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Novel epidemiological model of gastrointestinal nematode infection to assess grazing cattle resilience by integrating host growth, parasite, grass and environmental dynamics

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ABSTRACT

Gastrointestinal nematode (GIN) infections are ubiquitous and often cause morbidity and reduced performance in livestock. Emerging anthelmintic resistance and increasing change in climate patterns require evaluation of alternatives to traditional treatment and management practices. Mathematical models of parasite transmission between hosts and the environment have contributed towards the design of appropriate control strategies in ruminants, but have yet to account for relationships between climate, infection pressure, immunity, resources, and growth. Here, we develop a new epidemiological model of GIN transmission in a herd of grazing cattle, including host tolerance (body weight and feed intake), parasite burden and acquisition of immunity, together with weather-dependent development of parasite free-living stages, and the influence of grass availability on parasite transmission. Dynamic host, parasite and environmental factors drive a variable rate of transmission. Using literature sources, the model was parametrised for *Ostertagia ostertagi*, the prevailing pathogenic GIN in grazing cattle populations in temperate climates. Model outputs were validated on published empirical studies from first season grazing cattle in northern Europe. These results show satisfactory qualitative and quantitative performance of the model; they also indicate the model may approximate the dynamics of grazing systems under co-infection by *O. ostertagi* and *Cooperia oncophora*, a second GIN species common in cattle. In addition, model behaviour was explored under illustrative anthelmintic treatment strategies, considering impacts on parasitological and performance variables. The model has potential for extension to explore altered infection dynamics as a result of management and climate change, and to optimise treatment strategies accordingly. As the first known mechanistic model to combine parasitic and free-living stages of GIN with host feed-intake and growth, it is well suited to predict complex system responses under non-stationary conditions. We discuss the implications, limitations and extensions of the model, and its potential to assist in the development of sustainable parasite control strategies.

1. Introduction

Gastrointestinal nematode (GIN) infections have significant health, welfare and economic impacts in cattle and other grazing livestock species, often through the occurrence of sub-clinical disease (Armour, 1980; Fox, 1993; Charlier et al., 2020b). The dominant GINs of cattle in temperate climates are *Ostertagia ostertagi* and *Cooperia oncophora*, which cause parasitic gastroenteritis primarily in first grazing season (FGS) cattle (Michel, 1969; Forbes, 2020). The use of anthelmintic treatments remains a first line practice to safeguard the health and growth performance of grazing livestock. However, the sustainability of this practice is threatened by the emergence of anthelmintic resistance in cattle worldwide (Kaplan and Vidyashankar, 2012; Rose Vineer et al., 2020a) requiring alternative parasite control strategies to limit further development of resistance. Further challenges emerge with the increasing pace of climate change, which may affect parasite development, grass availability and host growth; these challenges require further decisions on how to adapt the management practices of grazing livestock (Skuce et al., 2013; Vercruysse et al., 2018). Mathematical models are an important tool for evaluating and comparing alternative treatment and management strategies given the practical difficulties of doing so in experiments (Smith, 2011). Such models

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are useful, for example, for evaluating targeted selective treatments applied to individuals on the basis of parasitological or performance indicators (Höglund et al., 2013; Charlier et al., 2014); and for assessing where the benefits of preserving parasite refugia (van Wyk, 2001; Hodgkinson et al., 2019) are balanced against the risks of reduced health and performance in untreated animals. Achieving these goals requires the availability of models that include the full life cycle of the parasite, as well as the dynamics of immunity, grass availability and consumption, and animal growth.

Models of the full transmission cycle of the most pathogenic GIN in cattle, *O. ostertagi*, have been developed and applied to field data (Grenfell et al., 1987a; Smith and Grenfell, 1994), but while these models have incorporated host and free-living (FL) parasite stages, and host acquired immunity, they have not included host performance traits (Smith, 1997). However, weight gain and feed intake are important variables in the host-parasite interaction and have economic significance due to reduction in gain, especially in young parasitized cattle (Symons, 1985; Bell et al., 1988; Coop and Kyriazakis, 1999). In practice, body weight, as well as parasite eggs in host faeces, can be monitored during grazing to guide the applications of anthelmintic treatment; and affordable technology for routine individual weighing is becoming increasingly available (González-García et al., 2018). Weight and intake have important roles in the system's behaviour and models thereof, not only as output variables but also because they affect parasite epidemiology. First, the rate at which infective larvae are ingested (transmission rate) (Grenfell, 1988) is controlled by the rate of feed intake, of which weight is a main determinant (NRC, 1987); it is also controlled by the density of grass on pasture (Henriksen et al., 1976; Nansen et al., 1988). Second, intake is reduced through parasite-induced anorexia (Bell et al., 1988; Coop and Kyriazakis, 1999). Models that incorporate host performance during infection with *O. ostertagi* have been developed (Berk et al., 2016a), but have not yet been incorporated with a realistic and parameterised model of the parasite FL stages, which has been developed separately (Rose et al., 2015). The aim of our paper is to contribute to the above goals by integrating these system layers, whilst also aiming to focus on fewer host performance variables than the previous models, in the interests of transparent model behaviour and simpler parameterisation.

Here, building on elements from the above models, we propose a dynamic transmission model of the full parasite life cycle, parameterised for *O. ostertagi* in cattle using parameter estimates from literature sources. The model incorporates (i) parasite load, acquired immunity, and weight and feed intake as host variables, (ii) FL parasite stages influenced by local weather and climate, and (iii) variable grass biomass. This model allows investigation of the consequences of parasite control practices on both parasitological and performance variables, while taking into account the variability in weather and seasonality in climate. We tested (validated) model predictions against field data from several studies in northern Europe; these were the only ones we found to satisfy our essential criteria, which require, in particular, experimental trials taking place during the FGS and under natural infection and immunity progression. In addition, we explored the potential of the model to predict the impacts of simplified anthelmintic treatments, leaving the effects of alternative anthelmintic treatments for later consideration. We anticipate there is potential to parameterise the model for other GIN species of grazing ruminants and to explore behaviour under future climate change and at alternative geographic locations. We hypothesise that interactions between growth, grass availability and intake, infection and immunity, and the dynamics of the parasite pasture stages, lead to interpretable non-linear responses in system behaviour, and that these can be explored to enhance the outcomes of treatment interventions. Further, we hypothesise that when calibrated to conditions in published experimental trials in FSG cattle, the model will reproduce observed patterns of animal infection and performance.

2. Materials and methods

2.1. Overview of the full transmission model

The model of GIN transmission in a herd of grazing cattle, including the full life cycle of the parasite, links four sub-models schematised in Fig. 1. In this section notation is defined loosely only to explain this figure. Two sub-models describe the animal host and its interaction with the parasite. First, the host infection and immunity sub-model (Section 2.2) describes host daily ingestion of infective L3s on herbage, L_{3h}, from the current grass G on pasture (determined by the daily grass intake, i.e. feed intake FI, and its contamination L_{3h}/G), the development of parasitic larval stages L (including L4 and L5) into adult worms W that produce eggs excreted onto pasture via the host faeces, E_p, and the development of acquired immunity, I_m, by the host concomitantly with its gradual infection. Second, the host growth sub-model (Section 2.3) describes the bodyweight BW, FI and growth of the host given its genetic propensity for growth, age, current level of infection (since the start of grazing, or turnout onto pasture), and the current immune state and response to the parasite loads L and W. The daily grass intake FI is calculated based on the current BW and maintenance functions; the faecal mass output is the non-digested intake and is used to calculate the current number of parasite eggs excreted per unit mass (faecal egg counts) given the current number of eggs produced by the resident worms.

Two further sub-models describe the grazing environment and the survival of the FL parasite population. First, the grass growth sub-model (Section 2.4) describes the availability of grass G through the grazing season in terms of dry mass per unit area of pasture, balancing grass growth and consumption through gazing by the herd; a net decrease in G will increase the larval concentration on herbage, L_{3h}, and its ingestion. Increases in intake during the host's growth trajectory, as well as parasite-induced anorexia, will also affect L3 ingestion. Second, the FL stages sub-model (Section 2.5) describes the development of parasite stages outside the host, from eggs excreted in host faeces, through intermediate first and second larval stages, L_{12}, that reside within the faeces, and into infective larvae on pasture, which migrate between herbage, L_{3h}, and soil, L_{3s}, and while present on herbage can be ingested through grazing. The development, survival and migration of these life stages depends on daily temperature and rainfall. The dynamics of the full transmission cycle are summarised by the parasite's effective reproduction number, which incorporates magnification or decline in each lifecycle stage through the effects of the weather and host-parasite interaction.

The full transmission model was built by linking the four sub-models and establishing suitable interactions between host, parasite and grass variables, and between the hosts in the herd as they share the FL parasites and the available grass. For tractability, the implementation of the model is deterministic, i.e. each set of input conditions generates a single model prediction. For simplicity, the grazing host population (herd) is characterised by a stocking density per hectare, and the host sub-models are assumed to represent the average state of the animals in the herd; individual demographic stochasticity is not included. The grazing movement and the grass intake and L3 ingestion by the animals are represented in an average sense, assuming spatially-mixed grass consumption and faecal deposition across the pasture; this is a mean-field rather than a spatially-explicit representation of the host-environment interactions. Parasites in all stages are also treated at a population

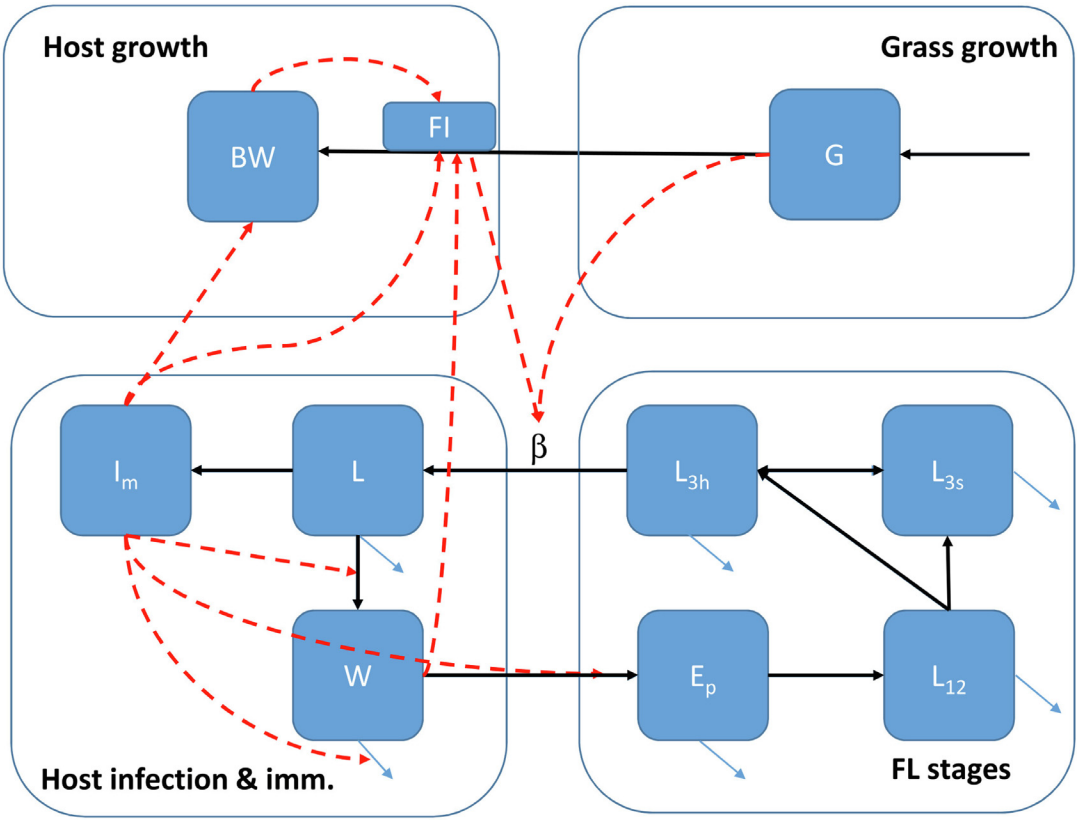

Fig. 1. Structure of the full cycle model of gastrointestinal nematode transmission in cattle. The model comprises four sub-models representing: host growth, grass growth, host infection and the development of immunity (imm.), and the free living (FL) parasite stages. The details of each sub-model are given in the Sections 2.2 to 2.5. Squares, state variables; arrows, flow or transition (black), mortality (blue (light grey)), influence (red (medium grey)). BW, body weight; FI, feed intake; G, grass biomass on pasture; L, parasitic larval stages (including L4 and L5); W, adult worms; I_m, acquired immunity; L_{3h}, L3s on herbage; L_{3s}, L3s in soil; L_{12}, L1 and L2; E_p, parasite eggs on pasture.

mean level. These assumptions are shared by the past mathematical models of GINs in FGS cattle that we have built on, which have similarly focused on *O. ostertagi* (Grenfell et al., 1987a; Rose et al., 2015; Berk et al., 2016a; Rose Vineer et al., 2020a). Each sub-model and supporting literature are described in detail next. All state variables and parameters of the model are described in Tables 1–4.

2.2. Sub-model 1: Host infection and immunity

The model dynamics of host infection are as follows. The influx (J) of infective L3s (L_3) by a grazing animal at a given time (t) during the FGS is given by

$$J = FIDM\, L_{3c} = \beta\, L_{3p}, \tag{1}$$

where FIDM is the animal's rate of dry matter (DM) intake and L_{3c} is the concentration of L3s on grass (distinct from the density of L3s per unit area, L_{3h}; Table 1). The second equality in Eq. (1) is for later use; it involves the rate of transmission per infective larva (β) and the density of L3s on pasture (L_{3p}). In cases where a dose of L3s is inoculated at turnout, as in some of the experimental trials used to validate the model, there is an additional pulse in J at t = 0. Ingested L3s that survive during establishment develop into stage L (number of combined stages L4 and L5 in a host) before developing to dioecious adult worms. This development is represented through n_L mathematical compartments, or phases (L_i, i = 1…n_L), that confer a gamma distribution to its time duration:

$$\frac{dL_1}{dt} = \varepsilon\prime J - \sigma L_1$$

$$\frac{dL_i}{dt} = \varepsilon\prime \sigma L_{i-1} - \sigma L_i (i = 2, \cdots, n_L), \tag{2}$$

with L = L_{nL} and ε' the probability of establishment (Table 1). This gamma distribution (in fact Erlang) is used instead of the common exponential distribution (n_L = 1) in order to ensure that pre-patency does not end prematurely and has the expected duration (Leclerc et al., 2014). The choice n_L = 5 ensures also that the distribution of times is approximately normal. Stages L become adult worms (W) at rate

$$\frac{dW}{dt} = \varepsilon\prime \sigma L - \mu W, \tag{3}$$

The female adult worms in a host produce eggs at a rate (Epd)

$$\frac{dE}{dt} = f_e(I_m, W)\, p_f\, W, \tag{4}$$

where f_e is the effective fecundity rate, which is reduced by the level of acquired immunity (I_m) and by the worm density

$$f_e(I_m, W) = f(I_m)\left(\frac{W_s}{W_s + W}\right)^{0.5}, \tag{5}$$

and where fecundity $f(I_m)$ is constrained by immunity but not by density. We modified the form of this density dependence in relation to (Bishop and Stear, 1997; Berk et al., 2016a) such that f_e = f (I_m) when W is small.

