



## Managing Marek's disease in the egg industry

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### ARTICLE INFO

#### Keywords:

Poultry  
Disease outbreaks  
Egg production  
Industrial farms  
Husbandry practices

### ABSTRACT

The industrialization of farming has had an enormous impact. To most, this impact is viewed solely in the context of productivity, but the denser living conditions and shorter rearing periods of industrial livestock farms provide pathogens with an ideal opportunity to spread and evolve. For example, the industrialization of poultry farms drove the Marek's disease virus (MDV) to evolve from a mild paralytic syndrome to a highly contagious, globally prevalent, deadly disease. Fortunately, the economic catastrophe that would occur from MDV evolution is prevented through the widespread use of live imperfect vaccines that limit disease symptoms, but fail to prevent transmission. Unfortunately, the continued rollout of such imperfect vaccines is steering MDV evolution towards even greater virulence, and the ability to evade vaccine protection. Thus, there is a need to investigate alternative economically viable control measures for their ability to inhibit MDV spread and evolution. In what follows we examine the economic viability of standard husbandry practices for their ability to inhibit the spread of both virulent MDV and very virulent MDV throughout an industrialized egg farm. To do this, we parameterize a MDV transmission model and calculate the loss in egg production due to MDV. We find that MDV strain and the cohort duration have the greatest influence on both disease burden and egg production. Additionally, our findings show that for long cohort durations, conventional cages result in the least per capita loss in egg production due to MDV infection, while Aviary systems perform best over shorter cohort durations. Finally, we find that the least per capita loss in egg production for flocks infected with the more virulent MDV strains occurs when cohort durations are sufficiently short. These results highlight the important decisions that managers will face when implementing new hen husbandry practices.

### 1. Introduction

The industrialization of farming empowers farmers to keep pace with the ever-increasing demands of consumers, but it also creates a situation highly conducive to pathogen evolution as a result of cramped living conditions and shorter rearing periods. A primary example of this is Marek's disease virus (MDV), which is a disease of poultry that has evolved from a relatively harmless paralytic syndrome into a highly virulent pathogen (Witter, 1997) as a result of industrialization (Atkins et al., 2012; Rozins and Day, 2017). To make matters worse, MDV is highly contagious, globally prevalent (Dunn and Gimeno, 2013), causes up to 100% mortality (Read et al., 2015; Witter, 1997), and imposes a colossal economic burden (Morrow and Fehler, 2004).

The economic burden of Marek's disease (MD) comes from both direct losses from hen mortality and morbidity (e.g., egg production loss), and indirect losses caused by industry wide use of vaccines and control measures. While indirect losses are substantial, the control of

MDV starting in 1969 through a succession of live vaccines has saved billions of dollars and helped to ensure the present economic stability of the industry (Churchill et al., 1969b, 1969a). Unfortunately, current vaccines for MDV have major drawbacks in that they only limit disease symptoms and permit both infection and transmission. Such drawbacks enable virulent MDV strains to go undetected and are attributed with being a major factor in the continued evolution of MDV virulence (Read et al., 2015), including its potential to evade vaccine induced immunity (Nair, 2005).

Detection and eradication of MDV is extraordinarily difficult. MDV spreads through freely circulating viral particles (Biggs and Payne, 1967) that are shed through the feather follicles of infected laying-hens. As infected laying-hens are likely symptom free due to vaccination, and cohort sizes range from 30,000–100,000 hens (Holt et al., 2011), the identification and removal of MDV infected hens is difficult. Additionally it has been shown that MDV is often reintroduced to barns as often as once per month (Kennedy et al., 2018). Thus, other measures

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<https://doi.org/10.1016/j.epidem.2019.01.004>

Received 24 March 2018; Received in revised form 30 January 2019; Accepted 31 January 2019

Available online 02 February 2019

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are needed to prevent or limit MDV infection.

