Epidemics xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Epidemics

journal homepage: www.elsevier.com/locate/epidemics

Modeling Marek's disease virus transmission: A framework for evaluating the impact of farming practices and evolution

David A. Kennedy[a,*], Patricia A. Dunn[b], Andrew F. Read[a]

[a] Center for Infectious Disease Dynamics, Departments of Biology and Entomology, The Pennsylvania State University, University Park, PA, USA
[b] Animal Diagnostics Laboratory, Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, PA, USA

ARTICLE INFO

Keywords:
Marek's disease virus
Poultry
Disease ecology
Model comparison
Plug-and-play model

ABSTRACT

Marek's disease virus (MDV) is a pathogen of chickens whose control has twice been undermined by pathogen evolution. Disease ecology is believed to be the main driver of this evolution, yet mathematical models of MDV disease ecology have never been confronted with data to test their reliability. Here, we develop a suite of MDV models that differ in the ecological mechanisms they include. We fit these models with maximum likelihood using iterated filtering in 'pomp' to data on MDV concentration in dust collected from two commercial broiler farms. We find that virus dynamics are influenced by between-flock variation in host susceptibility to virus, shedding rate from infectious birds, and cleanout efficiency. We also find evidence that virus is reintroduced to farms approximately once per month, but we do not find evidence that virus sanitization rates vary between flocks. Of the models that survive model selection, we find agreement between parameter estimates and previous experimental data, as well as agreement between field data and the predictions of these models. Using the set of surviving models, we explore how changes to farming practices are predicted to influence MDV-associated condemnation risk (production losses at slaughter). By quantitatively capturing the mechanisms of disease ecology, we have laid the groundwork to explore the future trajectory of virus evolution.

1. Introduction

Marek's disease virus (MDV), the causative agent of Marek's disease (MD), imposes a substantial economic burden on chicken meat and egg production, costing the worldwide poultry industry in excess of 1 billion USD per year (Morrow and Fehler, 2004). Historical control measures have at least twice been undermined by virus evolution, leading to speculation that future evolution could undermine current control (Nair, 2005). The ecology of the disease appears to be the driving force behind past evolution, with explanations invoking vaccination (Witter, 1997; Atkins et al., 2013a; Read et al., 2015), rearing period duration (Atkins et al., 2013a; Rozins and Day, 2017), and virus persistence during downtime between bird flocks (Rozins and Day, 2017). Understanding the ecology of the virus is thus a key component in predicting whether and when control efforts will lose efficacy. Such an understanding is also crucial in developing immediate responses should the efficacy of current control measures wane. Yet the ecology of MDV is poorly understood. This is perhaps most clearly exemplified by the conventional wisdom that the virus is ubiquitously found on industrialized poultry farms (Office International des-Epizooties, 2010; Dunn, 2013), despite recent surveillance data suggesting that the virus may not be present on a large fraction of farms (Groves et al., 2008; Wajid et al., 2013; Walkden-Brown et al., 2013; Bettridge et al., 2014; Kennedy et al., 2015b, 2017; Ralapanawe et al., 2015).

Mathematical models of disease ecology can provide valuable insight into infectious disease dynamics. Such models quantitatively relate changes in ecology to changes in disease dynamics, which is particularly useful when experimental manipulation is unethical or, as with commercial-scale chicken rearing, financially costly. Models provide cheap and safe opportunities to explore the impact of system manipulation on pathogen control, and this approach has been applied to MDV (Atkins et al., 2013a,b; Rozins and Day, 2016, 2017). The reliability of a model, however, can only be assessed by challenging it with data, and this has never been done for MDV. Here we develop a suite of models to describe MDV dynamics on commercial broiler farms, and we use model selection methods to identify the ecological mechanisms that are most important to explaining MDV dynamics in the field.

Poultry intended for consumption are inspected and condemned for a condition called "leukosis" at the time of processing. This condition can be caused by various diseases, but in chickens reared for meat, leukosis is almost exclusively caused by MD (Sharma, 1985). Current

* Corresponding author.
E-mail address: dak30@psu.edu (D.A. Kennedy).

https://doi.org/10.1016/j.epidem.2018.01.001
Received 7 September 2017; Received in revised form 21 November 2017; Accepted 9 January 2018

rates of condemnation due to leukosis are extremely low (Kennedy et al., 2015b), but future reductions in MD vaccine efficacy due to virus evolution might cause leukosis rates to increase, as was documented with the erosion of vaccine efficacy in the past (Witter, 1996). A method to relate changes in farming practices to changes in risk of condemnation would therefore be a useful tool should virus evolution continue along the trajectory of the past.

The concentration of MDV in dust can vary several orders of magnitude between farms and within farms over time (Walkden-Brown et al., 2013; Kennedy et al., 2017). The underlying cause of this variation is unknown. Explanations may include between-flock variability in virus susceptibility and in virus shedding that may arise from factors such as differences in bird breed, quality of chicks, efficacy of MD vaccines, and the presence of other pathogens. Explanations may also involve differences in husbandry and biosecurity, such as differences in the efficiency of virus removal, in the sanitization efficacy in houses, and in reintroductions of virus. By comparing mathematical models that include or exclude these potential sources of variation, we can identify the importance of these differences on MDV dynamics, and in turn, we can develop strategies to control the ecology, evolution, and economic burden of this pathogen.

2. Methods

2.1. Model construction

We model the transmission and persistence of MDV within and between flocks of broiler chickens on commercial poultry farms. Our models are constructed assuming standard rearing practices in Pennsylvania, United States. These practices are fairly standard for commercial poultry rearing across much of the developed world.