The faecal egg count (FEC) of a host is the egg output per gram of daily wet faecal output

$$FEC = \frac{Epd}{Faeces} = \frac{f_e(I_m, W)\, p_f\, W}{Faeces}, \tag{6}$$

where Faeces (Table 2) is the wet faecal output of a host (calculated in Eq. (22)) expressed as grams/day. FEC observations are usually

Table 1
Host infection and immunity. State variables and parameters defined in sub-model 1 (Section 2.2). State variables are time dependent. Parameters are constant or a function of the immunity level.

Variable	Description	Units		Comments
J	Intake of L3s by a host	larvae/d		Eq. (1)
L_{3c}	L3 concentration on grass	larvae/kgDM [a]		$L_{3c} = L_{3h}/(G/A_g)$ sub-model 3 [a]
L_{3h}	L3 density on herbage	larvae/ha		Sub-model 4
FIDM	Feed intake dry matter (DM)	kgDM/d		Sub-model 2
L_i	Development compartments between L3 and L	-		Number within host, i = 1…n_L
L	Larvae stage pre-adult (fourth and fifth) in a host	-		Number within host (L = L_{nL})
W	Adult worms in host	-		-
E	Cumulative number of eggs produced by adults	-		-
Epd	Eggs produced daily by female worms	eggs/d		-
FEC	Average faecal egg counts	eggs/g		Per daily wet faeces (Eq. (6))
C	Marker of cumulative exposure to L3	-		Unbounded
I_m	Level of acquired immunity of a host	-		Bounded between 0 and 1
Parameter		Units	Value	Source
$\varepsilon(I_m)$	Establishment probability from L3 to adult	-	-	[b], Eq. (7)
ε'	Per-compartment establishment probability of L3	-	$\varepsilon' = \varepsilon\hat{}(1/n_L)$	-
ε_0	Establishment probability of L3 (naïve animal)	-	0.60	[c]
ε_1	Establishment probability of L3 (immune host)	-	0.05	[c]
σ	Development rate of L3	1/d	n_L/T_L	-
T_L	Mean pre-patency	d	32	[d]
n_L	Number of L_i development compartments	-	5	This paper [e]
$\mu(I_m)$	Mortality rate of adult worms	1/d	-	Eq. (7)
μ_0	Mortality rate of adult worms (naïve host)	worms/d	0.025	[c,f,g]
μ_1	Mortality rate of adult worms (immune host)	larvae/d	0.06	[c,h]
p_f	Proportion of female adult worms	-	0.55	[c]
$f_e(I_m,W)$	Effective fecundity rate of female adults worms	eggs/d	-	[i,j]
W_s	Adult worm scale of density dependence	-	15,000	[i,k]
$f(I_m)$	Fecundity rate of worms (no density dependence	eggs/d	-	Eq. (7)
f_0	Fecundity rate of worms (naïve host)	eggs/d	350	[i,l]
f_1	Fecundity rate of worms (immune host)	eggs/d	30	[i,l]
n_f	Exponent relating f to I_m	-	0.2	This paper [m]
$I_m(0)$	Initial level of immunity of host	-	0	FGS, or as stated
C_m	Cum. L3 exposure at ~ 25% of maximum immunity	-	70 k	[c,h]
σ_C	Development rate of C	1/d	n_C/T_C	-
T_C	Mean time of development of C	d	32	See T_L
n_C	Number of C development compartments	-	5	This paper [n]
μ_C	Rate of loss of host immunity	1/d	ln(3)/180	[o]

[a] kgDM, kg dry matter (DM); G, grass dry matter available for grazing at given time; A_g, area of pasture available for grazing.
[b] Includes mortality or arrest at rate (1-ε') σ. Rate of transition to the next compartment: ε' σ.
[c] Verschave et al. (2014).
[d] Assuming the observed 21d (pp. 96–98 in Anderson, 2000; Verschave et al., 2014) corresponds to the 25th percentile of the gamma distributed development time assumed in Eq. (9) with shape parameter n_C.
[e] Text after Eq.(2).
[f] Michel et al. (1973).
[g] Grenfell et al. (1987b).
[h] Smith (1994).
[i] Berk et al. (2016a).
[j] Bishop and Stear (1997).
[k] Michel (1969).
[l] Smith et al. (1987).
[m] Text after Eq.(7).
[n] Text after Eq.(9).
[o] Mapped from an assumption of 70% decay in overall immunity level in 180d (Rose Vineer et al., 2020b).

based on faecal samples taken across the herd or pasture and thus represent an average over the grazing herd.

Three within-host parasite traits, L3 establishment, adult worm mortality, and female worm fecundity, are regulated by the host's immune response (Grenfell et al., 1987b; Smith et al., 1987; Churcher et al., 2006), each of which shifts between two parasite-specific limits as the level of immunity increases (Berk et al., 2016a):

$$\varepsilon(I_m) = \varepsilon_0 + (\varepsilon_1 - \varepsilon_0)\, I_m$$

$$\mu(I_m) = \mu_0 + (\mu_1 - \mu_0)\, I_m\,,$$

$$f(I_m) = \mu_0 + (\mu_1 - \mu_0)\, I_m^{nf}. \qquad (7)$$

We assume that the first two responses develop at equal speed and that the reduction in worm fecundity occurs faster, via the exponent $n_f < 1$ suggested by empirical observations (Smith et al., 1987; Dorny et al., 1997).

The level of acquired immunity is assumed to be bounded between 0 and 1; it is given by a sigmoidal growth function (here a von Bertalanffy-type function) of the cumulative exposure to L3s (C), given by

$$I_m(C) = \left(1 - (1 - I_m(0)) \exp\left(-\frac{C}{C_m}\right)\right)^3, \qquad (8)$$

where $I_m(0)$ is the level of immunity at turnout, from when cumulative exposure is measured. In the FGS we expect $I_m(0) = 0$.

The cumulative exposure C in a host, is a hypothetical memory of antigen stimulation from the incrementally ingested L3s (Smith and Grenfell, 1985); it emerges after a time delay required for the development of acquired effector mechanisms. The dynamics of C are represented in a similar way to the development of the within-host parasite stages,

Table 2
Host growth. State variables and parameters defined in sub-model 2 (Section 2.3). State variables are time dependent or may depend explicitly on other variables, e.g. $p_{dry}(BW)$.

Variable	Description	Units		Comments
BW	Body weight of an infected animal	kg		a,b
dBW/dt	Rate of BW gain per unit time	kg/d		[a]
t	Time (difference a- a_0 in age of animal) since turnout	d		Eq. (10)-(11), Supp. Text S2
FIDDM	Feed intake, digestible dry matter, of an infected animal	kgDM/d [c]		[a,d]
FIDM	Feed intake, dry matter, of an infected animal	kgDM/d		[b,e]
FaecesDM	Faecal output, dry matter	kgDM/d		-
Faeces	Faecal output, wet	kg/d		FaecesDM/DDM
$p_{dry}(BW)$	Proportion of gain that is dry matter at current BW	-		[a]
Wt	Body water content (of the gut-empty body)	kg		a_w eBW^{bw}
eBW	Empty body weight, excludes gut content	kg		p_{empty} BW
D_{maint}	Rate of biomass used for maintenance functions	kgDM/d		[a,d]
$D_{infection}$	Rate of biomass used for infection-related functions	kg/d		-
dIm/dt	Rate of increase in acquired immunity per unit time	1/d		-
A(Im,dW/dt)	Anorexia-induced change in FI in an infected animal	-		[e], <1 or > 1
Parameter		Units	Value	Source
BW_m	Mature body weight of host	kg	variable	[f]
BW_0	Initial BW at age a_0	kg	variable	[f]
b	Rate of host growth or inverse time scale of growth	1/d	variable	[f]
C_{maint}	Rate of biomass used for maintenance functions	$kg^{0.25}$/d	0.03	[g], Supp. Text S1
C_{I1}	Rate of biomass used to increase the immunity level	kg/uI	10	[g], Supp. Text S2
C_{I2}	Rate of biomass used to maintain acquired immunity	kg/uI/d	0.4	[g], Supp. Text S2
C_W	Rate of biomass used to repair damage per adult worm	kg/d	0	This paper [h]
p_{empty}	Proportion of BW that excludes gut content	-	0.91	[i]
a_w	Allometric magnitude of W in relation to eBW	-	1.997	j
b_w	Allometric exponent of W in relation to eBW	-	0.707	[j]
DDM	Apparent digestibility of DM grass	-	0.80	[k]
Exp(q)	Proportion of FI after reduction due to anorexia	-	0.80	[l]
DW_{max}	Scale controlling the nonlinear effect of dW/dt on A	worm/d	4000	Supp. Text S4
pFaecesDM	Proportion of DM in faeces	-	0.15	[m]

[a] Variables with underscore n refers to the naïve (not-yet infected) animal.
[b] In some empirical studies BW dropped at turnout (Balch and Line, 1957), which was included through a temporary drop in feed intake (Supp. Text S5).
[c] kgDM, kg dry matter (DM).
[d] DM: dry matter content. Other content is inclusive of water, if applicable.
[e] FI is limited by gastrointestinal tract (gut) capacity (Supp. Text S3).
[f] In the baseline model, literature values were used, BWm = 700 kg, b = 1/150d (English Beef and Lamb Executive. Planning Grazing Strategies for Better Returns, 2013, https://www.eblex.org.uk/wp/wp-content/uploads/2013/06/Manual-8-Planning-grazing_strategies 200313.pdf, accessed: July 2016; Berk et al., 2016a). In model validation, involving differing cattle breeds, values were estimated from the group of non-infected animals.
[g] Cmaint does not currently include the smaller contribution to maintenance costs associated with physical activity such as grazing. ul expresses units of immunity, up to a maximum level of 1.
[h] See text after Eq. (17).
[i] Williams et al. (1992).
[j] Carstens et al. (1991).
[k] Colucci et al. (1982); Bines et al. (2009); Hart et al. (2009); Johnson et al. (2019).
[l] Bell et al. (1988); Sandberg et al. (2006).
[m] Moore (1978); Smith et al. (1987); Nennich et al. (2005).

Table 3
Grass growth. State variables and parameters defined in sub-model 3 (Section 2.4). All parameters are currently assumed to be constant throughout the season.

Variable	Description	Units		
G	Grass DM available for grazing at a given time	kgDM [a]		
Parameters		Units	Value	Source
K_g	Carrying capacity density of the grazing system	kgDM/ha	3500	This paper [b]
G_0/A_g	Grass DM density of the grazing system at turnout	kgDM/ha	2500	[c,d,e]
A_g	Area of pasture available for grazing	ha	1	-
r_g	Rate of grass growth per hectare	kgDM/ha/d	70	[f]
N_h	Stocking density of grazing animals	-	5	[c,d]
H	Number of hosts in the grazing system	-	N_h A_g	-

[a] kgDM, kg dry matter.
[b] Set to exceed the largest pre-grazing grass covers for dairy and beef cattle reported in 2.
[c] Ulster Grassland Society, 2010, Grazing Management Booklet, Ulster Grassland Society, accessed Nov 2021.
[d] English Beef and Lamb Executive. Planning Grazing Strategies for Better Returns, 2013, https://www.eblex.org.uk/wp/wp-content/uploads/2013/06/Manual-8-Planning-grazing_strategies 200313.pdf, accessed: July 2016.
[e] Berk et al., 2016b.
[f] Time average of records in Ulster Grassland Society, 2010 (Grazing Management Booklet, Ulster Grassland Society, accessed Nov 2021) and in Grass Check GB (Grass Growth and Quality, https://www.grasscheckgb.co.uk/, Centre for Innovation Excellence in Livestock, accessed Nov 2021) from the location and period of the baseline system.

Table 4
Free-living stages. State variables and parameters defined in sub-model 4 (Section 2.5) by Rose et al. (2015). The dependency of the parameters on temperature and precipitation is given in Supplementary Table S1.

Variable	Description	Units	Comment
E_p	Density of eggs on pasture	eggs/ha	-
E_c	Cumulative eggs deposited on pasture	eggs/ha	-
L_{12}	Density of L1s and L2s in faeces on pasture	larvae/ha	-
L_{3f}	Density of L3s in faeces on pasture	larvae/ha	-
L_{3p}	Density of L3s on pasture migrated from faeces	larvae/ha	Herbage plus soil
L_{3h}	Density of L3s on herbage on pasture	larvae/ha	As in Table 1
L_{3s}	Density of L3s in soil	larvae/ha	-
Parameters		Units	Weather dependent
$\beta(\tau)$	Probability of ingestion (transmission) per L3 per host	1/d	Yes, new variable
δ	Rate of development from egg to L3	eggs/d	Yes (Suppl. Table S1)
μ_1	Rate of mortality of eggs on pasture	eggs/d	*idem*
μ_2	Rate of mortality of L1s and L2s in faeces	larvae/d	*idem*
μ_3	Rate of mortality of L3s in faeces	larvae/d	*idem*
μ_4	Rate of mortality of L3s in soil	larvae/d	*idem*
μ_5	Rate of mortality of L3s on herbage	larvae/d	*idem*
m_1	Rate of herbage-soil migration of L3	larvae/d	*idem*
m_2	Proportion of pasture L3s that are on herbage	-	*idem*

$$\frac{dC_1}{dt} = J - \sigma_c C_1$$

$$\frac{dC_i}{dt} = \sigma_c C_{i-1} - \sigma_c C_i (i = 2, \cdots, n_C - 1),$$

$$\frac{dC_{n_c}}{dt} = \sigma_c C_{n_c-1} - \mu_c C_{n_c} \quad (9)$$

with $C = C_{nc}$, and where we allow for loss of immunity through a constant-rate loss in C (μ_c). The equations for C are similar to those for L, but without mortality terms and with distinct rate parameters (Table 1). This representation builds on previous work (Anderson and May, 1985; Roberts and Grenfell, 1991; Smith and Grenfell, 1994) that related the theoretical level of acquired immunity directly to the cumulative number of L3s ingested and where immunity had a constant rate of loss. A difference in our approach is that we expressed loss of immunity through a loss in the cumulative marker C; and rather than using C directly as immunity level, we used the bounded immunity level I_m (Eq. (8)) for ease of interpretation, similarly to a previous within-host model Rose Vineer et al. (2020b). A second difference in our representation is the use of a multi-compartment distribution of the temporal delay in the emergence of C upon exposure; Eq. (9) prevents premature emergence by disallowing a skew towards zero. In addition, we assumed that the time scale of development of immunity is the same as that of the development of L_3 into adult worms (Table 1); this is a minimal working assumption as immunity could develop faster or more slowly than the with-host parasite stages; however, we have no evidence in favour of either case. A similar remark applies to the time delay; amid a lack of evidence we assumed that the number of development compartments (n_C) is the same as n_L in the development of adult worms, which could be revised amid fresh evidence. Hypobiotic arrest and re-emergence of parasitic larvae, which is affected by season and immunity (Charlier et al., 2020a), was not included since this comes into play only towards the end of the grazing season, and is in any case too poorly understood to parameterise.