Here, we evaluate the most common management scenarios in the egg industry for their ability to prevent MDV infection, while also mitigating any egg production loss. Specifically, we investigate how animal husbandry practices such as the density of laying-hens (reflecting alternative caging systems), the cohort duration, and the MDV strain influence MDV incidence, mortality, and egg production. Using data on MDV infection, in addition to data on the demographics of typical laying-hens in the egg industry, we evaluate the influence of management scenarios on MDV incidence, mortality, and egg production. To do this, we use an extension of a mathematical model presented in (Rozins and Day, 2016) calibrated to reflect ongoing industrial practices, namely those of Aviary, Conventional, and Enriched systems. We assess the effect of MD on egg production over a 10-year horizon to evaluate any effect of management scenario and MDV infection on egg production.

## 2. Materials and methods

To quantify the impact of management scenario on mitigating the effects of MDV infection on egg production, we use a mathematical model for MDV transmission in industrial poultry farms of laying-hens (Rozins and Day, 2016). As the vast majority of laying-hens are vaccinated (Payne, 1985), our model assumes full vaccination coverage with the current gold standard vaccine Rispen CVI988 (Ralapanawe et al., 2016a). We also assume two distinct mechanisms of MDV transmission: 1) transmission within a cohort of laying hens (those sharing a barn), and 2) transmission between consecutive cohorts of laying-hens occupying a barn (i.e. transmission through residual viral particles left in the barn).

### 2.1. Management scenarios

We evaluate 72 different management scenarios. These scenarios describe the typical egg industry, matching flock sizes to the stocking densities of Aviary (30,000 laying-hens), Conventional (80,000 laying-hens), and Enriched (50,000 laying-hens) systems. These scenarios also describe the typical egg industry in matching 12 different cohort durations to capture the most common molting practices (no molt (NM), one molt (OM) at 69 weeks, and two molts (TM), one at 69 weeks and another at 104 weeks) (Bell, 2003). Molting is a natural process in which hens lose and regrow their feathers and briefly stop laying eggs. The process rejuvenates laying-hen production, but has a diminishing effect over time, and occurs at most twice. Finally, we also consider a very virulent MDV strain (vvMDV) (pathotype FT158) and a virulent MDV strain (vMDV) (pathotype MPF57).

### 2.2. Egg production

To evaluate the impact of MD on egg production over a 10-year horizon, we base uninfected laying-hen egg production on a study of 25 million White Leghorns laying-hens (Fig. 1) (Bell, 2003). MDV infected laying-hens incur a 5% egg production loss ( $R$ ), which is an expected consequence of MDV infection (Purchase, 1985). Both uninfected and infected laying-hens' egg production is continuously discounted by the annual US 2016 inflation rate of 1.25%. Further details of parameters, including sources, are available in Table 1.

### 2.3. MDV transmission with-in a cohort

To describe MDV transmission within a cohort of laying-hens, we extended a compartmental model (Rozins and Day, 2016) to capture MDV prevalence levels in concurrent vaccinated flocks of laying-hens occupying a barn. We consider three classes of hens: susceptible laying-hens ( $S$ ), latent MDV infected laying-hens ( $E$ ), and MDV infected laying-hens ( $I$ ). In addition, to reflect laying-hen mortality due to MDV

infection, we stratify the laying-hens infection with MDV into  $m$  sub-compartments using the method of stages (Lloyd, 2001). The rate susceptible laying-hens become infected is governed by a constant transmission rate ( $\sigma$ ), and the density of viral particles ( $F$ ) in the barn. Once exposed to MDV, laying-hens have an average incubation period ( $1/\phi$ ), after which they become infected with MDV. Infected laying-hens experience disease related mortality at rate ( $\nu/m$ ), and shed viral particles at the rate ( $\kappa$ ). Finally, viral particles are removed, either through decay or through the ventilation system, at rate ( $\delta$ ). Overall, the system of differential equations that models MDV transmission within a cohort is:

$$\begin{aligned} \frac{dS}{dt} &= -\sigma FS, \\ \frac{dE}{dt} &= \sigma FS - \phi E \\ \frac{dI_1}{dt} &= \phi E - \nu I_1, \\ \frac{dI_j}{dt} &= \nu I_{j-1} - \nu I_j, \text{ for } j \neq 1, \end{aligned} \quad (1)$$

$$\frac{dF}{dt} = \frac{\kappa}{V} \sum_{j=1}^m I_j - \delta F,$$

where  $V$  is the volume of the barn. Note, implicit in the definition of system (1) is the assumption that the per capita contact rate between susceptible laying-hens and viral particles is density dependent, as the contact rate between susceptible laying-hens and viral particles increases with both the population of laying-hens and the density of viral particles within the barn.

