A stochastic model to investigate the effects of control strategies on calves exposed to *Ostertagia ostertagi*

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**SUMMARY**

Predicting the effectiveness of parasite control strategies requires accounting for the responses of individual hosts and the epidemiology of parasite supra- and infra-populations. The first objective was to develop a stochastic model that predicted the parasitological interactions within a group of first season grazing calves challenged by *Ostertagia ostertagi*, by considering phenotypic variation amongst the calves and variation in parasite infra-population. Model behaviour was assessed using variations in parasite supra-population and calf stocking rate. The model showed the initial pasture infection level to have little impact on parasitological output traits, such as worm burdens and FEC, or overall performance of calves, whereas increasing stocking rate had a disproportionately large effect on both parasitological and performance traits. Model predictions were compared with published data taken from experiments on common control strategies, such as reducing stocking rates, the ‘dose and move’ strategy and strategic treatment with anthelmintic at specific times. Model predictions showed in most cases reasonable agreement with observations, supporting model robustness. The stochastic model developed is flexible, with the potential to predict the consequences of other nematode control strategies, such as targeted selective treatments on groups of grazing calves.

Key words: calves, nematodes, management, *Ostertagia ostertagi*, parasite control, phenotypic variation, simulation, mathematical model.

**INTRODUCTION**

Gastrointestinal parasitism of calves, in particular with *Ostertagia ostertagi*, is a significant challenge to their health, welfare and productivity. As such, a variety of control strategies have been proposed to reduce the negative effects of parasitism (Cockroft, 2015). These include the Weybridge ‘dose and move’ strategy, a reduction in stocking rate and dosing at strategic time points of the grazing season (Michel and Lancaster, 1970; Hansen et al. 1989; Cockroft, 2015). More recently, targeted selective treatment, where specific individuals of a population as opposed to the whole population are treated, has been suggested as an alternative control strategy (Höglund et al. 2013a; O’Saughnessy et al. 2015).

Quantifying the effectiveness of such strategies is both time consuming and expensive, and in many respects it is difficult, if not impossible to make comparisons between them due to confounding variables (Höglund, 2010). Simulation modelling is a potential alternative to experimental and, provided that a model is based on sound principles and data, it has the potential to evaluate different approaches to control. In order to be able to assess the effectiveness of such control strategies, a stochastic (i.e. probabilistic, population-based) model allowing for individual-response differences is required. This is because individuals will affect parasite epidemiology and subsequently influence the effectiveness of control. Stochastic models (Renshaw, 1991) can help to evaluate such strategies, by simulating identical scenarios allowing a direct comparison of treatment effectiveness, and to identify potential interactions, thereby aiding in the assessment of the feasibility of novel control strategies. Currently, we are not aware of published simulation models that allow us to account for variation between individual calves within a group and variation in parasite supra population, i.e. parasite populations at all development stages across all hosts.

The aim of this paper was to develop a stochastic simulation model that was capable of accounting for such variation and can be utilized in future studies of parasite control strategies. The stochastic model was based on the deterministic approach previously developed by Berk et al. (2016). The deterministic model is able to account for the interactions between gastrointestinal parasites and an individual calf to predict parasite infra-populations, i.e. populations within individual hosts. By introducing variation in
growth and resistance traits amongst calves, along with an epidemiological-transmission layer, we aimed to develop a model which considers O. ostertagi-calf interactions along with their epidemiological consequences. Following model development, its behaviour was evaluated under simple manipulations such as variations in stocking rate and larval pasture contamination (PC). Finally, the model was validated against the prevailing management control strategies, such as reduced stocking rate, the ‘dose and move’ strategy and strategic anthelmintic drenching.

MATERIALS AND METHODS

A previously developed dynamic, deterministic model (Berk et al. 2016) to describe the interactions between gastrointestinal parasites and an individual calf, was extended to a stochastic one for a grazing population/herd of calves. A brief description of the individual calf model is given below, followed by a more detailed description of the additional features incorporated towards the development of a grazing population model. Abbreviations used throughout the paper are defined below and provided in Appendix Table A1.

**Individual calf model**

A schematic diagram representing the model interactions for an individual calf infected by O. ostertagi is provided in Fig. 1. Briefly, it was assumed that a healthy calf attempts to ingest sufficient nutrients to meet demands for growth and maintenance (Coop and Kyriazakis, 1999). In the presence of parasitic infection, a parasitized calf experiences an endogenous protein loss (Fox, 1993). Consequently, the calf is assumed to invest in an immune response to reduce the impact of infection (Claerebout and Vercruysse, 2000). However, despite the endogenous protein loss and the increased resource requirement for the development of immunity, a reduction in feed intake occurs as a result of immune components, e.g. cytokines and related pathological and inflammatory responses (Fox et al. 1989; Kyriazakis, 2014). This reduction was modelled as a function of the rate of acquisition of immunity (Laurenson et al. 2011). Consequently, the calf consumes insufficient food resources to fulfil its requirements. Ingested protein, after the loss due to parasitism, was assumed to be first allocated to maintenance and repair requirements (Coop and Kyriazakis, 1999). Remaining food resources were then allocated between growth and immunity, proportional to their requirements (Kahn et al. 2000; Doeschl-Wilson et al. 2008; Laurenson et al. 2011). Such requirements were defined in accordance to Vagenas et al. (2007).

**Herd population model**

In contrast to previously published models (Vagenas et al. 2007; Doeschl-Wilson et al. 2008; Laurenson et al. 2012), between-animal variation was only modelled at the phenotypic level, for the sake of simplicity. Phenotypic variation was assumed to occur in animal growth characteristics, maintenance requirements and host immunity to gastrointestinal parasitism.

**Fig. 1. Schematic description of the parasite–host interactions.** The rectangular boxes and solid lines indicate the flow of ingested feed resources; the oval boxes indicate the host–parasite interactions and the hexagonal boxes represent the key measurable stages of the parasite life cycle. Host immune response and related pathological and inflammatory responses were assumed to lead to parasite-induced anorexia (broken line).
Table 1. Calf traits for which phenotypic variation between individuals was assumed to occur within the model, with corresponding parameter values for their mean and coefficient of variation (CV).

| Category       | Parameter (units) | Description                                      | Mean      | CV       |
|----------------|-------------------|--------------------------------------------------|-----------|----------|
| Growth         | $P_M$ (kg)        | Mature protein content                           | 106       | 0·125    |
|                | LRRM$_M$ (kg)     | Mature lipid to protein ratio                     | 1·95      | 0·15     |
|                | $B^*$ (day$^{-1}$) | Protein growth rate constant                      | 0·025     | 0·15     |
|                | EBW$_i$ (kg)      | Initial empty body weight                         | 255       | 0·15     |
| Maintenance    | PR$_{maint}$      | Coefficient for protein maintenance requirements  | 0·004     | 0·15     |
|                | ER$_{maint}$      | Coefficient for lipid maintenance requirements    | 1·63      | 0·15     |
| Immunity       | $EM_{max}$ (day$^{-1}$) | Max. combined establishment/mortality         | 0·82      | 0·1      |
|                | $EM_{min}$ (day$^{-1}$) | Min. combined establishment/mortality      | 0·08      | 0·1      |
|                | $\mu_{max}$ (day$^{-1}$) | Max. mortality                                   | 0·12      | 0·2      |
|                | $\mu_{min}$ (day$^{-1}$) | Min. mortality                                   | 0·01      | 0·1      |
|                | $F_{max}$ (egg/female/day) | Max. fecundity                             | 39        | 0·3      |
|                | $F_{min}$ (egg/female/day) | Min. fecundity                             | 6         | 0·1      |
|                | $k_{EM}$          | Rate change parameter for establishment/mortality | $-2·7 \times 10^{-8}$ | 0·01 |
|                | $k_{mu}$          | Rate change parameter for mortality             | $4 \times 10^{6}$ | 0·01 |
|                | $k_{F}$           | Rate change parameter for fecundity             | $-2·9 \times 10^{-7}$ | 0·01 |

See the text for sources of parameter values.

Variation in growth characteristics. A growing calf was described by its empty bodyweight at weaning ($EBW$), protein mass at maturity ($P_M$), a growth rate parameter ($B^*$) and the lipid-to-protein ratio at maturity ($LPR_M$). These parameters were selected to minimize correlation to one another, hence preventing problems that would arise from correlated parameters for stochastic simulations (Symeou et al. 2016). Growth was assumed to be driven by protein and lipid retention, with expected growth rates described by adaptations of existing functions (Emmans, 1997; Emmans and Kyriazakis, 1997), such that:

$$\Delta P_{Growth_{max}} = P \cdot \left( \frac{B^*}{P_M^{27}} \right) \cdot \ln \left( \frac{P_M}{P} \right)$$

(1)

$$\Delta Lipid_{d_{LS}} = \Delta P_{Growth_{max}} \cdot LPR_M \cdot d \cdot \left( \frac{\Delta P}{P_M} \right)^{d-1}$$

(2)

where $\Delta P_{Growth_{max}}$ is the expected rate of protein retention (kg day$^{-1}$), $\Delta Lipid_{d_{LS}}$ is the expected rate of lipid retention (kg day$^{-1}$), $P$ is the current body protein mass (kg), and $d = 1·46 \cdot LPR_M^{27}$. Thus, differences in initial $EBW$ ($EBW_i$), $P_M$, $B^*$ and $LPR_M$ can result in between-animal variation in initial body weight, growth rate, mature body composition and mature body weight. As such, these input parameters were assumed to vary phenotypically and are given in Table 1.

