, proteins and biological pathways associated with resistance to MD. For genetic selection purpose, once genes or genes combination and underlying biological pathways are identified, it would be straightforward to integrate this information into the model by altering model parameters. The model outcomes then would clearly evaluate the potential of using single or combination of several genetic strategies for controlling the incidence of MD in the flock.

In conclusion, the proposed genetic-epidemiological model captured the epidemiology and underlying immunogenetic mechanisms of MD both under vaccinated and unvaccinated scenarios. The paper presents probable parameter values in the MD infection process, particularly the transmission coefficient, infectivity and recovery rate at different phases of infection. The present model would therefore be a valuable tool for evaluation of different genetic and non-genetic strategies for controlling MD in poultry population.

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