### 2.4. MDV transmission between cohorts

After a cohort duration of  $T$  days, the barn is emptied, cleaned, and restocked with the next cohort of new susceptible laying-hens. This emptying, cleaning, and restocking period is modelled as instantaneous, as the time to accomplish this is small relative to the duration of egg production. Thus, the laying-hens and viral particles after the farm is emptied, cleaned, and restocked is given by the difference equations:

$$\begin{aligned} \Delta S &= -S(t_n) + N, \\ \Delta E &= -E(t_n), \\ \Delta I_j &= -I_j(t_n), \\ \Delta F &= -(1-a)F(t_n), \end{aligned} \quad (2)$$

where  $N$  is the flock size,  $a$  is the proportion of viral particles that remain after the barn is emptied, cleaned, and restocked,  $t_n = nT$ , is the time directly before restocking, and  $n$  is an indexing for the cohort.

By combining the between cohort Eq. (2) and the within cohort Eq. (1), we have a model that describes the continual chain of transmission of MDV in cohorts of laying-hens over a 10-year horizon.

### 2.5. Parameter values

All model parameters were extracted from available data (Atkins et al., 2012, 2011; Cui et al., 2016; Kennedy et al., 2018; Ralapanawe et al., 2016b, 2016a; Zhang et al., 2015). Parameters associated to barn characteristics were obtained from communication with Burnbrae Farms in Ontario Canada, or the literature. We assume dust shed by MDV infected laying-hens contain viral particles proportional to the virulence level of the MDV strain (Ralapanawe et al., 2016a). To obtain the viral shedding rate, we took a model of daily dander shedding for a typical broiler bird (Atkins et al., 2011) and parameterized it according to a recent study on dust shed from MDV infected laying-hens that were vaccinated with Rispen CVI988 (Atkins et al., 2011; Ralapanawe et al., 2016b, 2016a). Then, we obtain the viral shedding rates  $\kappa$  for each MDV strain from data on the dust shed from a typical laying-hen (Table S4), and the viral copy number (VCN) of MDV per milligram of dust for

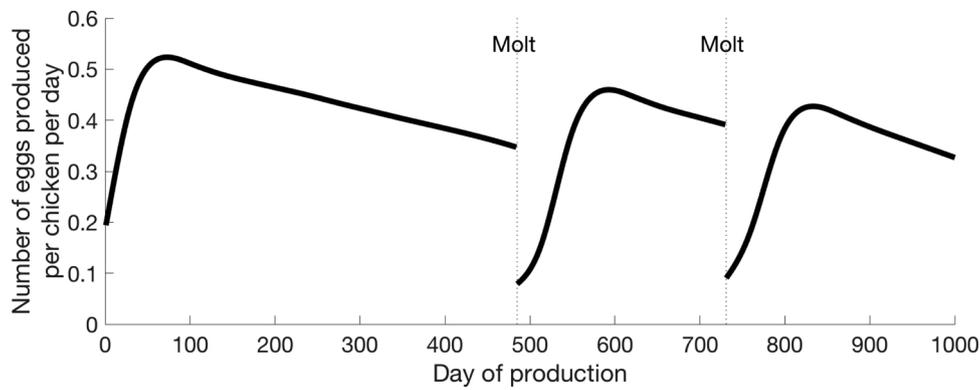


Fig. 1. Daily egg production. Mean daily egg production per hen over a 1000-day period for a laying-hen molting twice, once after 69 weeks (438 days) and again at 104 weeks (728 days).