Variation in host immunity. The immune response was represented by the host-controlled traits of parasite establishment, mortality ($\mu$, proportion of adult worms/day) and fecundity ($F$, eggs/female/day). Establishment was determined by subtracting the effect of mortality from the combined effect of establishment and mortality ($EM$, change in adult worm numbers/day). The functions used to describe these traits were characterized in Berk et al. (2016) as:

$$EM = (EM_{max} - EM_{min}) \cdot \exp\left( -k_{EM} \cdot LD \right) + EM_{min}$$

(5)

$$\mu = \frac{(\mu_{max} - \mu_{min}) \cdot (LD)^2}{k_{mu} + (LD)^2} + \mu_{min}$$

(6)

$$F = (F_{max} - F_{min}) \cdot \exp(-k_{F} \cdot LD) + F_{min}$$

(7)

where $LD$ is the larval days as a measure of parasite exposure; $EM_{max}$, $\mu_{max}$ and $F_{max}$ are the maxima of...
the combined effect of establishment and mortality, mortality and fecundity, respectively; $EM_{\min}, \mu_{\min}$ and $F_{\max}$ are the minima of the combined effect of establishment and mortality, mortality and fecundity, respectively; $k_{EM}$, $k_{\mu}$ and $k_F$ are the rate constants of the relationships between larval days and the combined effect of establishment and mortality, mortality and fecundity, respectively.

The calves were assumed to be initially naïve to gastrointestinal parasites and gradually acquired immunity as calf exposure to infective larvae increased. The rate of immune acquisition was therefore determined by the length of temporal exposure to infective larvae and the rate parameters $k_{EM}$, $k_{\mu}$ and $k_F$, for each of the host-controlled immunity traits. All parameters describing the maxima, minima and rate of acquisition for each of the host-controlled immunity traits were assumed to exhibit between animal variations.

**Variation in feed intake.** In addition to variation in the specified traits, a degree of random variation was assumed to reflect the influence of external factors controlling variation in day to day feed intake that were not explicitly accounted for by the model. Due to the correlation between growth and feed intake tending towards unity in this model, daily random deviation in feed intake was adjusted to give a more realistic phenotypic correlation between feed intake and growth rate of approximately 0.8 (Cammack et al. 2005; Laurenson et al. 2012).

**Parameter values and distributions.** The model was parameterized such that the calf and its growth represented a weaned, castrated male (steer) Limousin × Holstein Friesian born in autumn; this common cross currently represents the majority of beef cattle reared in the UK (Todd et al. 2011). Autumn born calves are capable of utilizing grass in spring and hence are turned out at 6 months of age and left at pasture until late autumn (Phillips, 2010). Parasitological parameters were based on those gathered from published literature (Berk et al. 2016). Each trait selected to be phenotypically variable was assigned a population mean and coefficient of variation (CV) as provided in Table 1 based on several sources. The immune development traits were assumed to follow a log-normal distribution, whereas all other traits were assumed to be normally distributed (Vagenas et al. 2007; Laurenson et al. 2012). Over recent years calves have been selectively bred to show favourable traits, such as growth rate (Prakash, 2009). However, immune traits are rather more difficult to select for (Frisch, 1981; Prakash, 2009). Log-normal distributions were assigned to the immune rate parameters to allow for higher levels of variation (several-fold increase or decrease) without the negative values that could arise from utilizing a normal distribution for these parameters. For the growth attributes the mean values were taken as presented by Berk et al. (2016) and CVs based on estimates for other ruminants (Vagenas et al. 2007; Laurenson et al. 2012). Similarly, the mean value of immune traits were taken as presented by Berk et al. (2016) and, owing to a lack of data to provide confident estimates, CVs were based on values for lambs infected with the closely related parasite *Teladorsagia circumcincta* (Laurenson et al. 2012).

All traits, other than those representing the host immune response, were assumed to be uncorrelated (Doeschl-Wilson et al. 2008). However, the acquisition of immunity was assumed to be a function of overlapping effector mechanisms (components of the Th2 immune response; Mihi et al. 2014). Thus, the rate-determining parameters ($k_{EM}$, $k_{\mu}$, $k_F$) were assumed to be strongly correlated (coefficient of correlation $r = +0.5$) (Laurenson et al. 2012). Establishment was calculated as the combined effect of establishment and mortality minus the effect of mortality alone, as such predictions for establishment and mortality were correlated. In order to counteract this, a negative correlation ($r = -0.2$) was applied to the parameters describing the maximum effect of combined establishment and mortality and the minimum mortality. For correlated traits a Cholesky decomposition of the variance–covariance matrix was used to generate the co-variances between the phenotypic input parameters of the individual animals.

**Epidemiological module**

To simulate natural infection of calves in the herd, it was necessary to consider external environmental conditions, including the epidemiology of free-living parasite stages. Many aspects of parasite epidemiology are affected by environmental conditions, in particular temperature and moisture (Stromberg, 1997). Temperature was considered to have the most prominent effect as described below, and moisture was assumed non-limiting under UK conditions. The potential effects of other environmental factors, such as moisture or UV light, were not considered (Stromberg, 1997).

**Grass quantity and quality.** The total grazing pasture available to the calf herd was defined in hectares ($H$, ha). The initial quantity of grass per hectare ($GPH_0$) was defined as 2500 kg DM ha$^{-1}$ in accordance with English Beef and Lamb Executive (EBLEX) Grazing Planning (2013) and an even grass coverage was assumed. As such, the initial quantity of grass available for grazing ($G_0$, kg DM) was calculated as:

$$G_0 = GPH_0 \cdot H$$

(8)
Each day ($t$), the total grass available for grazing ($G_t$, kg DM) was updated to take into account the grass consumed by the calf population and new grass growth. Thus, $G_t$ was estimated in accordance with Laurenson et al. (2012):

$$ G_t = G_{t-1} - \sum FI_{t-1} + (GG \cdot H) \quad (9) $$

where $\sum FI$ is the total feed intake for all simulated calves, and $GG$ is daily grass growth (kg DM ha$^{-1}$) which was estimated for the relevant grazing period using the average grass growth per day for each month reported by EBLEX (2013). $GG$ ranged from 30 to 60 kg DM ha$^{-1}$ over the 180 day simulated grazing season.

A reasonably consistent relationship between calendar month and quality of grass has been reported (Trouw Nutrition, 2010; AHDB, 2013). Consequently, the crude protein ($CP$, g kg$^{-1}$ DM) and metabolizable energy ($ME$, MJ kg$^{-1}$ DM) content of grass were time-dependent according to data obtained from fields grazed by cattle in the UK (Woodward et al. 1938; Dale et al. 2012). As such, over the simulated grazing period of 180 days, $CP$ ranged from 165 to 199 g kg$^{-1}$ DM, and $ME$ ranged from 11.2 to 12.0 MJ kg$^{-1}$ DM.

**Pasture contamination.** A given number of overwintered infective $L_3$ larvae were assumed to be resident on pasture and comprise the initial $L_3$ larval population on pasture ($LP_0$) as calculated:

$$ LP_0 = IL_0 \cdot G_0 \quad (10) $$

On subsequent days a small number of additional larvae were assumed to become resident on pasture as a result of the maturation and migration of a low level of overwintering eggs, $L_1$ and $L_2$ (Bairden et al. 1995; Urquhart et al. 1996). This was modelled as an exponential decay function (Pandey, 1972; Myers and Taylor, 1989), such that the infective $L_3$ larvae arising daily from an initial underlying $L_3$ larval population on pasture ($IL_0$) was estimated as:

$$ IL_t = 0.05 \exp(-0.05t) \cdot IL_0 \quad (11) $$

For simplicity, the assumption was made that there is a constant relationship between the initial $L_1$ contamination and subsequent development of $L_3$ from overwinter eggs, $L_1$ and $L_2$ larvae. However, this consideration was only made prior to the appearance of infective $L_3$ larvae arising from eggs deposited by the calf population. The time to earliest appearance of egg-producing adult female worms within the host population, and hence eggs deposited onto pasture, was assumed to be 17 days (Williams et al. 1974). The proportion of eggs that develop into infective $L_3$ larvae was assumed to be 0.15 (Young and Anderson, 1981). The number of days taken for the eggs to reach the infective $L_3$ stage, and the mortality rate of infective $L_3$ larvae, were assumed to be temperature dependent (Pandey, 1972; Smith et al. 1986).