2.3. Sub-model 2: Host growth

The variables and parameters of this sub-model are detailed in Table 2. The BW of a naïve host (FGS calf that has not yet been infected; BW_n) is assumed to increase with age (a) according to a Gompertz function (Forni et al., 2009; Berk et al., 2016a),

$$BW_n = BW_m \exp(-\ln\left(\frac{BW_m}{BW_0}\right) \exp(-b\,(a - a_0))), \quad (10)$$

where the growth rate (b) and mature weight (BW_m) are performance parameters inherent to the host species and breed, and BW_0 and a_0 are weight and age at turnout. The rate of weight gain is given by

$$\frac{dBW_n}{dt} = b\,BW_n \ln\left(\frac{BW_m}{BW_n}\right), \quad (11)$$

where t is time since turnout. The daily digestible (D) DM feed intake ($FIDDM_n$) is utilised by the animal as DM weight gain and in dry-mass flows associated with maintenance functions ($D_{maint,n}$):

$$FIDDM_n = p_{dry,n}\frac{dBW_n}{dt} + D_{maint,n} \quad (12)$$

where $p_{dry,n}$ is the proportion of gain that is DM, and $D_{maint,n}$ is expressed as DM.

An infected animal has reduced growth in relation to its potential growth if uninfected (Eq. (10)) because it has reduced intake (parasite-induced anorexia) and there are costs associated with infection (Coop et al., 1977; Fox et al., 1989; Coop and Kyriazakis, 1999). To derive the BW and daily digestible DM feed intake (FIDDM) of the infected animal we assume that, at a given time, its intake is reduced by a factor A < 1 in relation to that of the naïve (uninfected) animal of the same weight,

$$FIDDM = A\,FIDDM_n, \quad (13)$$

where 1-A is the proportion of reduction in FI caused by anorexia; it is also possible to have A > 1 during compensatory growth. We assume, furthermore, that intake resources are used in additional mass flows (Coop and Kyriazakis, 1999) associated with functions that tackle infection ($D_{infection}$):

$$FIDDM = p_{dry}\frac{dBW}{dt} + D_{maint} + p_{dry}D_{infection}. \quad (14)$$

We expect the maintenance costs of the infected and naïve animals to be the same when they have the same BW, i.e. $D_{maint} = D_{maint,n}$. Rewriting Eq. (14) and substituting in Eqs. (11)–(13), we derive the rate of gain of the infected animal as being:

$$\frac{dBW}{dt} = A\left[b\,BW\ln\left(\frac{BW_m}{BW}\right) + \frac{D_{maint}}{p_{dry}}\right] - \frac{D_{maint}}{p_{dry}} - D_{infection}, \quad (15)$$

where A, D_{maint}, $D_{infection}$ and p_{dry} are specified below in terms of dynamic state variables of the animal. Some previous models of parasite burden include a simplified form of host growth for the purpose of calculating faecal mass and egg output but where BW is not related to infection state (e.g. Singleton et al., 2011; Rose Vineer et al., 2020b), or with a different interaction between growth and parasite burden (Louie et al., 2007). We expect that in a non-infected animal A = 1 and $D_{infection} = 0$, giving the same gain as for the naïve animal (Eq (11)). In taking resources out of the allocation

to growth in Eq. (15), a prioritisation in resource allocation to maintenance and infection functions (Doeschl-Wilson et al., 2008) is implicit.

The DM cost of maintenance can be expressed approximately in terms of metabolic weight, $BW^{0.75}$ (Archer et al., 1997) assuming near thermal neutrality (Supplementary Data S1, Section 1):

$$D_{maint} = C_{maint} BW^{0.75}, \quad (16)$$

where C_{maint} is a parameter (Table 2). We assume that the costs of infection arise from the increment in the level of immunity (dIm/dt), the maintenance of the level of immunity I_m already acquired (Greer and Hamie, 2016), and the repair of damaged tissue associated with the current worm burden:

$$D_{infection} = C_{I1} \frac{dI_m}{dt} + C_{I2} I_m + C_W W, \quad (17)$$

where C_{I1}, C_{I2}, C_W are parameters (Table 2). Values of the parameters that are new, such as C_{maint}, C_{I1}, and C_{I2} are derived through relationships to other trait parameters reported in the literature (Supplementary Data S1, Section 2). In this paper we focus on the immunity-related losses and neglect the cost ($C_W = 0$) of repairing worm-induced damage to the intestine, which is thought to be comparatively smaller (Houdijk et al., 2001).

The DM proportion of gain, p_{dry}, is obtained by using an empirically-supported allometric relationship between body water content (Wt) and empty BW (eBW) (Carstens et al., 1991; Filipe et al., 2018), i.e. $W_t = a_w\ eBW^{bw}$, where a_w and b_w are allometric parameters, and which, upon differentiation gives

$$p_{dry} = \frac{d(BW - W_t)}{dBW} = 1 - b_w a_w (BW\, p_{empty})^{b_w - 1} p_{empty}, \quad (18)$$

where p_{empty} is the proportion of BW that excludes gastrointestinal tract content (Williams et al., 1992).

The daily feed intake DM (FIDM) is obtained from the FIDDM (Eq. (12) or (13)) by accounting for the apparent digestibility of grass DM (DDM) (Colucci et al., 1982):

$$FIDM = \frac{FIDDM}{DDM}. \quad (19)$$

There is evidence DDM is not significantly affected by *O. ostertagi* and other GINs (Roseby, 1973; Fox et al., 1989; Taylor et al., 1989); here, it is assumed to be constant throughout the season (Table 2). Substituting Eq. (14) for FIDDM and Eqs. (15)-(16) for the terms within, Eq. (19) gives

$$FIDM = \frac{A\left(p_{dry}\, b\, BW \ln\left(\frac{BW_m}{BW}\right) + C_{maint}\, BW^{0.75}\right)}{DDM}, \quad (20)$$

where BW and p_{dry} are given by Eqs. (10) and (18), and the anorexia-related factor A is described below. Note that the term within brackets is the FIDDM of a naïve animal with the same BW. The actual intake is constrained by the capacity of the gastrointestinal tract, which was assumed to be approximately proportional to BW (Supplementary Data S1, Section 3).

The daily faecal output that is DM is the total DM intake, FIDM, subtracted of the digestible intake:

$$FaecesDM = FIDM\,(1 - DDM). \quad (21)$$

The corresponding daily wet faecal output is:

$$Faeces = \frac{FaecesDM}{pFaecesDM}. \quad (22)$$

where pFaecesDM is the proportion of faecal output that is DM. For simplicity, pFaecesDM is assumed to be constant at 0.15 throughout the season and across studies (Table 2), although its variability is a known source of uncertainty in FEC observations (Le Jambre et al., 2007; Denwood et al., 2012). The average host FEC (Eq. (6)) is calculated using this dynamically varying prediction of wet faecal output.

The parasite-induced reduction in FI is thought to be of the order of 20% to 30% (Coop et al., 1977; Bell et al., 1988; Sandberg et al., 2006); while its causes are not well established (Coop and Kyriazakis, 1999), it is believed to be related to the establishment of new adult worms (Coop et al., 1977), which in the case of *O. ostertagi* occurs in the abomasum (Fox, 1993), where maturation of L4 in the gastric gland provokes inflammation (Charlier et al., 2020a). Therefore, we assumed that A is driven largely by the rate of change in the number of adult worms (dW/dt):

$$A = \exp\left[q \tanh\left(\frac{dW}{dt}\frac{1}{DW_{max}}\right)(1 - I_m)^{0.3}\right]. \quad (23)$$

where $q = \ln(0.8)$ (Table 2) determines the lowest proportion to which feed intake can be reduced. The function tanh(x), which ranges from −1 to 1, and the scale parameter DW_{max} (derived in Supplementary Data S1, Section 4) constrains the effect of dW/dt when its magnitude is of order DW_{max} or greater. When worm load increases (dW/dt > 0, tanh(x) > 0) then A < 1 because q < 1; and when the worm load decreases (dW/dt < 0, tanh(x) < 0) then A > 1. Therefore, in the model it is possible to have compensatory growth briefly while the worm number is stabilising, e.g. after the onset of an immune response on worm mortality or after drug treatment. Empirical observations of rebound in BW or FI at a faster pace than may be expected at the current BW (Coop et al., 1977, 1982; Bell et al., 1988; Fox et al., 1989; Szyszka et al., 2013) provide suggestive evidence that compensatory growth may occur under these conditions. Such rebounds in appetite and FI, observed rapidly after anthelmintic treatments, are mimicked in the model upon clearing of establishing and adult parasites (Section 2.7), after which parasite-induced anorexia halts, i.e. A = 1 as the worm load becomes constant. The immunity-dependent factor in Eq. (23) aims to modulate the magnitude of either effect (A < 1 or A > 1) when immunity has developed; e.g. when anthelmintic treatment is applied and, following its effects, the worm burden rebounds but immunity has not been lost. The effect of A on FI during compensatory growth was constrained by the capacity of the gastrointestinal tract (Supplementary Data S1, Section 3). Other models have made different attempts at incorporating parasite-induced reductions in feed intake based on host variables related to L3 exposure (Grenfell, 1988; Berk et al., 2016a) or adult worm burden W (Louie et al., 2007), while we assumed that change in appetite is driven by change in W.

It has been reported that grazing cattle can have a short-lived drop in BW at the point of turnout caused by a drop in FI and gastrointestinal content (Balch and Line, 1957; Fox et al., 1989) due to adaptation to grazing. We represented this BW drop through a rapid reduction factor in feed intake (Supplementary Data S1, Section 5). This correction to intake was applied when modelling empirical studies that exhibited this additional behaviour and when exploring model behaviour.

2.4. Sub-model 3: Grass growth

The grass DM available for gazing (G) in a given area of pasture (A_g), is assumed to be controlled by: the rate of grass growth per ha (r_g); a carrying capacity per ha (K_g) that limits grass growth according to characteristics of the grazing system; and the rate of grass intake by the grazing herd at given stocking density (N_h) and average daily intake per capita FIDM (Table 2). The net rate of grass growth is assumed to have the following growth and consumption terms:

$$\frac{dG}{dt} = r_g A_g\left(1 - \frac{G}{K_g A_g}\right) - FIDM\,H. \quad (24)$$

where $H = N_h A_g$ is the number of hosts in the grazing system. Parameter values are given in Table 3. In this formulation, growth is limited by local resources, i.e. when G/A_g approaches K_g growth stops and any further grazing will lead to decrease in sward availability, as is observed (Dimander et al., 2003; Larsson et al., 2006). The assumed value of G at turnout (Table 3) is such that the grazing system has not yet reached its limit capacity; hence, some increase in G ($dG/dt > 0$) is possible upon moderate consumption. Equation (24) assumes that the grass plants are only increasing in size and not propagating in number; the opposite assumption can be made through logistic growth, where the growth term in Eq. (24) would be multiplied by G (Grenfell, 1988; Louie et al., 2007). In using empirical measurements of r_g (Table 3) we have assumed that these were obtained without, or were discounted for the latter density effects, which is an approximation. Other authors have chosen not to include such limiting effects in grass growth (Berk et al., 2016b). The rate of grass growth and the carrying capacity are currently assumed to be constant throughout the season, i.e. independent of weather. In addition, in the current non-spatial formulation, all variables are assumed to be uniform across the grazing area: the herd grazes an evenly-distributed herbage and each animal grazes identically. The grass availability G/A_g is used to convert the density of L3s per ha into the concentration of L3s per kg of DM (Table 1), used to calculate the ingestion of L3s per animal.

2.5. Sub-model 4: Free-Living stages

A model of the dynamics of the parasite's FL stages has been fully developed previously (Rose et al., 2015). Building on past work (Grenfell et al., 1987a; Smith, 1994), the GLOWORM-FL model incorporated the migration of infective L3s between soil and herbage and the influence of weather variables on this movement. The model also contained fresh estimation of the influence of weather on the remaining parameters controlling the FL stages. In the current paper, we have added to this sub-model two dynamic flows linking the nematode FL and parasitic stages: the deposition of eggs in faeces and the ingestion of L3s by every host in the grazing herd. We briefly describe the model's variables and parameters (Table 4) and the additions to the model. Details, including parameter values for *O. ostertagi*, are given in Supplementary Table S1 and S1.