vMDV (pathotype MPF57) and vvMDV (pathotype FT158) (Table S3) over each cohort duration (Table S5) (Bell, 2003; Witter et al., 1968). Once infected, there is a delay until viral shedding begins, known as the latent period and was found by Atkins et al. (2011) to not vary significantly between viral strains or vaccine choice (Atkins et al., 2012). Data on the virulence level of the MDV pathotype, combined with techniques for non-exponentially distributed parameters (Greenhalgh and Day, 2017; Hethcote and Tudor, 1980; Lloyd, 2001), were used to estimate MDV mortality rates ( $v/n$ ) for each MDV strain (Ralapanawe et al., 2016a). We based the viral particle removal rate ( $\delta$ ) on the barn ventilation system and estimates of the decay rate of the viral particles (Kennedy et al., 2018). Therefore,  $\delta$  is taken as the sum of the decay rate and the average air exchange rate of a typical barn (Table 1, Webappendix). In practice, the air exchange rate of a barn depends on its stocking density, as more densely stocked barns require a

greater exchange of air. For simplicity, we consider a constant air exchange rate, which we estimate using available data and standard fitting techniques (Webappendix). Finally, we determine the transmission rate  $\sigma_v$  using both an estimate, and the mathematical formulation of the MDV effective reproductive number (Atkins et al., 2013, 2012; Renz, 2008) (Webappendix), yielding

$$\sigma_v = \frac{v}{m} \frac{\delta V}{N \kappa} R_e,$$

where  $\kappa$ ,  $\delta$ ,  $v$ ,  $m$ , are previously estimated (Table 1, Table S4, Table S5).

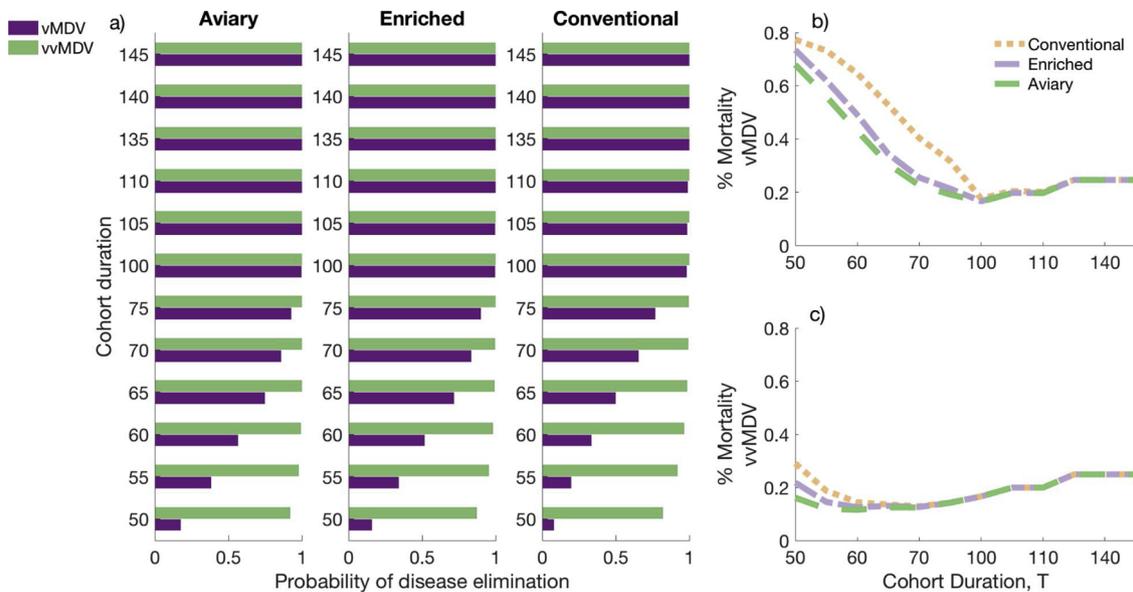
### 2.6. Sensitivity analysis

To quantify the contribution of each model parameter to the

Table 1  
Model parameter values.