To model temperature-dependent effects over the simulated grazing season, the mean of the average monthly temperatures observed by the UK Meteorological Office over a 3-year period (2010–2012) were used. A fourth-order interpolating polynomial was fitted to the average monthly temperatures to produce a 6-months temperature curve (Emmanouil et al. 2006), such that the maximum temperature ($Temp$, °C) on day $t$ was given by:

$$ Temp_t = 0.0000000013t^4 - 0.0000077t^3 $$

$$ + 0.00067t^2 + 0.084t + 6.3 \quad (12) $$

As such, over the simulated grazing period of 180 days, $Temp$ ranged from 7.8 to 15.4 °C.

An exponential relationship was fitted between paired data describing temperature and development time ($DT$), i.e. number of days taken to develop from egg to an infective $L_3$ larva on pasture (Rose, 1961). As a result, the mean development time of eggs deposited on day $t$, $DT$ (days, rounded to the nearest integer), was assumed to be dependent on $Temp$:

$$ DT_t = 146 \cdot e^{-0.189 \cdot Temp_t} + 2.92 \quad (13) $$

The stochastic nature of development time was represented as a uniform distribution (mean = $DT$, days, range = ±4 days), over whole day increments (Rose, 1961). As such, $DT$ ranged from 7 to 40 days over the simulated grazing period. Thus, the number of new infective $L_3$ larvae ($newIL$) arising from eggs previously deposited by the calf population was calculated from a convolution of egg deposition and egg maturation time distributions:

$$ newIL_t = \left( \sum_{i=0}^{t} U[0 \leq DT_i \leq PEI \cdot E_t] \right) \quad (14) $$

where $U[\sim]$ is a uniform probability distribution centred at zero with a range of −4 to +4 days, and $t$ is the current day, $i$ any previous day (from 0 to current day), $E_t$ the total egg output of the calf population on day $t$, $DT_i$ the mean development time for eggs deposited on day $i$, and $PEI$ the proportion of eggs that develop into infective $L_3$ larvae. $U$ has a value of ~11% probability of maturing on day $DT$ after deposition on pasture, and on the 4 days previous and following day $DT$.

The relationship between $Temp$ and the larval mortality rate ($L_3M$, proportion of infective $L_3$...
larvae dead day$^{-1}$) was defined using data from Young and Anderson (1981) for the temperature ranges observed in the UK. A linear relationship was assumed (Grenfell et al. 1986), such that $L_3 M$ on day $t$ was given as:

$$L_3 M = 0.0014 \cdot Temp_t + 0.018$$ (15)

Over the simulated grazing period, $L_3 M$ ranged from 0.029 to 0.040 (Young and Anderson, 1981).

Consequently, the total infective $L_3$ larval population on pasture ($LP_t$) at the start of day $t$ was given as:

$$LP_t = \left( LP_{t-1} - \sum LLI_{t-1} \right) \cdot (1 - L3M_t)$$

$$+ (LLI_t \cdot H), \text{ when } newIL_t = 0$$ (16)

$$LP_t = \left( LP_{t-1} - \sum LLI_{t-1} \right) \cdot (1 - L3M_t)$$

$$+ newIL_t, \text{ when } newIL_t > 0$$ (17)

where $LLI$ is the total larval intake of the calf population.

Larval intake. Calves were assumed to graze randomly across pasture. However, the spatial distribution of the larvae across the pasture was assumed to be aggregated (Boag et al. 1989; Grenfell et al. 1995; Verschave et al. 2015). A negative binomial probability distribution was used with the mean being mean larval contamination of pasture ($L_3$ km$^{-1}$ DM) and the exponent describing the degree of aggregation $k = 1.41$ (Verschave et al. 2015).

Hence, the larval intake ($LLI$, infective $L_3$ larvae) of an individual calf was determined by its feed intake ($FI$, kg DM) and by sampling the pasture according to the negative binomial distribution, such that:

$$LLI_t = FI_t \cdot NB \left( \frac{LP_t}{G_t}, k \right)$$ (18)

where $LP_t / G_t$ ($L_3$ larvae km$^{-1}$ day$^{-1}$) is the mean number of $L_3$ larvae per ha grazed on day $t$.

Simulations

The modelled herd comprised 500 calves generated using a stochastic Monte-Carlo simulation, created in MATLAB (2015). For the model inputs defined in Table 1, this population size resulted in a maximum relative s.e. of 1.34% (estimated for $F_{max}$), which was considered sufficiently large given that further increases in population size showed no further reduction in s.e.

Model behaviour. Model behaviour was evaluated by simulating a selection of $IL_0$ levels and stocking rates. To investigate model behaviour under differing $IL_0$ levels (0, 100, 200 or 500 $O. ostertagi$ $L_3$ kg$^{-1}$ DM), the grazing area was set to 100 ha to represent a conventional stocking rate of 5 calves ha$^{-1}$ (EBLEX, 2013). To investigate model behaviour under differing stocking rates, $IL_0$ was set to 200 $O. ostertagi$ $L_3$ kg$^{-1}$ DM, and the grazing area adjusted for low (3 calves ha$^{-1}$), conventional (5 calves ha$^{-1}$) and high (7 calves ha$^{-1}$) stocking rates, as defined by EBLEX (2013). In all cases, calves were assumed to be parasitologically naïve when turned out in early April for 180 days. Model outputs were calculated on a daily basis and presented as the population mean for: (1) parasite worm burden (WB, worms); (2) faecal egg count (FEC, eggs g$^{-1}$ feces); (3) feed intake ($FI$, kg DM); (4) relative reduction in calf bodyweight gain (BWG, kg) (comparative to a non-parasitized healthy calf); and (5) pasture larval contamination (PC, $L_3$ larvae kg$^{-1}$ DM).

Model validation (control strategies). To validate model outputs, predictions were compared with observations made in experimental studies investigating the impact of a variety of nematode control strategies (stocking rates, ‘dose and move’ and strategic anthelmintic treatment). Where possible, experimental observations were compared with the population mean for the following model outputs: (1) FEC (eggs g$^{-1}$ feces); (2) feed intake ($FI$, kg DM); (3) relative reduction in calf bodyweight gain (BWG, kg); and (4) pasture larval contamination (PC, $L_3$ larvae kg$^{-1}$ DM). Where observed percentages of $O. ostertagi$ present in relation to other parasites were recorded, direct quantitative comparisons were made. In cases where parasite species differentiation was not made the total numbers of strongyle eggs or pasture larval counts were used to provide a qualitative validation.

Experimental studies from available literature were selected for comparison on criteria stated in Appendix Table A2. A thorough literature review identified the following eight studies that met the specified criteria and were therefore used to validate model predictions for: (1) stocking rate (Nansen et al. 1988; Jacobs et al. 1989; Fisher and Jacobs, 1995; Taylor et al. 1995; Verscruysse et al. 1995; Satrija et al. 1996; Sarkūnas et al. 1999); and (3) dose and move (Michel and Lancaster, 1970). Initial model input values were taken from each study and included: (1) the initial larval contamination ($L_3$ kg$^{-1}$ DM); (2) calf stocking rate; (3) day of turnout; and (4) experimental treatment strategy. For cases where calves received unplanned supplementary feed or emergency anthelmintic treatments part way during the experimental period, measurements taken beyond these points were not included. The actions taken to ensure that the simulations were comparable with experimental observations are below.

Growth rates. The model required $P_M$ and $B^*$ as inputs. All studies meeting the criteria described
above were performed a number of years ago and hence it was necessary to account for changes that may have occurred in these traits as a result of selective breeding. This was done according to the method detailed in Berk et al. (2016). It was assumed that calf body composition has remained the same with no direct selection for lean cattle, but rather for heavier mature weights (Emmans and Kyriazakis, 2001; Hays and Preston, 2012).

Following this, the mean of parameter $B^*$ (Table 1) was adjusted such that model outputs reflected the growth rates observed for un-infected calves in each study. In the absence of un-infected experimental control groups, calves under a strategic ivermectin treatment were assumed to reflect the growth rate of un-infected calves. For example, in Michel and Lancaster (1970) calves receiving repeated anthelmintic treatments were assumed to reflect growth rates of un-infected calves.

**Epidemiological components.** To account for the variations in turnout date, the date of turnout was used as an input for each experiment. This allowed for seasonal factors such as grass growth, grass quality and temperature-dependent effects to be adjusted accordingly.

**Mixed Cooperia infections.** It was necessary to consider mixed infections of *O. ostertagi* and *Cooperia* due to limitations in the published literature for model validation. Such infections have been observed to cause a greater depression in growth than mono-specific infections (Kloosterman et al. 1984; Satrija and Nansen, 1993). It is widely recognized that although in a single *O. ostertagi* infection any protein loss can be reabsorbed in the small intestine, in a mixed infection the presence of *Cooperia* in the small intestine hinders the reabsorption process (Fox, 1993; Holmes, 1993). Thus, parameters describing the protein loss associated with both larval and worm mass were increased by 10% (Kloosterman et al. 1984).