Industrial-scale rearing of broiler chickens on farms tend to follow an "all-in, all-out policy," meaning that all chickens within a house are reared as a single-aged cohort of birds. We refer to a cohort of birds that occupy a single house on a farm as a flock. Birds are placed on litter that consists of wood chips and sawdust at one-day-old, and the birds are reared in this environment until they are ready for processing. Birds in houses are provided *ad libitum* food and water. Temperature, humidity, and air quality are maintained by a combination of active ventilation through fans or wind tunnels and heating. Flocks are collected for processing when sufficient time has elapsed for birds to reach a particular target weight.

While chickens are being reared, houses accumulate "chicken dust," a by-product of farming that consists of bits of food, epithelial cells, dander, bacteria, and feces (Collins and Algers, 1986; Pandey et al., 2016). The amount of dust produced by birds increases as birds grow (Islam and Walkden-Brown, 2007; Atkins et al., 2013a). Infectious MDV can be contained in this dust (Carrozza et al., 1973), being shed with the epithelial cells of infectious chickens and transmitted through the inhalation of virus-contaminated dust (Colwell and Schmittle, 1968). The concentration of MDV in dust can be measured through quantitative polymerase chain reaction (qPCR) (Baigent et al., 2005, 2016; Islam et al., 2006). Our model is constructed with this type of data in mind. We thus track the infection status of birds as well as total dust and total virus quantities.

Coming from extremely hygienic hatcheries, chickens are unexposed to MDV when first placed in a house. Shedding of virus from a bird can begin as early as one week post exposure to virus and tends to reach maximal levels two to three weeks post exposure (Islam and Walkden-Brown, 2007; Read et al., 2015). Once reached, virus shedding stabilizes at peak levels for the duration of a broiler chicken's life (Islam and Walkden-Brown, 2007; Read et al., 2015). Shed virus can infect other chickens, causing the pathogen to spread to other hosts in the flock. Even if virus were absent on a farm, it is possible that it may be introduced from outside sources, for example through dispersal in the air from nearby farms, on feed trucks, by service technicians, or by other farm visitors.

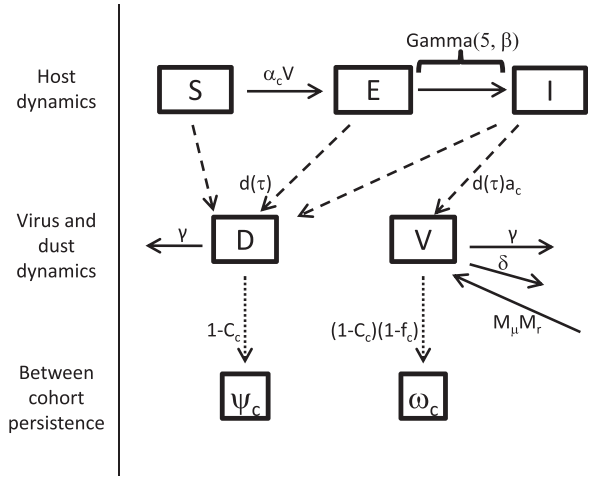

Fig. 1. Schematic of the model. States and parameters are as described in the main text and Table 1. Solid lines indicate transitions between model classes. Dashed lines indicate that producing dust and virus does not cause birds to leave their current model class. Dotted lines indicate the between flock persistence of dust and virus. Note that without altering the model, we depict the exposed class as a single group, where the time until an exposed host becomes infectious is gamma distributed with shape equal to 5 and rate equal to β.

Typical commercial broiler farms vaccinate against MD by using bivalent vaccination (Morrow and Fehler, 2004). Although vaccinated birds can still be infected with MDV and can still shed MDV (Witter et al., 1971; Islam et al., 2008; Ralapanawe et al., 2016), vaccination greatly reduces clinical signs of disease (Witter et al., 1971). This, along with other measures to ensure bird health, means that total mortality from hatch to processing is typically minimal ($\approx$3% and $\approx$8% in the two farms used for model inference below – in line with the national average of 4.8%, National Chicken Council, 2016). We therefore assume that bird mortality is negligible in our model. A schematic representation of the infection dynamics are shown in Fig. 1, corresponding to the following set of mathematical equations:

$$\frac{dS(t)}{dt} = -\alpha_c S(t) V(t), \tag{1}$$

$$\frac{dE_1(t)}{dt} = \alpha_c S(t) V(t) - \beta E_1(t), \tag{2}$$

$$\frac{dE_2(t)}{dt} = \beta E_1(t) - \beta E_2(t), \tag{3}$$

$$\frac{dE_3(t)}{dt} = \beta E_2(t) - \beta E_3(t), \tag{4}$$

$$\frac{dE_4(t)}{dt} = \beta E_3(t) - \beta E_4(t), \tag{5}$$

$$\frac{dE_5(t)}{dt} = \beta E_4(t) - \beta E_5(t), \tag{6}$$

$$\frac{dI(t)}{dt} = \beta E_5(t), \tag{7}$$

$$\frac{dD(t)}{dt} = d(\tau) S_0 - \gamma D(t), \tag{8}$$

$$\frac{dV(t)}{dt} = a_c d(\tau) I(t) - \gamma V(t) - \delta V(t) + M_r M_\mu, \tag{9}$$

where

$$\frac{\alpha_c}{\mu_\alpha} \sim \mathrm{LN}\left(-\frac{\sigma_\alpha^2}{2}, \sigma_\alpha\right), \tag{10}$$