The dynamics of the FL stages, including deposited eggs (E_p), stages developed within faecal pats (L_{12}, L_{3f}), and L3s on pasture (L_{3p}), whether on herbage (L_{3h}) or on soil (L_{3s}), are defined as densities per ha and given by the rate equations (Rose et al., 2015):

$$\frac{dE_p}{dt} = E_{in} - (\mu_1 + \delta)E_p$$

$$\frac{dL_{12}}{dt} = \delta E_p - (\mu_2 + \delta) L_{12}$$

$$\frac{dL_{3f}}{dt} = \delta L_{12} - (\mu_3 + m_1)L_{3f}$$

$$\frac{dL_{3p}}{dt} = m_1 L_{3f} - (\mu_4(1 - m_2) + \mu_5 m_2) L_{3p} - \beta H L_{3p}$$

$$L_{3h} = m_2 L_{3p}$$

$$L_{3s} = L_{3p} - L_{3h}$$

$$\frac{dE_c}{dt} = E_{in}, \quad (25)$$

All variables and parameters are described in Table 4. The assumed initial values of the variables at turnout are given in Supplementary Table S2. The last equation in Eq. (25), for the cumulative number of eggs deposited (E_c), was introduced by us for later use. The remaining equations are as in Rose et al. (2015), but with three exceptions. First, we have replaced the rate δ for 2δ in Rose et al. (2015). Second, the rate of egg deposition on pasture by all hosts per day per ha was 100 and is replaced with:

$$E_{in} = Epd\,H/A_g,$$

where Epd, H and A_g are as in Tables 1 and 3. Third, there is an additional term in the rate of change of L_{3p} representing the daily ingestion of L3s by every grazing animal per ha. This term required defining a new time-varying parameter. The average daily probability of ingestion per L3 per host ($\beta(t)$), known as rate of parasite transmission or instantaneous rate of infection, is the ratio of the L3s ingested per grazing host per day per ha (FIDM m_2 L_{3p}/G) to the L3s available on pasture per ha (L_{3p}):

$$\beta(t) = \frac{m_2 L_{3p} FIDM}{L_{3p} G} = m_2 \frac{FIDM}{G}, \quad (26)$$

where FIDM (Table 2, Eq. (20)) is determined by the host's BW, parasite burden and level of immunity; G (Table 3, Eq. (23)) is the current grass biomass available for grazing; and m_2 (Table 4, Eq. (24)) is the current weather-dependent availability of L3s on herbage. The ingestion term, $\beta H L_{3p}$, in Eq. (24) is analogous to the transmission term in other models (Smith and Grenfell, 1985; Grenfell et al., 1987a; Grenfell, 1988; Roberts and Grenfell, 1991; Kao et al., 2000; Louie et al., 2005; Singleton et al., 2011); the difference being in how β is defined, which we do in terms of a host state variable, grass mass, and environmental drivers. Other work defined β conceptually similarly but in terms of constant quantities (Singleton et al., 2011), through the ratio FIDM/G with FIDM determined by grass mass and reduced by larval exposure (Grenfell, 1988), or as a function of host age (Louie et al., 2005). Predictions of β are provided later. Note that Eq. (26) feeds into Eq. (1), which closes the loop of interdependency of model variables.

2.6. Reproduction number

To characterise the increase or decrease of the parasite population, and thus whether it is controlled, we quantify the average extent to which each individual parasite replaces itself during its lifetime. For macroparasites, the basic reproduction number (R_0) is defined as "the average number of (female) offspring per adult (female) worm that survive to reproduction in the absence of density-dependent constraints" (Anderson and May, 1992; Tompkins et al., 2001). Heuristic (Anderson and May, 1992) and formal (Heesterbeek and Roberts, 1995) calculations of R_0 have been provided for simple models of parasites with direct cycles; they quantify the parasite's maximum replacement rate when its inherent reproduction and survival traits are expressed to the full extent, typically early in an outbreak. Here, we focus on the overall dynamics of the parasite population towards stability by considering the effective reproduction number (R_e), which includes the regulatory effects imposed by the host and the environment on each parasite stage (Churcher et al., 2006). While it is not straightforward to calculate R_e amid the complexities of the current model (Filipe et al., 2005), R_e can be expressed via the following time-varying factors:

R_e = (L_3 multiplication in host)

x (egg multiplication on pasture)

x (probability an L_3 is ingested by a host), (27)

Each of these factors can be expressed approximately and respectively as:

$$R_e = \left(\frac{E_c}{C}\right)\left(\frac{L_{3h}}{E_c}\right)\left(\frac{\beta H}{\beta H + \mu_4(1-m_2) + \mu_5 m_2}\right) \quad (28)$$

In the first factor, E_c and C are the cumulative numbers of eggs produced and L3s ingested by a host; in the second factor, L_{3h} and E_c are the cumulative numbers of L3s on herbage and eggs released onto pasture; and the third term is the average proportion of L3s on pasture ingested by hosts, given by the ratio of the rate of L3 ingestion per day per ha (β H, Eq. (26)) to the rate of L3 departure from pasture through ingestion or mortality per day per ha (β H + μ_4 (1- m_2) + μ_5 m_2). This calculation is heuristic and approximate in its use of ratios of cumulative numbers of outgoing to incoming parasites per stage. The cumulative aspect tackles the fact that, under time varying conditions, changes in incoming and outgoing parasite stages are not synchronous; as it would be difficult to incorporate time lags explicitly, the calculation is approximated through the use of time averages. In a parasite population that stabilises, we would expect R_e to become close to 1, indicating no increase or decrease. However, full stabilisation through the regulatory factors that reduce R_e may take time to unfold on the scale of a single grazing season. In addition, there is variation in environmental conditions due to seasonal climate, weather and management actions likely to cause fluctuations before and after stabilisation. Nonetheless, a R_e that declines over time to magnitudes around 1 would provide a health check on the mutual consistency of the parameters of the host and free-living sub-models.

2.7. Model behaviour

2.7.1. Numerical implementation

The model involves processes defined in continuous time, but was solved numerically using Euler's method with a time step of 0.1 day. This step is small enough at the scale of all processes represented in the model and thus is likely to lead to solutions with satisfactory numerical accuracy. Using a step smaller than 0.1 led to no observable difference in the model output. In addition, this accuracy was assessed on simpler models with known analytical solution, giving an acceptable relative error of 0.37% with step 0.1 day, 3.6% with step 1 day, and 28% with step 10 days. In order to input daily weather data in the FL stages sub-model, we used the spline function of R to implement smoothing spline interpolation at intermediate time steps between data points. The model was coded in the R language and the results were generated using the free software R, version 4.1.1 (R Core Team, 2021. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). A code of the model is available (Filipe, 2022).

2.7.2. Baseline system

Predictions of the model, as defined in Sections 2.2 to 2.5 using parameter values from literature, were validated using the approach in Section 2.8. In addition, we explored how the model captures the effects of key factors on the epidemiology and control of *O. ostertagi*. For this purpose, we used baseline conditions defined by a representative location of temperate weather in northern Europe and a typical year among its records of daily weather. We chose as the location Large Park Hillsborough, BT26 6DR in Northern Ireland (coordinates 54°27′06.6″N, 6°04′30.7″ W). Weather data (daily mean temperature and total precipitation) for this location were collected from the E-OBS gridded dataset (Cornes et al., 2018). We chose 2014 as a typical year among the last 10 years of weather data (2011–2020) as the daily pattern and annual average of the temperature in 2014 were closest to those of the daily records averaged over 10 years. As a representative grazing period we used 01 May to 25 September (21 weeks) in 2014. Weather data were used raw, without smoothing. The weather variables are plotted in Supplementary Fig. S1.

The baseline parasitology at turnout had an average concentration of *O. ostertagi* on herbage of 200 L3s/kg of DM (Berk et al., 2016b), and assumed that no other FL stage overwintered (Supplementary Table S2). We note that, in the model this is the actual level of L3s on herbage, while in a real system an observation of L3s on herbage is likely to be an underestimation of its actual level (Supplementary Data S1, Section 8, and Section 4.2); e.g. an assumed level of 200 could correspond to an observed level of 100 or less. The baseline FGS calves were assumed to be naïve (parasite-free and with no acquired immunity), to have a body weight of 200 kg at turnout and growth parameters as in Table 2, which led to a BW trajectory in the range 200–400 kg over the 21-week grazing period. Daily FI was assumed to drop at turnout (Section 2.3 and Supplementary Data S1, Section 5) as observed in some of the empirical studies used for validation and often observed more generally (Balch and Line, 1957). The cattle herd was assumed to have a stocking density of five animals/ha (Table 3).

2.7.3. Behaviour explored

Assuming the model structure and the parameters values described in Sections 2.2 to 2.5, the behaviour of the baseline system was explored in a range of scenarios where one model parameter was varied at a time:

1) Effect of the initial level of herbage contamination, i.e. concentration of L3 son herbage at turnout: L_{3c} = 100, 200, 500 L3s/kg of DM (Michel et al., 1970).
2) Effect of the herd stocking density: N_h = 1, 5, 7 animals/ha, where 1–5 is the range found in the empirical studies used for model validation.
3) Effect of one anthelmintic treatment differing in the timing of application: T1 = 0, 4, 8 weeks after turnout.
4) Effect of two anthelmintic treatments with the first treatment applied at turnout (T1 = 0) but differing in the time of application of the second treatment: T2 = 3, 5, 7 weeks from turnout.

A simplified drug treatment was modelled, with 100% efficacy in clearing establishing and adult parasite stages during a period of 21 days and with no effect afterwards. The variation of some grass growth parameters (Table 3) was also explored but found to have limited influence on model behaviour under the current values of the other parameters. These explorations were not included in the results but confirmed that our choice of values for these parameters was not determining.

2.8. Model validation

2.8.1. Datasets

In order to test the predictions of the model defined in Sections 2.2 to 2.5, the literature was searched for empirical studies satisfying the criteria defined in Supplementary Data S1, Section 6. We identified only six studies that satisfied these criteria (Table 5). Studies with natural infections only: (i) Larsson et al. (2006); Larsson et al. (2007), and (ii) O'Shaughnessy et al. (2015). One study where the animals were inoculated with lower doses of L3s at turnout: Höglund et al. (2018), comprising (i) dairy cattle and (ii) crossbred cattle from dairy and beef breeds. Studies where the animals were inoculated with higher doses of L3s at turnout: (i) Dimander et al. (2003) and (ii) Höglund et al. (2013). All studies

Table 5
Six empirical studies used for model validation. Summary of the information provided.

Study	Location	Year	Duration (d)	Av. BW at turnout (kg)	Av. L3s on pasture at turnout (1/kgDM)[a]	Dose at turnout (L3)	Stock. dens. (1/ha)	Additional measures	Co-infection *O. ostertagi* (%) vs *C. oncophora*, serial observations
O'Shaughnessy et al. 2015	Ireland	2012	124	165	200[b]	-	1.4	L3c (SGS)	L3: 73%, 23%, 50% (SGS)
Larsson et al. 2006; 2007	Sweden	2002	148	189	250[c]	-	5	L3c (Y1, Y2), W (tracers 3w prior housing)	L3:<50% all season; W: 30%
Höglund et al. 2018, dairy	Sweden	2016	142	306	[d]	5000 [e]	2.25	-	L3: 47%, 80% (PCR)
Höglund et al. 2018, cross	Sweden	2016	142	332	[d]	5000 [e]	2.25	-	L3: 17%, 47% (PCR)
Höglund et al. 2013	Sweden	2008	154	238	[d]	40,000 [e]	2.4	W (tracers Y2, Y3)	W: 24%, 27%
Dimander et al. 2003	Sweden	1999	150	200	300	10,000 [e]	5	L3c (Y1, Y2); W (Y4 tracers)	L3: 20%, 75%

[a] kgDM, kg of dry matter
[b] Based on SGS.
[c] Average of first two observations.
[d] No data provided (c.f. note in Section 2.7.2).
[e] Doses comprised equal proportions of *O. ostertagi* and *C. oncophora*. FGS, SGS: first and second grazing season. Y1, Y2: Year 1, Year 2.

took place either in Ireland or in Sweden. Data were available from tables, text or figures in each article.

All studies reported mixed infections comprising predominantly *O. ostertagi* and *C. oncophora* (Table 5). The model, which was designed for a single-species *O. ostertagi* infection, was compared with these data as we lacked single species data.

2.8.2. Validation approach

For each empirical study, we compared the model predictions with the longitudinal observations of BW (or gain plus average start weight, as provided), and FEC. These data were reported as averages over the animals in each treatment group and at each time point from turnout to the end of the experiment. Where observations were available, we also compared model predictions with counts of L3s on pasture throughout the experiment, and with worm counts in tracer animals from within the untreated group or that grazed the same fields in subsequent seasons. There were no data on feed intake. Weather data (daily mean temperature and daily total precipitation) for the spatial coordinates and calendar dates reported in each study were collected from the same source as the baseline weather. The weather variables are plotted in Supplementary Fig. S1.

The local daily weather, initial L3 contamination of herbage (where available), any inoculation dose at turnout, cattle stocking density, and cattle breed growth parameters were the only quantities adjusted to describe the conditions of each empirical study. While many other parameters could have differed among studies, all other model parameters were assumed to be the same across all studies, i.e. there was no model fitting to data. In one study (O'Shaughnessy et al., 2015), the FEC at turnout was positive, hence it was necessary to assume initial non-zero values for the number of adult worms and immunity level.

Where no measures of L3s on herbage at turnout were available (Table 5), an initial herbage contamination was assumed based on studies in comparable regions (Michel et al., 1970), following a similar reasoning as for the baseline system (Section 2.7.2). Using the model's predicted mean trajectory of L3 concentration on herbage, we drew samples from a negative binomial distribution (Smith and Guerrero, 1993) with this mean and an aggregation parameter k = 1.4 (Verschave et al., 2015); the lower quartile of the samples was contrasted with the data in an attempt to account for low efficacy in the field recovery of L3s (Kloosterman A., 1971, Observations on the epidemiology of trichostrongylosis of calves, PhD Thesis, Wagenningen University, The Netherlands; Paras et al., 2018). As the breed of the animals differed across studies and their growth parameters were unknown, the average BW of the group of treated animals was used as a proxy for the BW of a naïve animal of the same breed, which unlike the infected animals is not affected by anorexia and infection costs; these BW data were used to estimate the performance parameters of the Gompertz BW gain curve of the infected animals (Eq. (11)). This estimation was derived using the non-linear model regression function nls of the software R, version 4.1.1 (R Core Team, 2021. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). Standard errors for mean BW and FEC observations were provided in a minority of studies and included in the plots where the model output and empirical data were compared.

To be able to tackle data from co-infections with two species (Section 2.8.1 and Table 5) and which do not specify parasite numbers by species (except for occasional relative proportions in some studies), we input the initial total concentration of L3s on herbage into the model and predicted the numbers of parasitic and FL nematode stages as totals for both species, which we then compared with the data. The working hypotheses here are that: (i) the parameters and processes in the model are adequate for describing each species and thus the total infection, and (ii) there are no interactions between species. In this way, the model is regarded as representing a typical parasite mixture with variable relative proportions of *C. oncophora* and *O. ostertagi*. Alternatively, if we knew the proportions of observed FEC and initial L3s corresponding to *O. ostertagi*, we could have modelled a single *O. ostertagi* infection (Smith and Guerrero, 1993), which would nevertheless still assume no interactions between species in the real system. Unfortunately, these proportions vary throughout the season (Högberg et al., 2021) and are largely unknown as indicated by the rare measurements in the current studies (Table 5); this was the case whether the animals were inoculated with known species mixtures at turnout or subject solely to natural infection. For these reasons, we considered it inevitable to take the above approach, which is simple and easily interpretable.