**Control via stocking rate.** The constant population size of 500 calves was used for all simulations. As such, the total grazing area ($H$, ha) was adjusted to match the differing stocking rates of each experimental study. In the experimental study of Nansen et al. (1988), which investigated two stocking rates, a mid-season rotation was incorporated whereby half of the calves were moved to clean pastures, thus halving the stocking rate on current pasture. To account for this, $H$ was doubled at the appropriate time-point. Further, to simulate calves that moved to a clean pasture the same parameters were defined; however, at the time of the mid-season rotation when $H$ was increased, the $PC$ was also reset to 10 $L_3$ kg$^{-1}$ DM as representative of a ‘clean’ pasture.

**Control via dose and move.** During the period for which Michel and Lancaster (1970) conducted their study, ivermectin was not available and thiabendazole was the drug of choice; the efficacy of this drug is likely to have been high at the time of this experiment and hence an efficacy of 0·99 and no residual activity (Prichard et al. 1981) were assumed. Following anthelmintic drenching, calves were immediately moved to a ‘cleaner’ pasture by re-setting the grass available for grazing ($G_t$) to 2500 kg DM ha$^{-1}$ (EBLEX, 2013) and $PC$ to 50 $L_3$ kg$^{-1}$ DM (with no resident egg, $L_1$ or $L_2$ population).

**Control via strategic anthelmintic treatment.** Although there are no universal guidelines for strategic anthelmintic dosing, the recommended timings for administration of ivermectin are 3, 8 and 13 weeks post-turnout in order to minimize worm egg output until mid-July, when most over-wintered larvae have died (Cockroft, 2015). Ivermectin, the most widely used anthelmintic, was assumed to have an efficacy of 0·99 against *O. ostertagi* with residual activity for three weeks (NOAH, 2015). Following this period of residual efficacy against *O. ostertagi*, ivermectin efficacy was assumed to decrease by 0·15 per day. This was parameterized such that model predictions for $FEC$ and $PC$ exhibited similar patterns to those observed in ivermectin treated calves (Vercruysse et al. 1988). Ivermectin was assumed to be equally effective against all worm and larval stages residing within the host.

**RESULTS**

**Model behaviour**

**Frequency distribution of output traits.** Output performance traits were normally distributed at all times. For example, the means (and s.d.) for body weight were 363 (32·7), 429 (41·5), 487 (51·5) and 534 (60·4) kg at 40, 80, 120 and 160 days post-turnout, respectively, for calves grazing clean pasture at a conventional stocking density (5 calves ha$^{-1}$). In contrast, although parasitological inputs were normally or log-normally distributed, the frequency distribution of predicted $WB$ and $FEC$ became increasingly right-skewed over time, as demonstrated for $FEC$ in Fig. 2.

**Increasing initial contamination ($IL_0$)**

**Parasitological traits.** The population mean of $WB$ and $FEC$ for $IL_0$ levels of 100, 200 and 500 $L_3$ kg$^{-1}$ DM are given in Fig. 3A and B. Whilst increasing $IL_0$ caused minor changes in the maximum predicted $WB$, the timing of peak $WB$ was predicted to decrease with increasing $IL_0$. The maximum mean $WB$ (and day of peak) for $IL_0$ levels of 100, 200 and 500 $L_3$ kg$^{-1}$ DM were 37159 (114), 37772...
Pasture contamination. Predictions for PC (L₃ kg⁻¹ DM) are given in Fig. 4E. Initially, similar patterns were observed for all IL₀ with PC decreasing up until day 52 when PC began to increase towards a peak. Increasing IL₀ resulted in an earlier peak, however, the maximum predicted PC did not relate directly to IL₀. The intermediate IL₀ of 200 L₃ kg⁻¹ DM showed the lowest peak PC. The maximum predicted PC (and day of maximum) for IL₀ levels of 100, 200 and 500 L₃ kg⁻¹ DM were 903 (116), 825 (82) and 901 (77) L₃ kg⁻¹ DM, respectively. Upon reaching the peak, PC then declined to similar levels, irrespective of IL₀.

Stocking rate

Parasitological traits. The population mean for WB and FEC for three stocking rates are given in Fig. 4A and B. Calf stocking rates had no effect on WB until day 78, at which point WB increased with increasing stocking rates as a reflection of patterns in PC. Higher stocking rates resulted in increased maximum WB. The maximum WB (and day of peak) for low, conventional and high stocking rates were 20749 (110), 37772 (109) and 61508 (109), respectively. Maximum FEC was similar for all stocking rates as was the day of FEC peak. The maximum FEC (and day of maximum) for low, conventional and high stocking rates were 48 (44), 48 (43) and 48 (38), respectively. A second peak in FEC was observed for conventional and high stocking rates; the second peak (and day of peak) for conventional and high stocking rates were at 38 (94) and 44 (90), respectively.

Performance traits. The population mean for FI and relative reduction in BWG are given in Fig. 3C and D. Increasing IL₀ resulted in an increased maximum reduction and earlier achievement of maximum reduction in FI, and a faster rate of recovery towards the FI of an uninfected calf. Across the duration of the grazing season the average FI for control calves on clean pasture was 7.64 kg DM day⁻¹; the average relative reductions were 5% for all IL₀ levels. Consistent with the predicted patterns for FI, reductions in BWG were greater for higher IL₀ in the early stages of infection; however, in the latter stages the magnitude of differences between IL₀ became negligible. The average relative reductions in average daily BWG across the season were 0.12, 0.12 and 0.10 kg day⁻¹ for IL₀ levels of 100, 200 and 500 L₃ kg⁻¹ DM, respectively.

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stocking rates resulted in an increased maximum PC. The maximum predicted PC (and day of maximum) for low, conventional and high stocking rates were 409 (82), 825 (82) and 1722 (108) L₃ kg⁻¹ DM, respectively. It was therefore observed that IL₀ did not affect performance or infestation significantly.

**Validation**

The following sections detail model outputs for the validation simulations.

**Stocking rates.** Graphical comparisons of FEC between the model and the experiments conducted by Nansen et al. (1988) are provided in Fig. 5A–D. In general, model predictions showed similar patterns to the observed data. FEC increased steadily to a peak and then began to decline, with the exception of observations made on calves kept at high stocking rates on the same pasture (Fig. 5C), for which a high FEC was observed at the final measurement. The majority of data were close to the predicted population mean, and all observations except one were between the estimated lower and upper extreme values of the modelled population.

A graphical comparison for observed and predicted levels of PC is provided in Fig. 5E–H. For calves remaining on the same pasture throughout the study (Fig. 5E and G), the model predicted PC to increase to a peak and then decline. A slight dip was predicted on day 60 when the stocking rate was halved. For the calves moved to clean pasture on day 60 post-turnout (Fig. 5F and H), the model predicted an increase in PC up until day 60 when PC was reset to low levels; after which PC increased to a peak then slowly declined. For both comparisons of PC, a more pronounced effect was seen at the higher stocking rate. Although there was some lack of consistency in the patterns of observed values the model predictions appear to show a reasonable likeness to individual observed points upon graphical comparison, with the exception of the final measurements taken for calves remaining on the same pasture for both stocking rates; the latter appears to be an outlier among the other observations.

**Dose and move.** A graphical comparison of PC was made for the three dose and move experiments conducted in successive years (Michel and Lancaster, 1970). For calves remaining on the same pasture (Fig. 6A, C and E) similar patterns were seen for observed and predicted outputs with an increase in PC up to a peak followed by a decline. The calves moved mid-July (Fig. 6B, D and F) showed a reduced contamination from the move date with only a small increase in PC on the new pasture.

**Strategic dosing.** Graphical comparisons of FEC for each of the six previously identified strategic anthelmintic dosing studies are presented in Fig. 7A–F. Predicted FEC in the untreated groups were
Fig. 5. Comparison of experimental observations (●) of Nansen et al. (1988) to simulated mean prediction (-) for fecal egg count (FEC, eggs g\(^{-1}\) feces) (A–D) and pasture contamination (L3 kg\(^{-1}\) DM grass) (E–H), along with the lower and upper extreme values (…) for individuals within the simulated population. Calves were kept at a moderate stocking rate (11·7 calves ha\(^{-1}\)) for the first half of the grazing season, and on day 60, split into two equal groups (5·8 calves ha\(^{-1}\)) and either: (A) remained on the same pasture or (B) moved to a cleaner pasture (10 L3 kg\(^{-1}\) DM grass). This was repeated for a high stocking rate (17·5 calves ha\(^{-1}\)), and on day 60, groups of calves (8·8 calves ha\(^{-1}\)) either: (C) remained on the same pasture or (D) moved to a cleaner pasture (10 L3 kg\(^{-1}\) DM grass).