Parameter	Symbol	Value(s)	Distribution/Parameter range	Reference
Flock size <sup>1</sup> (x10,000) (laying-hens)	$N$	3, 5, 8	$U(3,8)$	Pers. comm. (2016) <sup>3</sup> (Webappendix)
Transmission rate (per VCN/m <sup>3</sup> per day)	$\sigma_v$	$\frac{v}{m} \frac{\delta V}{N \kappa} R_e$		
Latent period (days)	$1/\phi$	4.7	$\text{Exp}(\phi)$	(Atkins et al., 2012)
MDV mortality rate (day <sup>-1</sup> )	$\frac{v}{m}$		$\Gamma(m, v)$	(Ralapanawe et al., 2016b), (Webappendix)
vMDV		$\frac{1}{89.5}$	$m = 17, v = 0.19$	
vvMDV		$\frac{1}{65.4}$	$m = 17, v = 0.26$	
vMDV shedding rate <sup>2</sup> (log <sub>10</sub> VCN per day)	$\kappa$			(Atkins et al., 2012; Ralapanawe et al., 2016b), (Webappendix)
NM			Tri(9.721, 9.847, 9.905)	
OM			Tri(10.004, 10.019, 10.033)	
TM			Tri(10.004, 10.020, 10.033)	
vvMDV shedding rate <sup>2</sup> (log <sub>10</sub> VCN per day)				
NM			Tri(9.940, 10.041, 10.090)	
OM			Tri(10.173, 10.186, 10.197)	
TM			Tri(10.173, 10.186, 10.197)	
Viral particle removal rate per hen (day <sup>-1</sup> )	$\delta$	$0.1 + (2.61 \times 10^{-8})N$		Pers. comm. (2016) <sup>2</sup> (Webappendix) (Purchase, 1985)
Reduction in egg production due to MDV infection (%)	$R$	0.05	$U(0.015, 0.05)$	
Egg Price (USD/dozen)		1.40		(National Egg Market Summary, (2018))
Large caged		1.60		
Large cage free				
Cohort duration (weeks)	$T$		$U(50,75)$	
NM			$U(100,110)$	
OM			$U(135,145)$	
TM				
Cleaning coefficient	$a$		$U(0.01, 0.10)$	(Kennedy et al., 2018)
Barn volume (m <sup>3</sup> )	$V$	6000		Pers. comm. (2016) <sup>2</sup> (Webappendix)
Effective Reproductive number	$R_e$	4.71		

<sup>1</sup> Flock sizes are selected to achieve stocking densities that reflect those found in Aviary, Conventional, Enriched systems. <sup>2</sup>Personal Communications refer to the Director of Poultry Operations (John Heuthorst), and the Farm Manager (Fred Lozo) at Burnbrae Farms, Ontario, Canada.



**Fig. 2.** MDV elimination and mortality. (a) Likelihood of MDV elimination within 10 years for particular cohort duration, MDV strain, and caging system. The mortality due to (b) vMDV and (c) vvMDV for Aviary, Conventional, and Enriched systems.

variability of the outcomes measured, we calculated 95% quantiles and first-order sensitivity indices. Specifically, first-order sensitivity indices attribute the variation in model outputs to uncertainty in model inputs.

### 3. Results

We found that the strain of MDV circulating within the barn, along with the cohort duration, have the greatest impact on egg production. With regards to egg production, the most surprising result was that for short cohort durations, barns infected with vvMDV out-produced barns infected with the less virulent vMDV strain.

#### 3.1. Disease

Our findings show that the introduction of MDV leads to infection for the majority of a flock, regardless of management scenario. We also found that MDV spread was very rapid, infecting the majority of a flock well before the end of the cohort. For flocks infected with MDV, mortality due to infection varied significantly across management scenarios, and was largely dependent on the cohort duration and the MDV strain virulence level (Fig. 2b, c).

#### 3.2. Cohort duration and molting

Barns employing longer cohort durations typically suffered the greatest per capita egg production loss due to MDV infection, with the worst-case scenario occurring in barns infected with vvMDV (Table S7 and Fig. 3). For shorter cohorts, egg production loss depended highly on the circulating viral strain (Fig. 3), with the greatest difference between vMDV and vvMDV of 16.88 eggs lost per hen occurring for a cohort durations of 55 weeks (Fig. 3).