2.8.3. Statistical approach

A statistical comparison of the BW and FEC predicted by the epidemiological model with the empirical data was made using a standard validation approach (Mayer and Butler, 1993). In this

approach, the observed data are linearly regressed on the model output, i.e. the first is treated as a response and the latter as a predictor; the intercept of the relationship is fixed at zero. The outcomes of this regression are an estimated slope, a *P*-value on an F statistic assessing the fitted line against a constant response, a 95% confidence interval (CI) on the estimated slope, and a coefficient of determination adjusted for the number of model parameters (R^2_{adj}). For further details see Supplementary Data S1, Section 7. We report the *P*-value, CI on the slope, and R^2_{adj}. The statistical analyses were done using the linear model regression function lm of the software R, version 4.1.1 (R Core Team, 2021. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).

2.9. Data accessibility

Data that were used to perform the study are publicly available or stated within the main text and in the Supplementary files. Code for the model is available (Filipe, 2022).

3. Results

3.1. Model behaviour

The response of the model to differing conditions was explored using the model structure and parameters of Sections 2.2 to 2.5. Further results on the validation of the model are presented in Section 3.2.

3.1.1. Effect of the initial level of herbage contamination

Varying the herbage contamination at turnout (L_{3c} = 100, 200, 500 L3s/kg of DM) caused a considerable peak shift (earlier peak) in calf FEC and in adult worm burden (Fig. 2). A higher starting pasture contamination caused an earlier, higher peak and an earlier decline in FEC. For the adult worm burden, however, a higher initial contamination caused an earlier but lower peak and a later decline; this difference can be due to the fact FEC is affected by additional and earlier effects, i.e. reduction in fecundity due to acquired immunity and density dependence. The effects on BW were appreciable, with greater differences in cumulative gain between 10–15 weeks, but were followed by some recovery in lost gain and more modest BW differences by the end of season. The differences in contamination at turnout were reflected in the temporal trajectories of L3 contamination, but were much reduced by the end of the season.

3.1.2. Effect of the herd stocking density

Higher stocking densities (N_h = 1, 5, 7 ha^{-1}) enhanced transmission and amplified infection pressure, leading to earlier, higher peaks in FEC and in worm burden, which then declined towards the end of the grazing season (Fig. 3). At lower stocking densities, egg shedding from animals persisted longer due to lower levels of immunity. However, as stocking density increased, pasture contamination increased markedly and persistently as a result of a larger number of hosts shedding eggs and infective larvae developing from earlier, higher shedding. In addition, the greater parasite challenge at high stocking densities resulted in slower weight gain that produced persistent differences in body weight through to the end of the grazing period (Fig. 3). Across weather in different years, these patterns were robust but the strength of peak shifts in FEC and differences in BW by the end of season varied across years (not shown); e.g. these effects were stronger in 2011 than in the current example of 2014. Compared with increases in the initial pasture larval contamination, increases in stocking density drove later but more persistent differences in FEC, herbage larval level, and weight gain; and, for worm burden and FEC, drove differences mostly in magnitude rather than timing. These differences result from the time lag between host infections, through egg shedding to larval maturation, and from the greater number of hosts carrying and transmitting parasites. Note that the red curves are identical between Figs. 2 and 3. Increased L3 abundance late in the season at higher stocking densities (Fig. 3) could affect starting L3 levels in the next season (Fig. 2).

3.1.3. Effect of one anthelmintic treatment differing in the timing of application

A key management parameter when a single round of drug treatment is applied after turnout, is the timing of application during the grazing season. The model predicted that an intermediate time after turnout (among 0, 4 or 8 weeks post turnout) is optimal (Fig. 4) in the following sense: it led to greater cumulative BW gain and to lower cumulative parasite burden in the host, and thus to potentially lower risk of production loss and clinical disease, while still leading to end-of-season pasture contamination and parasite burden comparable to those of the late treatment. Early treatment (at turnout) delayed infection but also immunity, leading to higher overall worm burdens and late-season L3 levels than in the later treatments, although still lower than in the absence of any treatment (Fig. 3, red line).

3.1.4. Effect of two anthelmintic treatments differing in the timing of the second treatment

When two anthelmintic drug treatments are applied, it is natural to apply the first at turnout and to examine the best timing for application of the second treatment. The model predicted that when varying the latter (among 3, 5, 7 weeks post turnout), there was not much difference in the final BW (Fig. 5). In all cases, the lowered infection pressure led to lower levels of immunity, which allowed adult worm populations to continue increasing throughout the grazing period. However, there was considerable difference in the level of pasture contamination potentially carried over to the next season and in the cumulative parasite burden (Fig. 5), with the latest application being the best in this respect, but with the intermediate timing being next best.

3.1.5. Effective reproduction number

In the four model behaviour examples, the predicted effective reproduction number R_e exhibited a clear pattern (shown on a logarithmic scale, Figs. 2-5). In the initial phase R_e had very large values likely influenced by the assumed initial numbers of parasite stages and by specifics of the calculation of R_e (Eq. (28)). Hence, during this phase, we sought meaning in patterns rather than in values. Subsequently, there was a sharp decline in R_e followed by oscillations within the range 10–1, i.e. above but not far from the value 1. This pattern confirms our expectations about the model output (Section 2.6): it indicates convergence to a state of quasi stability in the parasite population superimposed by short-term fluctuations, likely due to variation in host response and weather (the same in the four examples). In these examples, the curve with the lowest final value of R_e does not always correspond to the case with the lowest final value of L3s; we expect this to be because R_e is also affected strongly by parasite burden and the current level of feed intake.

3.2. Model validation

Predictions of the model defined in Sections 2.2 to 2.5 were tested against data from empirical studies. The studies were organised in pairs that had, respectively, natural infection only (Fig. 6), a low artificial parasite dose followed by natural infection (Fig. 7), and a higher artificial parasite dose followed by natural infection

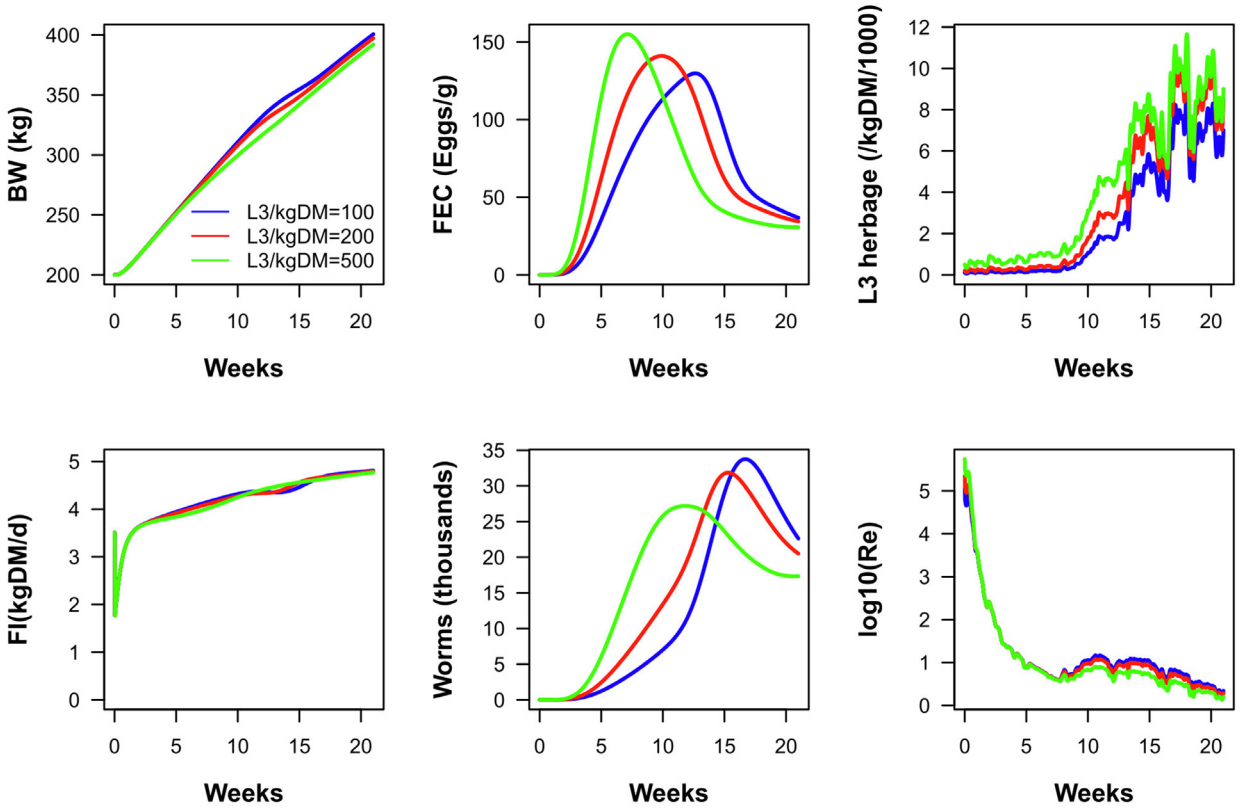

Fig. 2. Model behaviour: effect of the initial level of herbage contamination. Progression of *Ostertagia ostertagi* infection of cattle during the grazing season of the baseline herd and grazing system under differing initial concentrations of L3s on herbage, 100, 200, 500 larvae/kgDM (i.e. per kg dry matter). Traits shown: body weight (BW), faecal egg count (FEC) in wet faeces, density of L3s on dry herbage, daily feed intake (FI), number of adult worms, and logarithm of the effective reproduction number R_e.

(Fig. 8). The values of L3s on herbage at turnout were either observed (Table 5) or assumed based on comparable studies (Section 2.8.2). These figures show the predicted BW, daily FI, FEC, and number of adult worms per FGS calf, and the predicted L3 contamination of herbage and R_e. The figures also show the observations on BW and FEC and, where data were available, on other traits. Overall, validation on these studies provided support for the model.

3.2.1. BW and FEC

Visual comparison of the predictions with the empirical data indicates the model was generally in reasonable agreement with the BW and FEC data across the studies (Figs. 6-8). There is formal statistical support for this agreement in almost all cases (Table 6): the 95% CI of the slope of the relationship between observed data and prediction includes the value 1 and not the value 0 (as confirmed by a low *P*-value) and the data relate linearly to the predictions (as indicated by a R^2_{adj} close to 1). Where SEs were reported for BW and FEC (O'Shaughnessy et al., 2015; Höglund et al., 2018) and BW (Dimander et al., 2003), the deviations between data and prediction were generally in reasonable agreement with the estimated SEs (Figs. 6-8) except for the FEC in O'Shaughnessy et al. (2015); it is possible that the latter SEs are conservative indicators of uncertainty as they have constant values and may not fully account for overdispersion in egg counts. There was an exception, however, in the studies where the animals were inoculated with larger L3 doses (Dimander et al., 2003; Höglund et al., 2013); here, the magnitude of the peak of the FEC (at 5 weeks post turnout) was considerably underestimated by the model (Fig. 8), although there was agreement at the remaining time points; possible causes are discussed later.

3.2.2. L3 on herbage, adult worms, and effective reproductive number

Comparison of model predictions against observations of GIN L3s on herbage and parasitic adult worms, for the empirical studies that reported such observations, is addressed in Supplementary Data S1, Section 8. The range of dynamic patterns of the effective reproductive number across these studies is also discussed in Supplementary Data S1, Section 8.

4. Discussion

We developed a novel mathematical model of the epidemiology of GIN infections in gazing animals. While the parasite population model uses a well-established framework for the dynamics of macroparasite infections (Anderson and May, 1978, 1992) and follows previous attempts for GINs in cattle (Grenfell et al., 1987a; Roberts and Grenfell, 1991; Smith and Grenfell, 1994), the interactions with grass, weather data, and animal growth are novel and allow for the exploration of climate-driven effects, and eventually the optimisation of treatment strategies based on performance as well as parasitological criteria. Therefore, we consider the inclusion of these variables central to the use and further development of models as tools to help address the challenges set out in the Introduction, i.e. the evaluation of alternative treatment and management strategies to current practices required by emerging anthelminthic resistance and climate change. Our first hypothesis, that the interactions within the model lead to interpretable nonlinear responses in the system that can be explored to enhance the outcomes of parasite control interventions, was supported by the study of model behaviour. Our second hypothesis, that the model is able to represent patterns of animal infection and perfor-

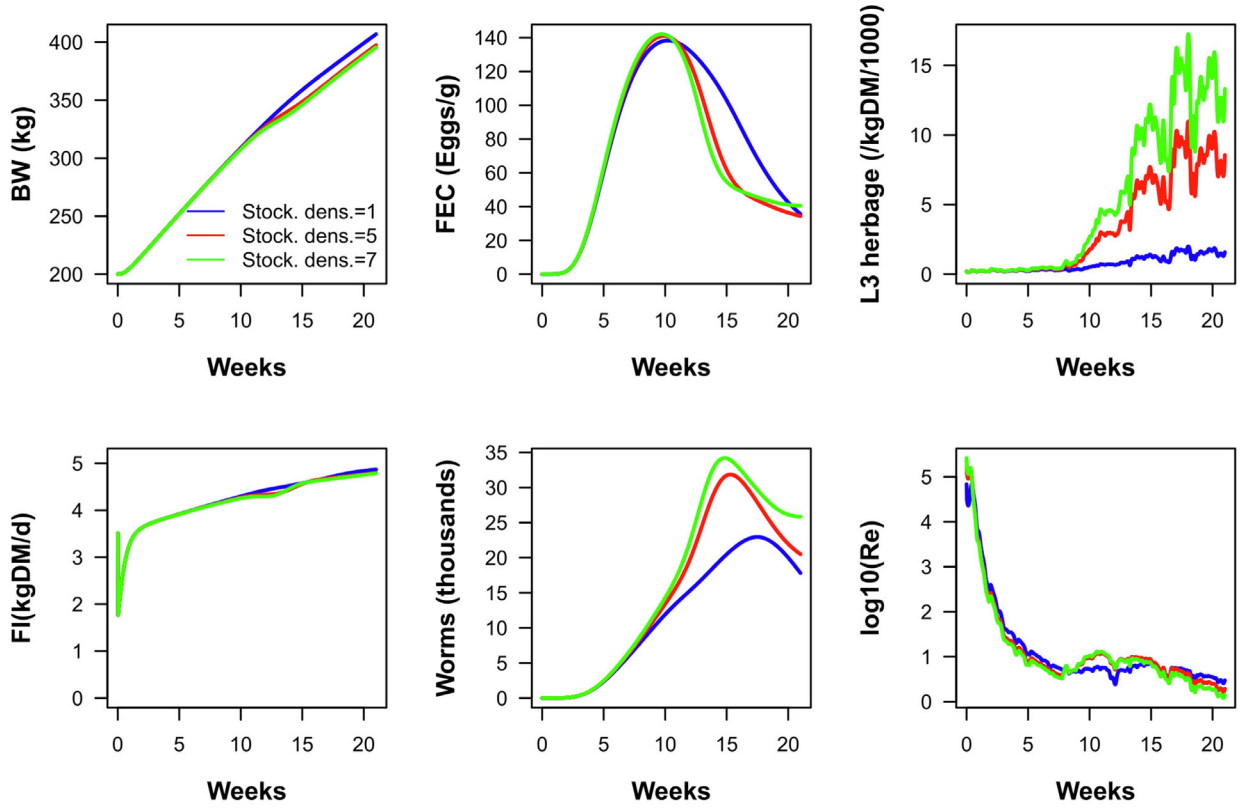

Fig. 3. Model behaviour: effect of the herd stocking density. Progression of *Ostertagia ostertagi* infection of cattle during the grazing season of the baseline herd and grazing system under differing herd stocking densities, N_h = 1, 5, and 7 animals/ha. Traits shown: body weight (BW), faecal egg count (FEC) in wet faeces, density of L3s on dry herbage, daily feed intake (FI), number of adult worms, and logarithm of the effective reproduction number R_e. kgDM, kg dry matter.

mance in experimental trials, was supported by the outcomes of the model validation.