Fig. 4. The mean parasitological and performance traits for 500 calves grazing pasture initially contaminated with 200 *Ostertagia ostertagi* L3 kg\(^{-1}\) DM grass, and kept at stocking rates of either 3, 5 or 7 calves ha\(^{-1}\). The parasitological traits provided are: (A) mean worm burden, and (B) mean fecal egg count (eggs g\(^{-1}\) feces) for the population. The performance traits provided are: (C) mean feed intake (kg DM) and (D) mean relative body weight gain (kg) in relation to the un-infected calf population. The epidemiological trait provided is: (E) pasture larval contamination (L3 kg\(^{-1}\) DM grass). The group of untreated calves showed no differences in feed intake and growth due to the assumption of optimal grass availability at the start of the grazing season.

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similar to observed FEC. Observed FEC increased as time progressed, and in studies conducted for a sufficient time period (>150 days) FEC reached a peak and began to decline (Jacobs et al. 1989; Taylor et al. 1995; Satrija et al. 1996) although rebounded later. Model predictions were consistently similar to observations made for the ivermectin treated groups (Fig. 7G–L) which showed low FEC across time, with the exception of data from Fisher and Jacobs (1995). For all comparisons, the majority of data were close to the predicted population mean for FEC, falling between the estimated lower and upper extreme values for individuals of the modelled population. Additional graphical comparisons were made for PC for five of the studies; a graphical comparison for untreated calves is given in Fig. 8A–E, both observed and predicted patterns showed initially an increase in PC as time progressed. Congruent with FEC, PC also reached a peak and began to decline (Taylor et al. 1995). However, this was not supported by Satrija et al. (1996), where predictions diverged from observed PC from day 100. For the graphical comparisons of ivermectin treated groups (Fig. 8F–J), all observations and predictions showed a low level of PC, with the exception of Satrija et al. (1996) where a notable increase in PC was observed at the latter stages of the experiment.

DISCUSSION

A stochastic model was developed to account for the impacts of variation between calves in their ability to deal with O. ostertagi, under management conditions that have the potential to affect parasite infra- and supra-populations. Previous comparable studies where calves received the same, or similar, levels of parasite challenge indicated disparities in the immune response exhibited by individuals (Michel, 1969; Michel and Sinclair, 1969). A recent meta-analysis on O. ostertagi infections of calves (Verschave et al. 2014) found large variations between studies when predicting immune responses. Thus, introducing such variation in simulation models is necessary, as individuals affect parasite epidemiology and can influence the effectiveness of controls. This cannot be captured by models that assume that all individuals within a group are alike and deal with an ‘average’ animal, as is the case for deterministic models (Smith and Guerrero, 1993; Grenfell et al. 1995; Fox et al. 2013).

Stochastic models enable to address uncertainty and variability in the various factors believed to be important in the behaviour of the system, which in this case comprises the cattle herd, the parasites and their environment. The major issues explored here was variation within the herd and how the distribution of parameter values could affect herd performance and parasitological outputs. The mean characteristics of the system reflect complex interactions of the model parameters, which were defined as probabilistic distributions rather than fixed values. Beyond the mean characteristics, the model also predicted the expected range of outcomes for FEC, such as those shown in Figs 5 and 7. For the purposes of comparability, the simulations presented here were
performed on a fixed number of calves \((n = 500)\) while stocking density values were set by specifying different values for the grazing area; hence, it was possible to compare directly the predicted averages and extremes. It would be possible to model smaller, more typical, herd sizes, but in this case would be necessary to perform multiple simulations to obtain a proper statistical description of herd characteristics. The emphasis in this work has been on describing variation within the calf population, but the approach can be extended to capture uncertainties in other factors. For example, the historical average temperature profile used here could be replaced by a stochastic representation; multiple simulations over time would then give insights into the range of possible outcomes.

Converting our deterministic model into a stochastic one presented us with two major challenges. The first one was to introduce variation between the individuals of a herd. Values that enable parameterization of the variation between individual calves in growth characteristics exist or at least can be deduced (Ferreira et al. 1999; Laurenson et al. 2011; Mc Hugh et al. 2011). This, however, is not
the case for traits that are associated with the ability of hosts to deal with the parasite. For this reason, we resorted to values that have been assumed for sheep (Vagenas et al. 2007; Laurenson et al. 2011). As there is an increased requirement for characterizing animals for a number of phenotypic and genetic traits (Goddard and Hayes, 2009), the hope is that animal breeders will provide such information for health-related traits, in a manner already done for other animals, such as for resistance to mastitis in dairy cattle (Gernand et al. 2012).

The second challenge was to introduce an epidemiological component to the model. Previous attempts to quantify free-living stages of *O. ostertagi* have become increasingly complex (Gettinby and Paton, 1981; Grenfell et al. 1987; Smith et al. 1987a; Chaparro et al. 2013; Rose et al. 2015). As our focus was on host–parasite interactions we kept this aspect relatively simple. Moisture was assumed to be a non-limiting factor, although in reality rainfall and moisture levels may have a notable effect on aspects of parasite epidemiology (Young and Anderson, 1981). However, the net impact on PC levels can be considered to be small due to counteracting mechanisms. For example, heavy rainfall increases larval mortality and accelerates the passage of larvae from pasture downward into the soil reservoir (Al Saqur et al. 1982; Gruner et al. 1982; Grenfell et al. 1986), whilst increased moisture helps the transmission of larvae from fecal pats to herbage by translocation and by splash dispersal (Grunvold and Hög-Schmidt, 1989; Stromberg, 1997). Only temperature was accounted for in the model, as being the most influential climatological feature on PC levels (Stromberg, 1997). Development time (*DT*) for eggs to reach infective *L_3* larvae was dependent on the average daily temperature on the day of excretion alone. A cumulative measure of temperature was not used due to the non-linear relationship between temperature and development, and daily fluctuations in temperature. The sensitivity of the average *DT* to temperature was tested by adding random variation (CV = 0.5) in temperature; however, there was little to no impact on the outputs generated suggesting this to be a fair assumption.

Additionally, demographic stochasticity was incorporated into the model in the form of variation in feed intake and random aggregated distribution of
larvae in the pasture. Random variation in calf feed intake impacts on calf growth and the larval intake of an individual, whilst aggregated variation in pasture larvae will influence the larval intake of an individual. Seasonal effects are perceived to impact upon the levels of larval aggregation across pasture; this is an almost ubiquitous feature of parasitic infections due to weather-dependent dispersal patterns of L3 larvae from fecal pats. It has previously been observed that significant aggregation was only apparent during particular months, with the level of aggregation correlating to larval numbers (Flota-Bañuelos et al. 2013). High PC related to low aggregation and low PC to high aggregation (Flota-Bañuelos et al. 2013; Verschave et al. 2015).

Although mitigating factors, such as passive dispersal or fecal avoidance behaviours (Hutchings et al. 2007) are recognized, an aggregated pasture is still expected (Grenfell et al. 1995) and accounted for. The negative binomial is known to provide a good empirical relationship for this overdispersion (Barger, 1987; Boag et al. 1989; Fox et al. 2013); however, to avoid model complexity the level of aggregation (k) was assumed the same for all contamination levels.

Contrary to horizontal aggregation, distribution of larvae along the sward was assumed to be evenly distributed. Due to factors such as distance of larvae from the feces, seasonal variations and vertical migration of larvae, modelling the vertical distribution would be incredibly complex (Pandey, 1974). Often greater proportions of larvae are found lower on herbage; this may have implications for calves kept at high stocking rates where calves graze closer to the base of the sward. An exaggerated increase in larval uptake can be observed relative to lower stocking rates (Gruner and Sauvé, 1982), inducing a more rapid immune acquisition.

An investigation of model behaviour highlighted the importance of interactions between immune acquisition and epidemiology. Parasitological burdens of those individuals that exhibited a slow immune acquisition and epidemiology. Parasitological burdens of those individuals that exhibited a slow immune acquisition began to recover earlier than might be expected due to the effect of immunocompetent calves within the herd, which produced fewer eggs, acting to reduce PC levels. Increasing levels of initial pasture contamination (IL0) resulted in earlier peaks in PC and parasitological outputs (WB and FEC) arising from higher parasitic exposure and hence a more rapid immune acquisition. Differences between peak values were marginal due to assumed density-dependent effects on parasite fecundity (Michel et al. 1978; Smith et al. 1987b) and the mid-summer rise in PC. The faster immune acquisition by calves exposed to high IL0 enabled them to counteract the mid-summer rise in L1 in comparison to a lower IL0. This is supported by the hypothesis that turnout date, ultimately defining the degree of immune acquisition prior to the mid-summer rise in PC, is perhaps more important than IL0 (Eysker, 1986; Höglund et al. 2013b; Taylor et al. 2015). The final PC and net impact of parasitism on performance was similar for all IL0 levels; this is in line with a meta-analysis which suggested the relationship between weight gain and IL0 was insignificant (Shaw et al. 1998b). However, this is not to say IL0 levels are not important to consider. When accompanied by different control strategies the IL0 will likely have an impact on parasitological and performance outcomes.

Changes in stocking rate had comparatively greater parasitological and performance effects than changes in IL0. The effect is generally inconsequential early in the season due to high grass growth and low PC; however as the season progresses grass growth subsides and a mid-summer rise in PC occurs (Henriksen et al. 1976; Nansen et al. 1988).