#### 3.3. Stocking density

Despite the different stocking densities of Aviary, Conventional, and Enriched systems, all had similar per capita egg production losses, and economic losses for each cohort duration (Fig. 3b, Fig. 4). While similar, the stocking density of the Aviary system yielded the most eggs per hen over short cohort durations when the vMDV strain was circulating (Table S7). When the vvMDV strain was circulating, the Aviary system yielded the most eggs per hen for cohort durations of 50 and 55 weeks.

For cohort durations of 65-weeks or longer, the Conventional system yielded a per capita gain of approximately 1.6 eggs per hen when compared to an Aviary system, and a per capita gain of 0.75 eggs per hen when compared to an Enriched system (Table S7).

#### 3.4. MDV strain

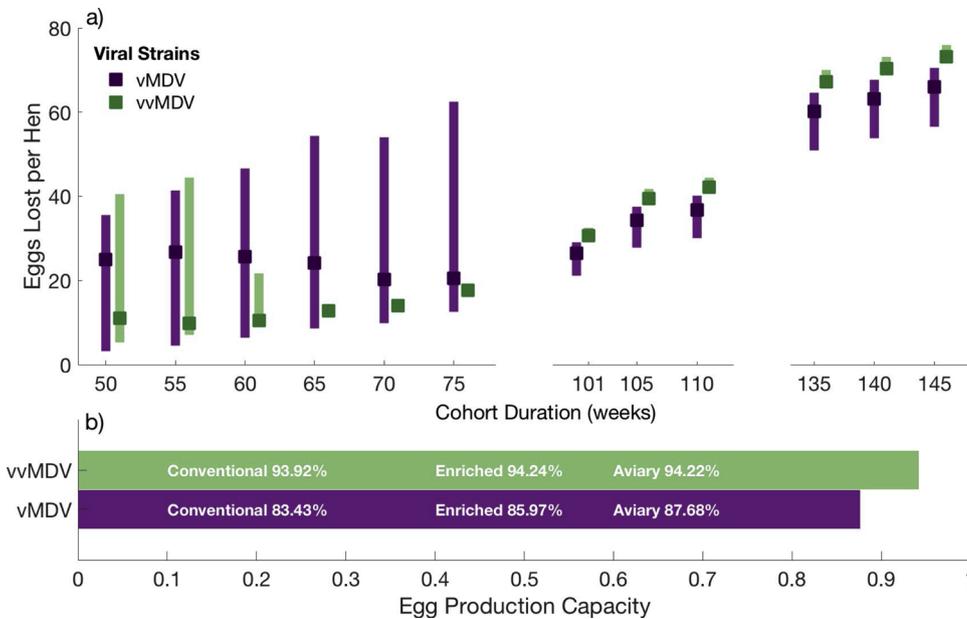
With regards to MDV strain virulence level, for short cohort durations, the vvMDV strain would often burn out due to rapidly killing the entire flock, and ultimately leave an insufficient quantity of viral particles for the infection of subsequent cohorts of laying-hens (Fig. 2). In contrast, the slower spread of the vMDV strain allowed it to persist in the barn for subsequent cohorts, resulting in a higher proportion of infected laying-hens over the 10-year study period (Figs. 2 and 3).

#### 3.5. Sensitivity analysis

To quantify the contribution of parameters to the variability in predicted egg production, we calculated variance-based first-order sensitivity indices (Sobol, 2001) (Table S6). First-order sensitivity indices indicate how uncertainty in a particular parameter contributes to the variability of model outcomes. Details of the probability distributions used in the calculation of first-order sensitivity indices are available in Table 1. Predictions in egg production were most sensitive to the cohort duration, and the latent period of MDV infection (Table S6). The sensitivity of predictions increased as the cohort duration increased, while the opposite relation was observed for the latent period of MDV infection (Table S6).