4.1. Modelling approach and scope

The model was parameterised, using literature sources, specifically for *O. ostertagi* in grazing cattle in temperate climates. We did so due to the clinical and economic importance of this species, particularly in young cattle (Armour, 1980; Charlier et al., 2020b; Forbes, 2020) and due to the greater knowledge of the relevant parameters for this species (Michel, 1969; Michel et al., 1973; Grenfell et al., 1987b; Smith et al., 1987; Verschave et al., 2014; Rose et al., 2015). In addition, model predictions were tested against datasets on FGS as this comprises all young cattle and in an attempt to develop and test the processes of acquisition of immunity from a known, naïve state, which avoids confounding effects from parasitological history.

We integrated processes relating to infection and immunity in cattle with the dynamics of the FL stages, grass availability and animal growth. Epidemiological models of the full *O. ostertagi* life cycle have been previously developed (for reviews of models of GINs in cattle see Smith and Grenfell, 1994; Cornell, 2005; Verschave et al., 2016a), but stopped short of incorporating all these factors. The first innovation added here is a model of the dynamics of parasite FL stages (Rose et al., 2015) that extended earlier work (Grenfell et al., 1986, 1987a; Smith et al., 1986; Smith, 1990) by including the influence of weather on soil-herbage migration, and to which we added egg shedding and larva ingestion by the cattle herd (sub-model 4). The second innovation is a model of the dynamics of the host state that builds on and adapts past work on parasite load and acquired immunity processes (Grenfell et al., 1987a, b; Roberts and Grenfell, 1991; Smith and Grenfell, 1994) (sub-model 1) and adds further variables describing host growth similarly to Vagenas et al. (2007) and Berk et al. (2016a, 2016b) (sub-model 2). Our host-state model differs from that of Berk et al. in using fewer host state variables, distinct parameters and parameter values, and a revised representation of parasite-induced anorexia (Coop and Kyriazakis, 1999) on feed intake and the addition of compensatory growth. We note also that Berk's model included a simplified representation of the parasite FL stages. Thirdly, our model includes (sub-model 3) dynamic variation in grass availability (Grenfell, 1988), which influences both animal growth and the concentration, and hence the ingestion, of infective parasite stages.

One novel aspect that emerged in this integrated model is an explicit relationship of the rate of parasite transmission, or instantaneous rate of infection, Eq. (27), to variables relating to the host, parasite and grazing environment:

$$\beta = \frac{[\text{proportion of pasture L3 on herbage}] \times [\text{feed intake by a host}]}{[\text{grass biomass}]}. \quad (29)$$

This relationship builds on previous work (Anderson and May, 1978; Smith and Grenfell, 1985; Grenfell et al., 1987a; Grenfell, 1988; Kao et al., 2000; Louie et al., 2005; Singleton et al., 2011) and adds a dynamic trade-off between host and environmental variables. Epidemiological models are very sensitive to the value of the rate of transmission, which is often treated as a constant parameter (Grenfell et al., 1987a); in our model, however, β is a variable controlled by simultaneously changing variables whose effects may either add or counterbalance each other. Based on the current parameters of the model, the variation of β during the grazing season was in the range 10^{-3} – 10^{-4}/day/larva/host (c.

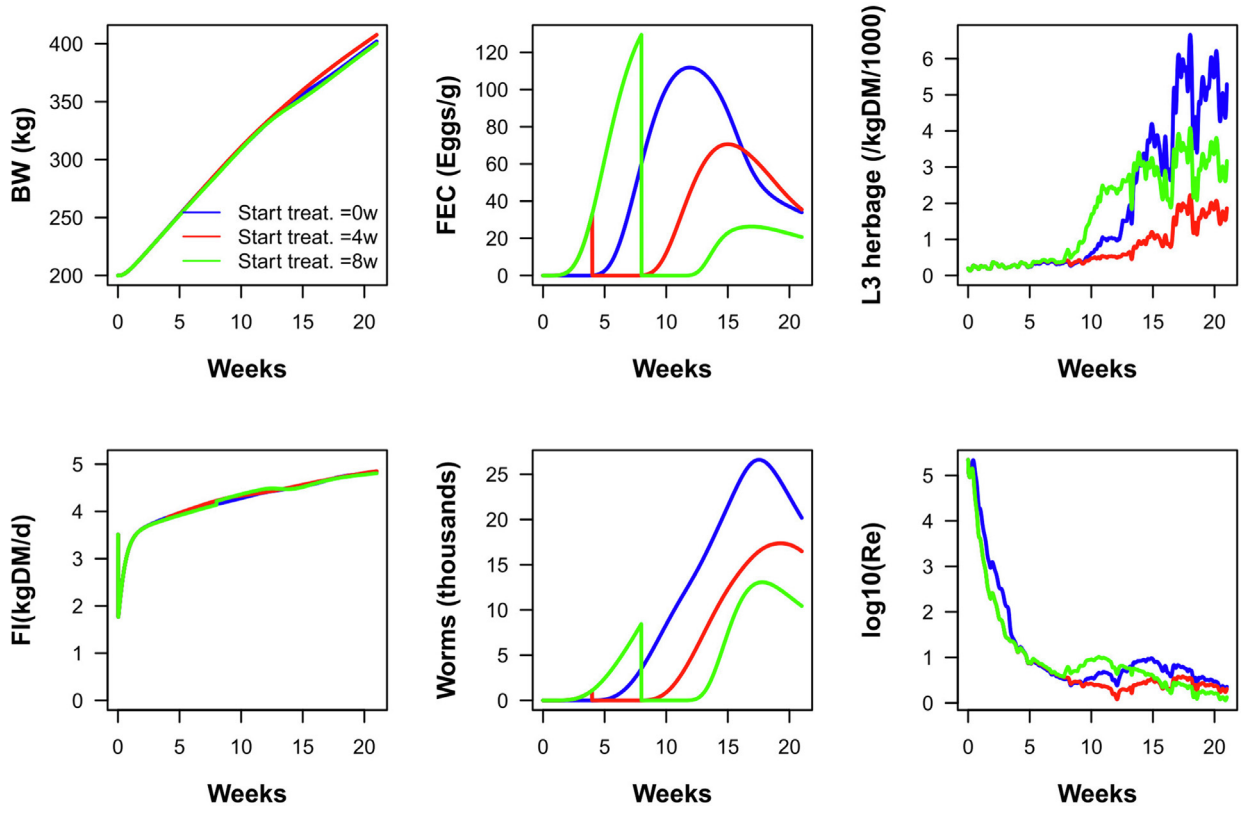

Fig. 4. Model behaviour with one anthelmintic treatment: effect of the timing of application. Progression of *Ostertagia ostertagia* infection of cattle during the grazing season of the baseline herd and grazing system with one round of anthelmintic treatment with differing times of application, 0, 4 and 8 weeks after turnout (see Section 2.7.3 for details on drug treatment). Traits shown: body weight (BW), faecal egg count (FEC) in wet faeces, density of L3s on dry herbage, daily feed intake (FI), number of adult worms, and logarithm of the effective reproduction number R_e. kgDM, kg dry matter.

f. model behaviour example in Supplementary Fig. S2), in agreement with estimates of β for *O. ostertagi* in cattle (Smith and Grenfell, 1985) and for other GINs in sheep (Kao et al., 2000).

As the processes modelled are not specific to *O. ostertagi*, the model has the potential to be re-parameterised for application to other parasites with a similar direct life cycle, i.e. where transmission occurs through free-living eggs and larvae (Anderson and May, 1992; Smith and Grenfell, 1994). Such parasites include GINs in cattle such as *Cooperia* spp., and highly pathogenic parasites in regions outside northern Europe, such as *Haemonchus placei*. First steps have already been taken in extending the FL stage dynamics (Grenfell et al., 1986; Sauermann and Leathwick, 2018) and the parasitic stage dynamics (Rose Vineer et al., 2020b) to these species, although not yet in an integrated full-cycle model. Further availability of parameters for other parasites and other empirical datasets will support future extensions of the model to temperate regions beyond northern Europe, likely to involve different weather patterns, parasite species, and management practices. In principle, the model can also be adapted to GINs in other ruminant species. While several full-cycle models have been developed for other ruminants (Verschave et al., 2016a) such as sheep (Kao et al., 2000; Louie et al., 2007; Singleton et al., 2011), the current model incorporates additional variables that are relevant when seeking to predict outcomes and optimise interventions for both performance and parasite control, as recommended to attenuate the development of anthelmintic resistance (Charlier et al., 2014).

Given the many sources of uncertainty in the parasite and host dynamics, including uncertainty in the model parameters, reliable forecasting for a specific situation cannot be reasonably expected (Grenfell et al., 1987a; Smith and Grenfell, 1994; Cornell, 2005); this is even more so as strong influencers such as weather and pasture contamination cannot be predicted at a future time. Instead, this and related models (Verschave et al., 2016a) are suited for predicting system responses to given parasite control strategies in order to classify their relative efficacies (Cornell, 2005; Smith, 2011). Therefore, agreement with observed patterns of infection and growth in published trials is important to build confidence in the use of the model under different conditions.

4.2. Model validation

Validation was carried out on empirical studies in northern Europe, which were the ones we found available that satisfied our criteria. The criteria included reporting BW and FEC variables, containing a non-treated group, and the animals having been infected naturally through grazing such that the parasite dynamics were controlled by weather and host-parasite interactions alone. Some studies included inoculation of L3s at turnout, but subsequent infection was exclusively through grazing. The model predictions compared satisfactorily against the observations of BW and FEC across all studies, both graphically and in formal statistical testing. However, there were two studies, whose animals were inoculated with larger L3 doses at turnout, where the model underestimated considerably the magnitude of the FEC peak, although there was good agreement at the remaining time points. One explanation for this outcome stems from the fact that the animals were subjected to co-infection, predominantly by *O. ostertagi* and *C. oncophora* (Table 5), as is typical in natural field infections (Michel et al., 1970; Henriksen et al., 1976; Högberg et al., 2021), and that the FEC data used did not differentiate parasite species. As *C. oncophora* has considerably higher maximum fecundity (prior to being regulated) (Kloosterman et al., 1984; Verschave et al.,

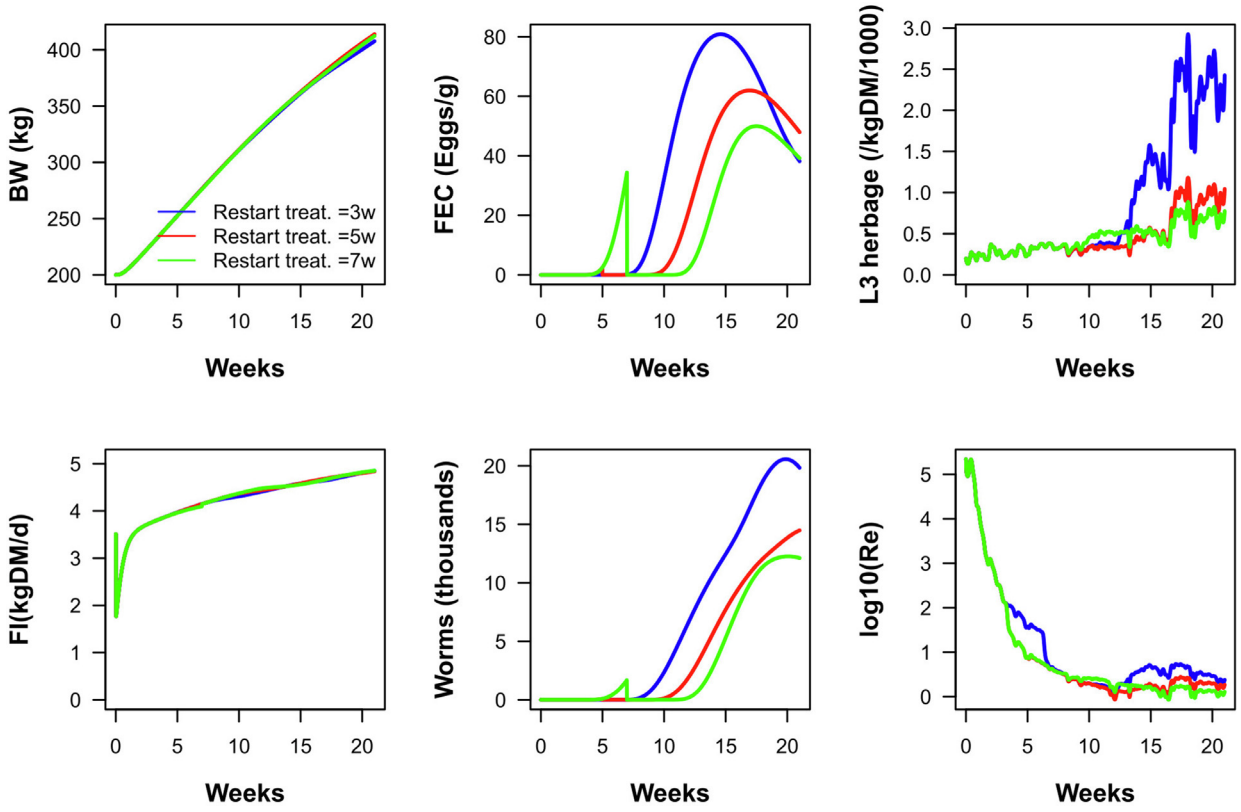

Fig. 5. Model behaviour with two anthelmintic treatments: effect of the timing of the second treatment. Progression of *Ostertagia ostertagi* infection of cattle during the grazing season of the baseline herd and grazing system with a first round of anthelmintic treatment at turnout but differing in the time of application of the second round, at 3, 5, and 7 weeks after turnout. Drug efficacy is maintained for 3 weeks (see text for details on drug treatment). Traits shown: body weight (BW), faecal egg count (FEC) in wet faeces, density of L3s on dry herbage, daily feed intake (FI), number of adult worms, and logarithm of the effective reproduction number R_e. kgDM, kg dry matter.