At high stocking rates, the intensity of hosts results in lower grass availability and increased total egg excretion, causing a more dramatic rise in PC. Consequently, the peak parasitological outputs increased with increased stocking rate, as observed experimentally (Hansen et al. 1989; Thamsborg et al. 1998). There was a significant difference predicted in the final net performance of calves kept at each stocking rate. Since it was assumed that pasture availability was non-limiting, this was purely a result of infection. This was in line with experimental work showing significant reductions in mean weight gains for conventional and high stocking rates comparative with a low stocking rate (Hansen et al. 1989; Thamsborg et al. 1998). Although experimentally it is difficult to ascertain whether these losses resulted from parasitism or a lack of grass availability, Nansen et al. (1988) concluded that parasitism was the major cause of poor performance at high stocking rates. The model predicted a reduction in BWGs of between 5 and 16%; interestingly meta-analyses conducted on a variety of breeds have shown average reduction in BWG of 5-4% (Shaw et al. 1997) and 22-7% (Shaw et al. 1998a) for sub-clinical infections. Although breed may affect observed reductions, it should also be noted these may be slightly larger as a result of concurrent Cooperia infections; this is discussed later.

To validate the model, the most common control strategies aiming to reduce the parasitic challenge and burden were identified; these included reduced stocking rate and the Weybridge ‘dose and move’ technique (Michel and Lancaster, 1970). ‘Dose and move’ incorporates a planned move coinciding with an anticipated peak in PC, generally mid-July for most of the UK (Smith, 2014). It has previously proved to be a successful control strategy (Michel and Lancaster, 1970; Henriksen et al. 1976; Nansen et al. 1989; Eysker et al. 1998). However, lack of pasture availability has made it increasingly difficult to implement low stocking rates and ‘dose
and move’ strategies (Herd, 1988; Shaw et al. 1997). The ‘dose and move’ strategy is also believed to accelerate the development of anthelmintic resistance by removing refugia on pasture (van Wyk, 2001). As a result, strategic anthelmintic dosing at specific time points has become critical to maintaining calf health. The objective is to prevent the build-up of PC by limiting fecal egg output during the early part of the grazing season (Vercruysse and Claerebout, 1997). This is achieved by strategic treatment with anthelmintics, which has been observed to be effective against parasitic gastroenteritis for a full season, under conditions where the parasitic challenge is large enough to induce severe parasitic gastroenteritis in controls (Hollanders et al. 1992; Vercruysse et al. 1995).

Previous quantitative evaluation of the deterministic model on which the current stochastic one was based, revealed the former model as reasonably proficient at estimating mean parasitological traits. This places a degree of confidence on the current model, provided that its sources of stochastic variation have been estimated accurately. Based on comparing observed and predicted FEC for the current, stochastic model in order to estimate parameter values for calf variation and parasite epidemiology, the model appeared to be proficient at estimating observed outputs under the specified scenarios. In cases where discrepancies between predicted and observed FEC were observed, contributory factors were identified. Some studies did not distinguish between parasite genera, stating only that O. ostertagi were the most prevalent species, whilst in others calves were treated with anthelmintics on clinical grounds following the final measurements used for validation suggesting disease may have been border-line clinical at the time of measurements.

Additional comparisons were made between observed and predicted values for average PC; in most cases the predictions provided a good fit, however a few discrepancies were apparent. As previously mentioned, the aggregated nature of PC is likely to influence the sampling of PC; if sufficient repeated measures are not taken then under or overestimation of the PC level may occur (Verschave et al. 2015). Upon sampling PC some experimenters have opted to consciously avoid fecal pats, where the highest concentrations of larvae exist: this may have resulted in an under estimation of observed PC (Henriksen et al. 1976; Nansen et al. 1988). Poor grass growth causes a higher concentration of larvae on pasture (Vercruysse et al. 1995) and, as for FEC, the lack of distinction between parasite genera may also result in discrepancies between observed and predicted PC. A clear example comes from Satrija et al. (1996) whereby PC switches from predominantly O. ostertagi to predominantly Cooperia in August; from this point onwards the model does not predict PC well.

Should these factors not account for the differences observed in predicted PC it may be a result of a model oversimplification. These may result in inaccurate predictions made on PC which in turn would affect the larval intake due to the self-proliferating nature of the relationships defined in the model. If this is the case, explanations for why FEC still provide a good fit must be considered, implying that the within-host relationships may over or under compensate for these differences.

Monospecific and concurrent artificial infections of O. ostertagi and Cooperia suggested an absence of inter-species interactions (Kloosterman et al. 1984; Satrija and Nansen, 1993; Hilderson et al. 1995). Concurrent infections did, however, show greater than additive FEC in comparison with the two monospecific infections (Kloosterman et al. 1984; Satrija and Nansen, 1993; Hilderson et al. 1995), thought to be a consequence of enhanced pathological effects (Parkins et al. 1990). This has been suggested to reflect the fact that Cooperia increases the rate of protein loss leading to a reduced growth rate and growth requirements. Slower growth will be accompanied by lower feed intake, which will have a concentration effect on FEC due to lower output of feces (Parkins et al. 1990). This is supported by reduced pepsinogen levels, reflecting abomasal damage (Parkins et al. 1990), and almost doubled plasma losses for concurrent infections comparative to monospecific O. ostertagi infections (Kloosterman et al. 1984; Parkins and Holmes, 1989). To account for a mixed infection the most comprehensive method would be to create a model component for predicting the effects of Cooperia on the host, and determine species interactions. Although some data exists on artificial Cooperia infections as has been summarized by Verschave et al. (2016), there is very limited data on artificial mixed infections and hence it would be difficult to decipher species interactions for a full range of infection levels.

The development of a stochastic model to account for host–parasite interactions opens up a number of opportunities for future developments. Firstly, it enables the effectiveness of different control strategies to be assessed, including targeted selective treatments where specific individuals of a population are treated, as opposed to the whole population (Höglund et al. 2013a; O’Shaughnessy et al. 2015). This method has been advocated as a potential way to reduce parasite resistance to anthelmintics, but hard, non-confounded data to support this does not exist (Höglund, 2010). Introduction of potential parasite resistance mechanisms would allow for such refugia-based strategies to be assessed for effectiveness and sustainability over short- and long-term periods; this would provide a useful tool considering the challenges of experimentally investigating long-term effects. Further to this, the addition of second
grazing season (SGS) calves would allow exploration of the impact of different control strategies on the immune acquisition of SGS calves and effects of hypobiosis. The model is also flexible enough to allow the investigation into the consequences of breeding for parasite resistance through the addition of a genetic component. Although breeding of resistant cattle stock would prove challenging (Kloosterman et al. 1978) there is large potential for genetic progress, more so than sheep (Kloosterman et al. 1992).

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REFERENCES

Agriculture and Horticulture Development Board (AHDB) (2013). Technical Article: Season Overview. Agriculture & Horticulture Development Board, UK. http://dairy.ahdb.org.uk/news/technical-articles-archive/december-2013/season-overview/#.VZ5LZPIViko.

Al Saqur, I., Armour, J., Bairden, K., Dunn, A. M., Jennings, F. W. and Murray, M. (2013). Exploring the assumptions underlying genetic variation in host nematode resistance. Genetics Selection Evolution 45, 294-306.

Barker, P. J., Corden, A. D. and Murray, M. (2008). Exploring the assumptions underlying genetic variation in host nematode resistance. Genetics Selection Evolution 40, 241-264.

Emmanouil, G., Galanis, G. and Kallos, G. (2006). Statistical methods for the prediction of night-time cooling and minimum temperature. Meteorological Applications 13, 169.

Emmans, G. C. (1997). A method to predict the food intake of domestic animals from birth to maturity as a function of time. Journal of Theoretical Biology 186, 189–200.

Emmans, G. C. and Kyriazakis, I. (1997). Models of pig growth: problems and proposed solutions. Livestock Production Science 51, 119–129.

Emmans, G. C. and Kyriazakis, I. (2001). Consequences of genetic change in farm animals on food intake and feeding behaviour. Proceedings of the Nutrition Society 60, 115–125.

English Beef and Lamb Executive (EBLEX) (2013). Planning Grazing Strategies for Better Returns. EBLEX, UK. http://www.eblex.org.uk/wp/wp-content/uploads/2013/06/Manual-8-Planning-grazing-strategies_200313.pdf.

Eysker, M. (1986). The prophylactic effect of ivermectin treatment of calves, three weeks after turnout, on gastro-intestinal helminthiasis. Veterinary Parasitology 22, 95-103.

Eysker, M., van der Aar, W. M., Boersema, J. H., Dop, P. Y. and Kooyman, F. N. (1998). The efficacy of Michèle’s dose and move system on gastrointestinal nematode infections in dairy calves. Veterinary Parasitology 75, 99–114.

Ferrira, E. B., MacNeil, M. D. and Van Vleck, L. D. (1999). Variance components and breeding values for growth traits from different statistical models. Journal of Animal Science 77, 2641–2650.