### 4. Discussion

This study evaluates the burden of MDV on the most common management scenarios in the egg industry using mathematical models. Additionally, the mathematical model developed is also calibrated to the Rispens CVI988 vaccine (Rispens et al., 1972), the current gold standard vaccine in the poultry industry. Given these facts, we evaluated the effects of two MDV strains on laying-hen production in Aviary, Conventional, and Enriched systems, including the typical laying-hen cohort durations for a 6000 m<sup>3</sup> barn. For each scenario, we estimated MDV prevalence, the potential for disease elimination, and the per capita egg production loss due to MDV infection.

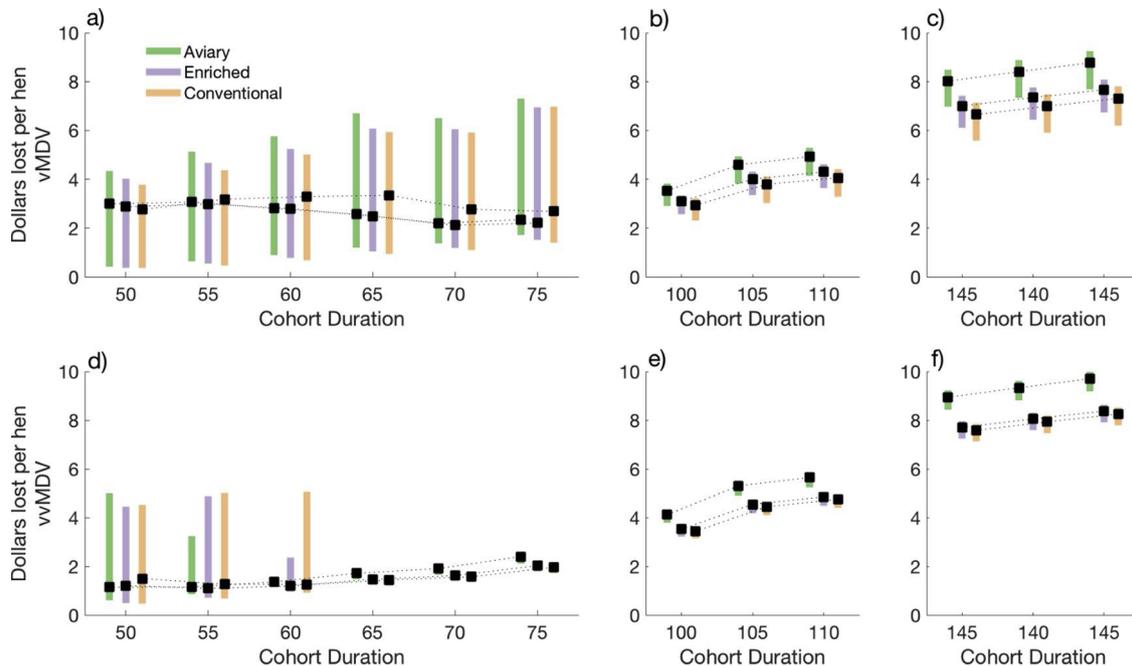


**Fig. 3.** Egg loss and production capacity. a) Average eggs lost per hen with 95% quantiles for all cohort durations and molting practices (no molts, one molt, and two molts). b) Egg production capacity for a 60-week cohort, measured as the total eggs produced over the total eggs produced in the disease-free scenario, for each stocking densities.

While theory suggests less densely stocked barns should make disease elimination easier [13], we found that this is the case only for management scenarios with short cohort durations. Under such scenarios, Aviary systems had the least per capita loss in egg production for all no-molt scenarios when the vMDV strain circulated within the barn, and for all cohort durations less than 65 weeks when the vvMDV strain circulated within the barn. This advantage of Aviary systems stems from the greater likelihood of interrupting transmission by disease burnout and effective cleaning, whereas Conventional and Enriched systems, due to their larger stocking densities, typically had persistent MDV infection. However, caution should be used in relying on this ability of Aviary systems. Specifically, their open design could promote

MDV transmission from direct contact, and such sources of heterogeneity in transmission may hamper elimination efforts. In addition, Aviary systems also have littler floors, which are a known factor that affects hen welfare and disease transmission (Dawkins et al., 2004; Lay et al., 2011)