2014, 2016a), a model parameterised for *O. ostertagi* would be expected to lead to lower FEC prediction, particularly in studies where parasite inoculated doses and loads are higher and at the peak of egg production, i.e. prior to the strong regulation of fecundity imposed by the developing acquired immunity and worm burden. A similar occurrence has been reported in previous model validation exercises (Smith and Guerrero, 1993). Experimental studies have also suggested that the FEC may differ between species at its peak but not necessarily at other time points (Kloosterman et al., 1984; Hilderson et al., 1995).

The use of studies with co-infection was imposed by a lack of data on single-species infections under natural weather conditions, which is required in order to test a full-cycle model. However, testing models under realistic field conditions, where co-infection by parasite species is common, can be regarded as desirable. As we described earlier, the initial L3 concentrations input in the model and the parasite loads predicted were interpreted as representing total infection by both parasite species. Our working hypotheses were that: (i) there are no interactions between the species within the host, and (ii) the parameters and processes in the model are adequate for describing the dynamics of both species. Under these hypotheses, the model can be regarded as representing a typical parasite mixture where e.g. *C. oncophora* dominates early and *O. ostertagi* dominates later (Dimander et al., 2003; Högberg et al., 2021).

Regarding the first hypothesis, there is no experimental evidence of interaction between the host responses to *O. ostertagi* and *C. oncophora* in grazing calves (Satrija and Nansen, 1993; Hilderson et al., 1995; Dorny et al., 1997), although there is some evidence of cross-immunity (Kloosterman et al., 1984). There is evidence of interaction between other co-infecting GIN species in cattle (Herlich, 1965) and in sheep and goats (Sykes et al., 2009; Lello et al., 2018; Basripuzi et al., 2020). Accounting for possible interaction between *O. ostertagi* and *C. oncophora* in cattle would require more experimental knowledge and further model advancement (see below).

Regarding the second hypothesis of adequacy of our model to describe both parasite species, it is likely that the same basic mechanisms are suitable to describe both species, at least at the level of simplification of the models, e.g. the location of establishment in the gastrointestinal tract, which differs between *O. ostertagi* and *C. oncophora*, is not specified in the model. However, there may be differences in parameter values between parasite species, e.g. in rate of acquisition of immunity (Hilderson et al., 1995; Dorny et al., 1997), although only some of the parameters have been quantified for both species (Verschave et al., 2014, 2016a; Rose et al., 2015; Rose Vineer et al., 2020b). One reason why the model may have approximated satisfactorily many of the variables in these studies, is that several of the parameters may be similar enough between the two parasite species (Grenfell et al., 1986; Verschave et al., 2014, 2016b; Rose Vineer et al., 2020b), and among those that differ more they could have contrasting effects on the overall dynamics, e.g. through characteristics of the immune response versus fecundity, as suggested by experiments (Hilderson et al., 1995). Moreover, where there are differences, we expect them to be greater when egg production and parasite loads are higher, which, due to the regulatory effects of immunity and density-dependency, may be relatively short-lived and occur predominantly near the peak of FEC. Therefore, there is a cautious indication the model may, to a degree, be able to capture typical seasonally varying mixtures of these parasites in the field, although this is an area where future research is clearly needed.

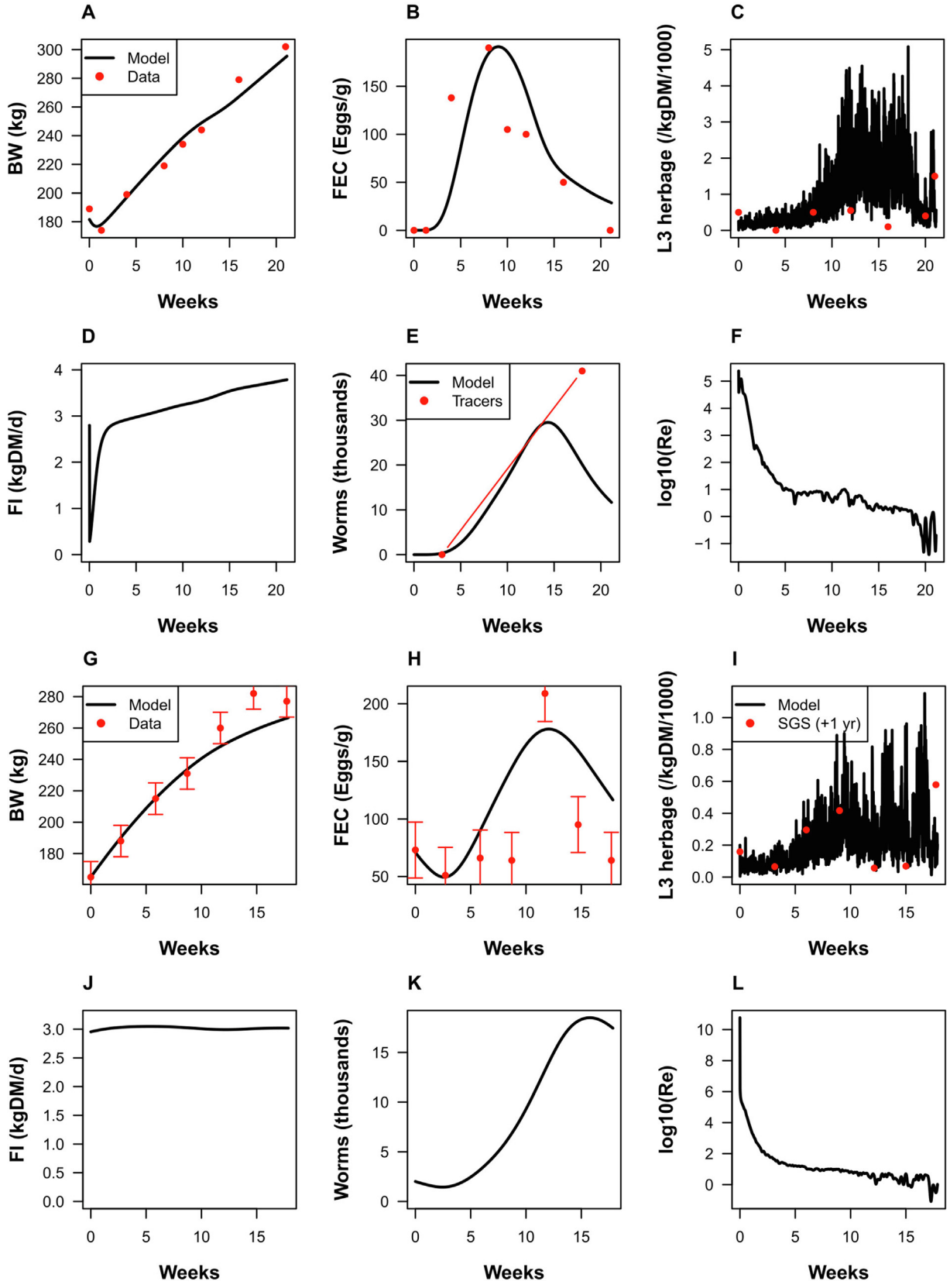

Fig. 6. Model comparison with studies involving natural infection of cattle: Larsson et al. (2006) (A-F) and O'Shaughnessy et al. (2015) (G-L). Traits shown: body weight (BW), faecal egg count (FEC) in wet faeces, density of L3s on dry herbage, daily feed intake (FI), number of adult worms, and logarithm of the effective reproduction number R_e. kgDM, kg dry matter. Animals were infected with a mixture of *Ostertagia ostertagi* and *Cooperia oncophora*. The results of the statistical tests are given in Table 6. Panels with predictions but no empirical data are included for cross-comparison among variables and studies.

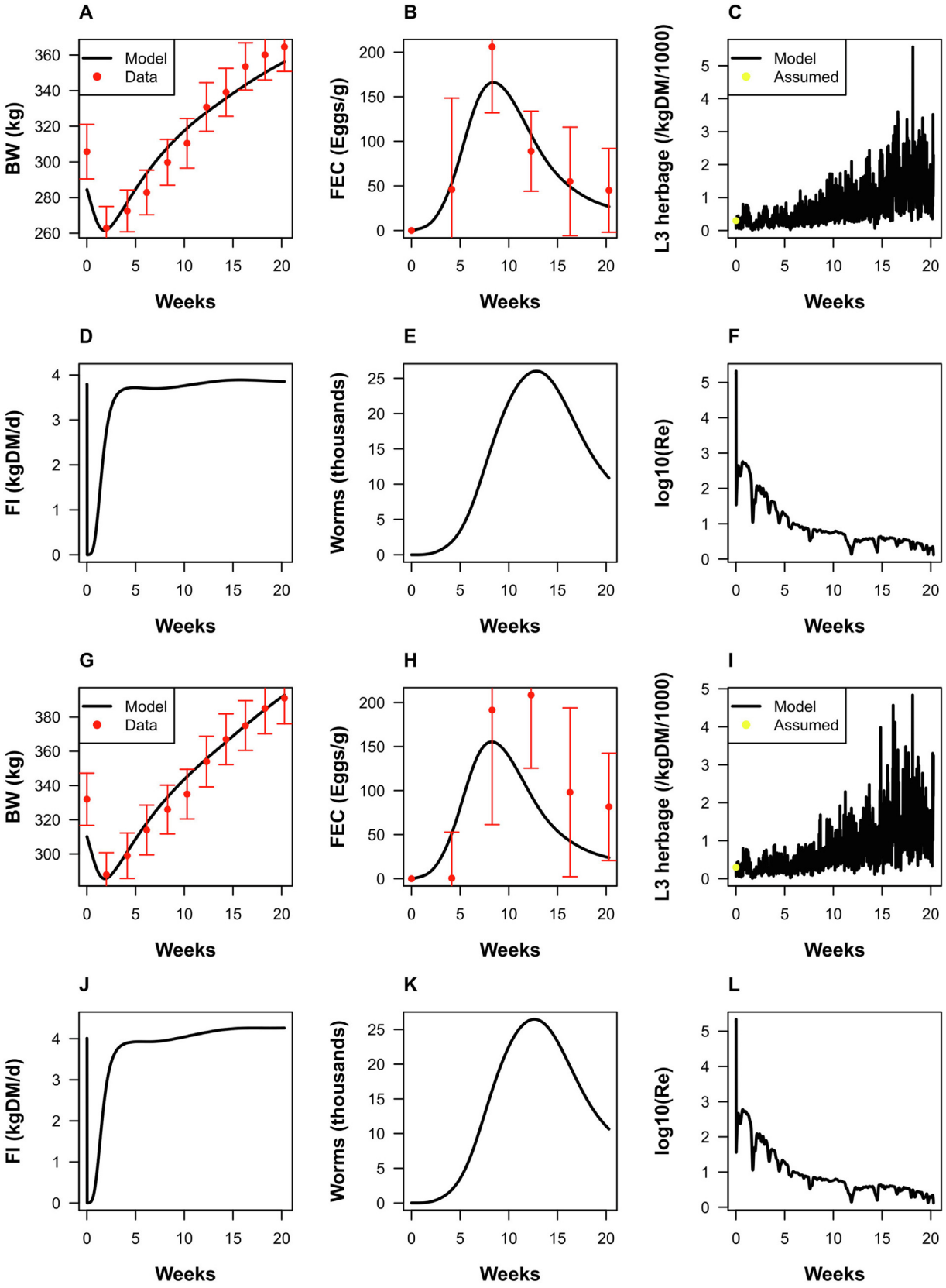

Fig. 7. Model comparison with studies providing a low parasite dose pre-turnout followed by natural infection of cattle: Höglund et al. (2018) dairy breed (A-F) and cross breed (G-L). Traits shown: body weight (BW), faecal egg count (FEC) in wet faeces, density of L3s on dry herbage, daily feed intake (FI), number of adult worms, and logarithm of the effective reproduction number R_e. kgDM, kg dry matter. The parasite dose at turnout was a 5000 even mixture of *Ostertagia ostertagi* and *Cooperia oncophora*. The results of the statistical tests are given in Table 6. Panels with predictions but no empirical data are included for cross-comparison among variables and studies. See Section 2.8.2 regarding assumed values of L3s on herbage at turnout (yellow (light grey)).