Fisher, M. and Jacobs, D. (1995). Evaluation of doramectin in a programme for season-long control of parasitic gastroenteritis in calves. Veterinary Record 137, 281–284.

Flota-Bañuelos, C., Martínez, I., López-Collado, J., Vargas Mendoza, M., González Hernández, H. and Fajersson, P. (2013). Spatio-temporal pattern of larvae and eggs of gastrointestinal nematodes in cattle pastures in veracruz, mexico. Revista De Biología Tropical 61, 1747–1758.

Fox, M. T. (1993). Pathophysiology of infection with Osterotaga ostertagi in cattle. Veterinary Parasitology 46, 143–158.

Fox, M. T., Gerrelli, D., Pitt, S. R., Jacobs, D. E., Gill, M. and Gale, D. L. (1989). Osterotaga ostertagi infection in the calf: effects of a triazole challenge on appetite, digestibility, rate of passage of digesta and live-weight gain. Research in Veterinary Science 47, 294–298.

Fox, N. J., Marion, G., Davidson, R. S., White, P. C. L. and Hutchings, M. R. (2013). Modelling parasite transmission in a grazing system: the importance of host behaviour and immunity. Parasites & Vectors 6, 279.

Frish, J. E. (1981). Changes occurring in cattle as a consequence of selection for growth rate in a stressful environment. Journal of Agricultural Science 96, 23.

Gernand, E., Rebbein, P., von Borstel, U. U. and König, S. (2012). Incidences of and genetic parameters for mastitis, claw disorders, and common health traits recorded in dairy cattle contract herds. Journal of Dairy Science 95, 2144–2156.

Gettinby, G. and Paton, G. (1981). The role of temperature and other factors in predicting the pattern of bovine Osterotagia spp. infective larvae on pasture. Journal of Thermal Biology 6, 395–402.

Goddard, M. E. and Hayes, B. J. (2009). Mapping genes for complex traits in domestic animals and their use in breeding programmes. Nature Reviews Genetics 10, 381–390.

Grenfell, B. T., Smith, G. and Anderson, R. M. (1986). Maximum-likehood estimates of the mortality and migration rates of the infective larvae of Osterotaga ostertagi and Cooperia oncophora. Parasitology 92, 643–652.

Grenfell, B. T., Smith, G. and Anderson, R. M. (1987). A mathematical model of the population biology of Osterotaga ostertagi in calves and yearlings. Parasitology 95, 389–406.

Grenfell, B. T., Wilson, K., Isham, V. S., Boyd, H. E. G. and Dietz, K. (1995). Modelling patterns of parasite aggregation in natural populations: trichostrongyloid nematode-ruminant interactions as a case study. Parasitology 111, 135–151.

Grenvold, J. and Hegg-Schmidt, K. (1989). Factors influencing rain splash dispersal of infective larvae of Osterotaga ostertagi (Trichostrongyliidae) from cow pats to the surroundings. Veterinary Parasitology 31, 57–70.

Gruner, L., Mauleon, H. and Sauge, C. (1982). Migrations of trichostrongyloid infective larvae: experiments with ovine parasites in soil. Annals of Veterinary Research 13, 51–59.

Gruner, L. and Sauge, C. (1982). The distribution of trichostrongyli infective larvae on pasture and grazing behaviour in calves. Veterinary Parasitology 11, 203–211.

Hansen, J. W., Zajac, A. M., Eversole, D. E. and Gerken, H. J. (1989). The effect of stocking rate and parasite control on the performance of replacement beef heifers on pasture. Veterinary Parasitology 34, 103–115.

Hays, W. V. and Preston, R. L. (2012). Nutrition and feeding management to alter carcass composition of pigs and cattle. In Low-fat Meats: Design Strategies and Human Implications (ed. Hats, H. D. and Zinkelman, R. G.), pp. 13–33. Academic Press, London, UK.
Parasitology

Henniksen, S., Jørgensen, R. and Nansen, P. (1976). Ostertagiasis in calves. I. The effect of control measures on infection levels and body weight gains during the grazing season in Denmark. Veterinary Parasitology 2, 259–272.

Herd, R. (1988). Control strategies for ostertagiasis. Veterinary Parasitology 27, 111–123.

Hilderson, H., Vercruysse, J., Claerebout, E., De Graaf, D. C., Fransen, J. and Berghen, F. P. (1995). Interactions between Ostertagia ostertagi and Cooperia oncophora in calves. Veterinary Parasitology 56, 107–119.

Höglund, J. (2010). Parasite surveillance and novel use of anthelmintics in cattle. Acta Veterinaria Scandinavica 52, 825.

Högland, J., Dahlström, F., Sollenberg, S. and Hesse, A. (2013a). Weight gain-based targeted selective treatments (TST) of gastrointestinal nematodes in first-season grazing cattle. Veterinary Parasitology 196, 358–365.

Högland, J., Hesse, A. and Dahlström, F. (2013b). Calving season is a stronger determinant of worm burdens in pasture-based beef production than the level of residual larval contamination at turnout. Veterinary Parasitology 196, 362–365.

Hollander, W., Berghen, P., Dorny, P., Hilderson, H., Vercruysse, J. and Ryan, W. G. (2009). Genetic variation among calves in resistance to nematode parasites. Genetics and Molecular Research 8, 307–315.

Hutcheson, M. R., Knowler, K. J., Mcanulty, R. and Mcewan, J. C. (2014). Interactions between Ostertagia ostertagi and Cooperia oncophora in calves. Veterinary Parasitology 196, 362–365.

Hutchings, M. R., Knowler, K. J., Mcanulty, R. and Mcewan, J. C. (2015). Parasite surveillance and novel use of anthelmintics in cattle. Acta Veterinaria Scandinavica 52, 825.

Höglund, J., Dahlström, F., Sollenberg, S. and Hesse, A. (2013a). Weight gain-based targeted selective treatments (TST) of gastrointestinal nematodes in first-season grazing cattle. Veterinary Parasitology 196, 358–365.

Högland, J., Hesse, A. and Dahlström, F. (2013b). Calving season is a stronger determinant of worm burdens in pasture-based beef production than the level of residual larval contamination at turnout. Veterinary Parasitology 196, 358–365.

Hollanders, W., Berghen, P., Dorny, P., Hilderson, H., Vercruysse, J. and Ryan, W. G. (2009). Genetic variation among calves in resistance to nematode parasites. Genetics and Molecular Research 8, 307–315.

Hutcheson, M. R., Knowler, K. J., Mcanulty, R. and Mcewan, J. C. (2014). Interactions between Ostertagia ostertagi and Cooperia oncophora in calves. Veterinary Parasitology 196, 362–365.

Höglund, J., Dahlström, F., Sollenberg, S. and Hesse, A. (2013a). Weight gain-based targeted selective treatments (TST) of gastrointestinal nematodes in first-season grazing cattle. Veterinary Parasitology 196, 358–365.

Claerebout, E. and Geldhof, P. (2014). Analysis of the mucosal immune responses induced by single and trickle infections with the bovine abomasal nematode Ostertagia ostertagi. Parasite Immunology 36, 150–156.

Myers, G. H. and Taylor, R. F. (1989). Ostertagiasis in cattle. Journal of Veterinary Diagnostic Investigation 1, 195–200.

Nansen, P., Foldager, J., Hansen, J. W., Henniksen, S. A. and Jørgensen, R. J. (1988). Grazing pressure and acquisition of Ostertagia ostertagi in calves. Veterinary Parasitology 27, 325–335.

Nansen, P., Grunvolt, J., Jørgensen, R. J., Henniksen, S. A., Foldager, J. and Jeysen, R. (1989). Outbreak of early-season trichostrongylosis in calves in Denmark. Veterinary Parasitology 32, 199–211.

National Office of Animal Health (NOAH) (2015). http://www.noahcompendium.co.uk/merial_animal_health_ltd/ivomec_classic_injection_for_cattle_and/sheep/646181.html.

O’Shaughnessy, J., Earley, B., Mee, J. F., Doberty, M. L., Crosson, P., Barrett, D. and de Waal, T. (2015). Nematode control in suckler beef cattle over their first two grazing seasons using a targeted selective treatment approach. Irish Veterinary Journal 68, 13.

Padyak, V. S. (1972). Effect of the season of turnout on survival of the free-living stages of Ostertagia ostertagi. Journal of Parasitology 58, 1042–1046.

Pandey, V. S. (1974). Ecological observations on the free-living stages of Ostertagia ostertagi. Annales de Recherches Viticoles 5, 261–279.

Parkins, J. J. and Holmes, P. H. (1989). Effects of gastrointestinal helminth parasites on ruminant nutrition. Nutrition Research Reviews 2, 227–246.

Parkins, J. J., Taylor, L. M., Holmes, P. H., Bairden, K., Salmon, S. K. and Armour, J. (1990). Pathophysiological and pathological studies of a concurrent infection of Ostertagia ostertagi and Cooperia oncophora in calves. Research in Veterinary Science 48, 201–208.