Over longer cohort durations, we found the more densely stocked Conventional systems held a financial advantage over Aviary systems. This outcome is likely understated due to factors, like the cost of eggs, hen cannibalism, and upkeep costs. To elaborate, caged eggs (Conventional and Enriched systems) have less value than free-run eggs (Aviary systems), and thus impose a lower financial burden per egg lost. Combining this result with lower hen cannibalism rates (Ahmed



**Fig. 4.** Economic loss (USD) caused by mortality and the reduction in egg production due to MD. Production is scaled by stocking density and future egg-earnings are discounted by the 2016 US inflation rate of 1.25%. To calculate the total loss in USD, the total revenue for the disease-free scenario (Table 1) was subtracted from the total revenue when MDV was introduced. Finally, to normalize across stocking densities, we divide this by the total number of laying-hens. Plots a–c) examine vMDV, and plots d–f) examine vvMDV. Plots a) and d) reflect a barn that does not molt its hens, plots b) and e) a single molt, and plots c) and f) two molts. The bars represent the 95% quantiles while the points represent the mean.

et al., 2014), a 13%–36% lower upkeep cost (Matthews and Summer, 2015), and the fact that higher stocking densities have been shown to select for less virulent strains of MDV (Rozins and Day, 2017), show that Conventional systems have substantial utility in the fight against MD.

Mathematical models inevitably involve simplifying assumptions. For instance, our model treated all eggs produced as equal in value and quality. This assumption understates the productivity of longer cohort durations, as older hens produce larger eggs that are often worth more. Furthermore, we did not account for the increased cost associated to the 47% more hens required over a ten-year period for husbandry practices that avoid molts (Bell, 2003). We also did not account for multiple factors that may affect MDV persistence, such as transmission from direct contact of laying-hens in open environments, the effects of litter floors, seasonally-varying ventilation rates, or potential breaches in biosecurity. Incorporating such additional modes of transmission would likely strengthen the utility of Conventional systems, as multiple modes of transmission would make elimination more difficult. In addition, while parameterizing our model we used information derived from studies on broiler birds (Atkins et al., 2011) when information was not available for laying hens. Finally, we do not account for the effects of disease coinfection, although with additional compartmentalization a new co-infection model could be developed to capture such dynamics. With this in mind, the methods used to construct our impulsive compartmental model could also easily be applied to study other avian diseases, such as the highly pathogenic H7 avian influenza recently found in a Tennessee commercial flock (Karlsons and Cole, 2017), as the impulse feature of the model naturally describes the all-in-all-out dynamics of poultry farms.

Overall, our findings illustrate that there are management scenarios that hold promise both in terms of eliminating MDV in egg farms, and in mitigating MDV evolution, all the while maintaining economic viability. While many factors likely affect the effectiveness of such management scenarios on the control of MDV, the work here illustrates the importance of cohort duration, and cohort size on MD transmission, and the associated impact on egg production. With this in mind, future work might expand upon our model using control theory to incorporate more realistic ventilation practices, the effect of restocking schedules, and their influence on MDV evolution.

## 5. Conclusion

Due to the fear that prolonged use of Rispsens CVI988 is masking the emergence of extremely virulent MDV strains (Report of the Committee on Transmissible Diseases of Poultry and Other Avian Species, 2015), the enhancement of current husbandry practices to combat MDV is of the utmost importance. Our results suggest that for flocks that undergo molts, increasing stocking densities helps to reduce the per capita egg production loss due to MD. On the other hand, for flocks that do not undergo a molt, the lower stocking densities that promote disease burnout appear to be the best scenarios to reduce the burden of MD on per capita egg production. While at first these results may seem surprising, they call to light that improving long-term hen welfare is not as simple as solely reducing stocking densities or cohort durations, and that the improvement of hen welfare is not necessarily distinct from the goals of economics.

## Author's contributions

SG and CR came up with the study design and they parameterized the model. All authors participated in the drafting and editing of the paper.

## Funding

This work has been funded by the Egg Farmers of Canada. The Egg

Farmers of Canada had no involvement in the study design, interpretation of the results, preparation of the article, nor did they have any decision in where to submit the article.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.epidem.2019.01.004>.

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