Phillips, C. J. C. (2010). Principles of Cattle Production, 2nd Edn. CABI, Cambridge, UK.

Prakash, M. (2009). Introduction to Veterinary Genetics, 1st Edn. Discovery Publishing House Pvt. Ltd., New Delhi.

Pritchard, R. K., Steel, J. W. and Henssey, D. R. (1981). Fenbendazole and thiabendazole in cattle: partial of gastrointestinal absorption and pharmacokinetic behaviour. Journal of Veterinary Pharmacology and Therapeutics 4, 295–304.

Renshaw, E. (1991). Modelling Biological Populations in Space and Time, 1st Edn. Cambridge University Press, Cambridge, UK.

Rose, H., Wang, T., Van Dijk, J. and Morgan, E. R. (2015). GLOWORM-FL: a simulation model of the effects of climate and climate change on the free-living stages of gastro-intestinal nematode parasites of ruminants. Journal of Veterinary Pharmacology and Therapeutics 4, 295–304.

Sarkunias, M., Malakaukas, A., Nansen, P., Hansen, J. W. and Paulikas, V. (1999). Effect of protective treatments with ivermectin on parasitism of set-stocked calves exposed to natural trichostrongyle infection in Lithuania. Acta Veterinaria Scandinavica 40, 163–171.

Satrija, F. and Nansen, P. (1993). Experimental concurrent infections with Ostertagia ostertagi and Cooperia oncophora in the cattle. Research in Veterinary Science 55, 92–97.

Satrija, F., Nansen, P. and Jorgensen, R. (1996). The effects of first-season strategic and tactical ivermectin treatments on trichostrongylosis in the first-and second-season grazing. Veterinary Parasitology 64, 219–237.

Shaw, D. J., Vercruysse, J., Claerebout, E., Agneessens, J. and Dorny, P. (1997). Gastrointestinal nematode infections of first-season grazing calves in Belgium: general patterns and the effect of chemophylaxis. Veterinary Parasitology 69, 103–116.

Shaw, D. J., Vercruysse, J., Claerebout, E. and Dorny, P. (1998a). Gastrointestinal nematode infections of first-grazing season calves in Western Europe: general patterns and the effect of chemophylaxis. Veterinary Parasitology 75, 115–131.

Shaw, D. J., Vercruysse, J., Claerebout, E. and Dorny, P. (1998b). Gastrointestinal nematode infections of first-grazing season calves in Western Europe: associations between pathological, physiological and pathological factors. Veterinary Parasitology 75, 131–153.

Smith, B. P. (2014). Large Animal Internal Medicine, 5th Edn. Mosby Inc., Elsievier Health Sciences, Missouri, USA.

Smith, G. and Guerrero, J. (1993). Mathematical models for the population biology of Ostertagia ostertagi and the significance of aggregated parasite distributions. Veterinary Parasitology 46, 243–257.

Smith, G., Grenfell, B. T. and Anderson, R. M. (1986). The development and mortality of the non-infective free-living stages of Ostertagia ostertagi in the field and in laboratory culture. Parasitology 92, 471–482.

Smith, G., Grenfell, B. T., Anderson, R. M. and Beddington, J. (1987a). Population biology of Ostertagia ostertagi and anthelmintic strategies against ostertagiasis in calves. Parasitology 95, 407–420.
Smith, G., Grenfell, B. T. and Anderson, R. M. (1986). The regulation of Ostertagia ostertagi populations in calves: density-dependent control of fecundity. *Parasitology* 95, 373–388.

Stromberg, B. E. (1997). Environmental factors influencing transmission. *Veterinary Parasitology* 72, 247–264.

Symeou, V., Leinonen, I. and Kyriazakis, I. (2016). Quantifying the consequences of nutritional strategies aimed at decreasing phosphorus excretion from pig populations: a modelling approach. *Animal* 10, 578–591.

Taylor, M. A., Coop, R. L. and Wall, L. (2015). *Veterinary Parasitology*. 4th Edn. John Wiley & Sons, Chichester, UK.

Taylor, S. M., Mallon, T. R., Kenny, J. and Edgar, H. (1995). A comparison of early and mid grazing season suppressive anthelmintic treatments for first year grazing calves and their effects on natural and experimental infection during the second year. *Veterinary Parasitology* 56, 75–90.

Thamsborg, S. M., Jørgensen, B. J. and Nansen, P. (1998). Internal parasitism of steers grazing at different stocking rates. *Acta Agricultura Scandinavica* 39, 311–323.

Todd, D. L., Wooliams, J. A. and Roughsedge, T. (2011). Gene flow in a national cross-breeding beef population. *Animal* 5, 1874–1886.

Trouw Nutrition (2010). *Trouw Nutrition Insight: Milk Yield from Grazing Update 2010*. Frank Wright Trouw Nutrition International, UK.

Urquhart, G. M., Armour, J., Duncan, J. L., Dunn, A. M. and Jennings, F. W. (1996). *Veterinary Parasitology*. 2nd Edn. Blackwell Publishing, Oxford, UK.

Vagenas, D., Doeschl-Wilson, A., Bishop, S. C. and Kyriazakis, I. (2007). In silico exploration of the effects of host genotype and nutrition on the genetic parameters of lambs challenged with gastrointestinal parasites. *International Journal for Parasitology* 37, 1617–1630.

Van Wyk, J. A. (2001). Refugia – overlooked as perhaps the most important factor concerning the development of anthelmintic resistance. *Veterinary Research* 38, 55–67.

Vercruysse, J. and Claerebout, E. (1997). Immunity development against *Ostertagia ostertagi* and other gastrointestinal nematodes in cattle. *Veterinary Parasitology* 72, 309–326.

Vercruysse, J., Hilderson, H., Dorny, P. and Berghen, P. (1988). Efficacy of early season anthelmintic treatment against gastrointestinal nematodes. *Veterinary Quarterly* 10, 225–229.

Vercruysse, J., Hilderson, H. and Claerebout, E. (1995). Effect of chemoprophylaxis with avermectins on the immune response to gastrointestinal nematodes in first-season grazing calves. *Veterinary Parasitology* 58, 35–48.

Verschave, S. H., Vercruysse, J., Claerebout, E., Rose, H., Morgan, E. R. and Charlier, J. (2014). The parasitic phase of *Ostertagia ostertagi*: quantification of the main life history traits through systematic review and meta-analysis. *International Journal for Parasitology* 44, 1091–1104.

Verschave, S. H., Levecke, B., Duchateau, L., Vercruysse, J. and Charlier, J. (2015). Measuring larval nematode contamination on cattle pastures: comparing two herbage sampling methods. *Veterinary Parasitology* 210, 159–166.

Verschave, S. H., Rose, H., Morgan, E. R., Claerebout, E., Vercruysse, J. and Charlier, J. (2016). Modelling *Cooperia oncophora*: quantification of key parameters in the parasitic phase. *Veterinary Parasitology* 223, 111–114.

Williams, J. C., Roberts, E. D. and Todd, J. M. (1974). *Ostertagia ostertagi*: establishment of patent infections in calves by intravenous inoculation. *International Journal for Parasitology* 4, 55–61.

Woodward, T. E., Shepherd, J. B. and Hein, M. A. (1938). The *Hohenheim System in the Management of Permanent Pastures for Dairy Cattle*, Volumes 651–729. United States Department of Agriculture, USA.

Young, R. and Anderson, N. (1981). The ecology of the free-living stages of *Ostertagia ostertagi* in a winter rainfall region. *Australian Journal of Agricultural Research* 32, 371–388.

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**APPENDIX**

**Table A1.** A table of common abbreviations used throughout the text

| Abbreviation | Definition |
|--------------|------------|
| BW           | Bodyweight |
| BWG          | Bodyweight gain |
| DM           | Dry matter |
| EBW          | Empty bodyweight |
| FEC          | Fecal egg count |
| FI           | Feed intake |
| H            | Hectares |
| IL           | Initial pasture contamination |
| LI           | Larval intake |
| PC           | Pasture contamination |
| WB           | Worm burden |

**Table A2.** A list of the required criteria that were achieved by experimental studies in order for them to be appropriate for use in validating the model

| Criteria | Description |
|----------|-------------|
| 1        | The only available feed was grass |
| 2        | The experiment was conducted on calves grazing in spring months and maintained in a temperate environment |
| 3        | All calves were infected during the growing phase |
| 4        | No calves had exposure to parasites prior to the experiment (i.e. first grazing season calves) |
| 5        | Infections were either single *O. ostertagi* or mixed with *Cooperia* spp. (due to the lack of single species *O. ostertagi* infections in literature it was necessary to consider mixed infections; the consequences of *Cooperia* infections were accounted for as described in the main text) |
| 6        | Any dosing with ivermectin was administered at the recommended dose of 200 µg kg⁻¹ by subcutaneous injection |
| 7        | Any dosing with thiabendazole was administered orally at the recommended dose of 200 mg kg⁻¹ |

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