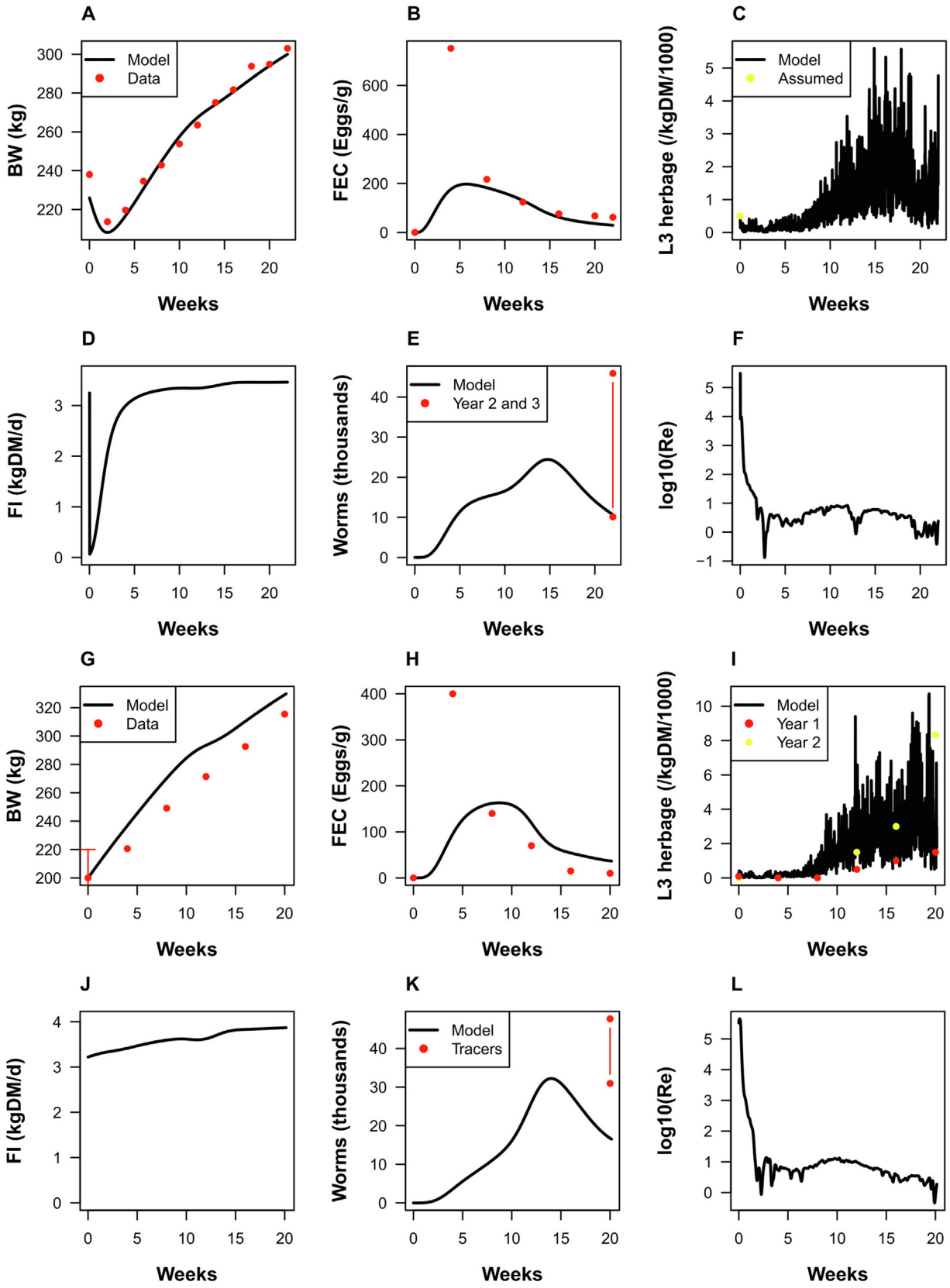

Fig. 8. Model comparison with studies providing a higher parasite dose pre-turnout followed by natural infection of cattle: Höglund et al. (2013) (A-F) and Dimander et al. 2003 (G-L). Traits shown: body weight (BW), faecal egg count (FEC) in wet faeces, density of L3s on dry herbage, daily feed intake (FI), number of adult worms, and logarithm of the effective reproduction number R_e. kgDM, kg dry matter. The parasite dose at turnout was a 40,000 (top) and 10,000 (bottom) even mixture of *Ostertagia ostertagi* and *Cooperia oncophora*. Results of the statistical tests are given in Table 6. Panels with predictions but no empirical data are included for cross-comparison among variables and studies. See Section 2.8.2 regarding assumed values of L3s on herbage at turnout (yellow (light grey)).

Table 6
Statistical tests on the relationship between the datasets and the model predictions. Residual sum of squares (RSS) on given degrees of freedom (df); 95% confidence interval (CI) of the slope of the linear relationship between observation data and prediction.

Trait	Statistic	O'Shaughnessy et al., 2015	Larsson et al., 2006	Höglund et al., 2018, dairy	Höglund et al., 2018, cross	Höglund et al., 2013	Dimander et al., 2003
BW	*P*-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	R^2_{adj}	0.99849	0.99909	0.99904	0.99943	0.99969	0.99935
	RSS (df)	9.1 (6)	7.0 (7)	9.9 (10)	8.2 (10)	4.6 (11)	6.7 (5)
	lower CI	0.993	0.981	0.987	0.983	0.997	0.918
	upper CI	1.067	1.031	1.029	1.015	1.019	0.969
FEC	*P*-value	<0.001	<0.001	<0.001	0.00356	0.01029	0.07687
	R^2_{adj}	0.84926	0.77949	0.96251	0.81074	0.64229	0.39640
	RSS (df)	39.7 (6)	46.6 (7)	19.0 (5)	55.2 (5)	181.0 (6)	136.4 (5)
	lower CI	0.474	0.458	0.882	0.733	0.758	−0.204
	upper CI	1.067	1.17	1.341	2.184	3.757	2.815

Compared with the predictions of BW and FEC, prediction of the L3 concentration on herbage was in less quantitative agreement with the data (where available); the model overestimated the abundance of L3s on pasture relative to that observed, although the patterns of the predicted time trends were consistent with those of the data. However, many factors can contribute to low efficiency and sampling variation in the field recovery of L3s. These factors include the recovery method and the analyst (Kloosterman A., 1971, Observations on the epidemiology of trichostrongylosis of calves, PhD Thesis, Wagenningen University, The Netherlands; Verschave et al., 2015; Paras et al., 2018; Cain et al., 2021), differing grass growth and under-sampling of the sward at the lowest level (Tontini et al., 2019), soil-herbage migration of L3s, and avoidance of faecal pats or dung beetles, which associate with higher L3 concentration (Henriksen et al., 1976; Nansen et al., 1988). Measurement variation within a study can result from limited sampling of highly aggregated L3s, and this possibility cannot be excluded in the studies where L3 counts dropped to zero and rebounded during the season. On the other hand, the use of differing recovery methods can lead to differences in recovery rate between studies (Verschave et al., 2015). Therefore, we would not regard the above overestimation as significant.

A very small subset of model parameters or variables was informed by factors reported in the studies used for validation. Factors that were not measured in these experiments may have influenced the observations. These could include weather (beyond temperature and rainfall, which were included in the model), management, initial pasture contamination, immune status (naïve), faecal moisture content, sampling variation of the FEC method used, density and growth of the grass biomass, apparent digestibility of grass DM and use of feed supplements, and genetic strength and speed of the immune response. As we did not have information on any of these factors and we were not fitting the model to the data, we assumed that all remaining parameters of the model did not differ between studies. Given the potentially unaccounted-for variables, the ability of the model to produce estimates of parasite population and animal growth so close to observed values provides confidence in its ability to predict system dynamics under different, broader conditions.

4.3. Model behaviour

We have analysed some of the model behaviour by changing each of a small number of parameters. This analysis served to confirm expected qualitative outcomes and gain further confidence in the model, and to demonstrate some of the insights that can be derived from an integrated full-cycle model by exploring 'what-if' scenarios.

Changing the parasitological history of the pasture by increasing its contamination level at turnout led to earlier peaks in the predicted FEC and worm burden; these time shifts are similar to known peak-shift effects on the prevalence of macroparasites when increasing the force of infection on the host population (Anderson and May, 1985; Woolhouse, 1998). These results also agree with earlier model predictions (Berk et al., 2016b), except the latter contained two successive peaks, while we predicted a single peak during the season and none of the empirical FEC datasets used for validation indicated the occurrence of two peaks. The difference could stem from differing weather or from differing modelling of the parasite FL stage dynamics, which in Berk et al. (2016b) excluded the influence of precipitation.

Similarly, altering the size of the host population in our model by increasing the cattle stocking density led to similar time shifts in the peak excretion of transmission stages and in the peak worm burden. The magnitude of the peak worm burden increased with increasing stocking density in agreement with earlier model predictions (Grenfell et al., 1987a; Berk et al., 2016b). We predicted this same pattern for the peak FEC, which agrees with Berk et al. (2016b) but is opposite to the pattern in Grenfell et al. (1987a), who highlighted that the worm burden, W, is a more indicative prediction as the FEC is known to be a poor index of parasite burden; although W is more rarely measured for obvious reasons.

Overall, these results confirmed expectations about the behaviour of the model; they also illustrate the importance of measuring L3s on pasture at turnout as some aspects of prediction can be uncertain if this variable is unknown. In addition, in each of the scenarios above there were appreciable effects on BW gain, with the differential between BW trajectories reducing by the end of the season (due to compensatory growth) in the case of differing initial contamination, but with little or no recovery in lost gain in the case of differing stocking densities. Similarly, the levels of L3 herbage contamination converged by the end of the season in the first case, but diverged in the case of differing stocking densities. These outcomes are consistent with lasting effects of higher stocking density (Hansen et al., 1989; Thamsborg et al., 1998) and further confirm expected model behaviour. Overall, the above results highlight that the effects of parasitological history due to grazing in the previous season can be transient, while those of more intense grazing can dominate and be long lasting. Figs. 2-8 could provide insights for management prior to and during a grazing season; they predict the dynamics of six host and parasitological variables of which only BW and FEC (and occasionally L3s on herbage) are observed; the predictions only rely on knowledge or assumption of these variables at the time point when predictions start. For example, assuming a past weather scenario, a decision

maker could predict gain and infection levels by the end of a season under a chosen treatment and management strategy.

Exploring a set of simple drug treatment strategies, we obtained the following results. First, implementing a single anthelmintic treatment, the model predicted that the optimal application is at an intermediate time after turnout, e.g. 4 weeks, rather than immediately on turnout or later in the season. This choice is based on multiple criteria: it led to the highest cumulative BW gain and to lower cumulative parasite burden and parasite excretion by the host, and thus to potentially lower risk of clinical disease; on the other hand, herbage contamination was comparable to that in the late treatment. This outcome agrees with the expectation that delaying treatment to mid-season allows the development of immunity and leads to better parasite control in the long-term, while curbing the delay pre-empts the onset of parasite-induced anorexia and leads to better performance. Second, implementing treatment at turnout, the model predicted that the best timing for application of a second treatment is within a time window of 5 to 7 weeks after turnout, rather than immediately after the end of the first treatment at 3 weeks after turnout. This strategy led to a lower level of herbage contamination carried over to the next season and to lower cumulative parasite burden, although it did not lead to significant differences in performance. These treatment scenarios were illustrative and not chosen to mimic specific treatment regimens, although administration of persistent anthelmintic formulations early in the grazing season tend to be favoured due to their strong suppression of egg outputs and consequently of L3 levels. This strategy, however, has been posited to slow the acquisition of immunity (Vercruysse et al., 1994) and could therefore be counterproductive. Overall, these results illustrate the usefulness of a full-cycle epidemiological model for analysing and choosing treatment and management strategies, in particular accounting for performance and not only parasitological outcomes.

The predicted effective reproduction number, R_e, exhibited a similar pattern across the empirical studies and the model behaviour analyses: very large initial values, a rapid decline due to the limiting effects of acquired immunity and density dependency, followed by narrow-ranged variation nearly containing the value of 1. We interpret this pattern as being reassuring. First, across a range of differing parasitological, host and weather conditions, it agrees with the expectation that the parasite populations will have converged to a state of quasi stability superimposed by short-term fluctuations due to variable host response, weather and seasonal climate. Second, this result supports, rather than questions, the consistency of the parameters of the host and free-living model components that we have attempted to integrate into a full-cycle model.

4.4. Model assumptions and extensions

The model makes several simplifying assumptions already stated. One of the assumptions was that, to first approximation, the growth rate and DM content of the grass biomass did not vary with the weather and throughout the season. Such dependency could be included; however, a fuller account of environmental influence may involve further variables such as soil moisture saturation, and in turn soil type and topography, as well as management factors in relation to grass cultivar and fertiliser application. Similarly, stocking density could directly influence the rate of grass growth per hectare (r_g), for example through the mechanical effect of cattle walking and trampling, on which we lack data; nevertheless, the dynamics of grass availability (Eq. (24)) include the limiting effect of the current grass density and loss from grazing under a given stocking density. These refinements go beyond our current purpose and would require substantial empirical support. The current constant rate of grass growth is the average of empirical records from the location and period of the baseline system (Table 3). Furthermore, we assumed there was no additional feeding on pasture, consistent with the data used for model development and validation. The model also did not include the arrest or hypobiosis of parasitic larval stages and their subsequent re-emergence (Michel et al., 1976; Armour, 1980; Smith and Grenfell, 1985), although this would become relevant only towards the end of the FGS and beyond. First attempts with this purpose have been taken in Rose Vineer et al. (2020a). Nevertheless, the higher late season levels of L3s predicted under some scenarios could drive important epidemiological consequences, for example by causing higher risks of type II ostertagiosis through the re-emergence of arrested larvae, or by increasing the levels of pasture contamination in the following season through increased L3 emergence or L3s overwintering on pasture. The consequences of parasite exposure for immunity in older age classes could also be explored in an extended model, including the application of targeted treatment approaches in herds with differing levels of immunity (Ravinet et al., 2017).

The model describes the dynamics of an average animal and characterises the grazing population through its stocking density. In particular, the model does not include genetic and phenotypic variation. In fact, Smith and Guerrero (1993) have suggested that host heterogeneity in parasite load can be ignored in models aiming to evaluate control strategies that treat all animals in the same way. However, individual-based approaches have been evaluated for sheep (Louie et al., 2005) and cattle (Berk et al., 2016b). The current model could be extended to explore optimal strategies for targeted selected treatments based on individual infection or performance status (Höglund et al., 2013; Charlier et al., 2014; Merlin et al., 2017). Such host heterogeneity provides one of the mechanisms thought to generate the observed aggregation in parasite load and FEC among hosts, the other being the observed aggregation of L3s on pasture (Anderson and Gordon, 1982; Cornell et al., 2004). An alternative, empirical way of accounting for the latter is to make the number of ingested L3s a random variable with an empirical overdispersed distribution such as the negative binomial (Smith and Guerrero, 1993; Berk et al., 2016b) (we took this approach when comparing predictions with empirical data but not in the inherent parasite dynamics). Alternatively, individual-based formulations with stochastic dynamics and spatially heterogeneous exposure allow both forms of aggregation to be linked mechanistically (Cornell et al., 2004; Cornell, 2005; Fox et al., 2013), but are usually applied to simpler representations of the GIN lifecycle for tractability (Smith and Grenfell, 1994); moreover, the current addition of weather-driven variation will account for part of the dynamic stochasticity in the system. The inclusion of aggregation would strengthen the evaluation of control strategies further when it is relevant to account for heterogeneity in the parasite population; it is expected to influence the dynamics of invading anthelmintic-resistant strains and persisting non-resistant refugia (van Wyk, 2001; Cornell, 2005). Due to aggregation and other factors already discussed, observations of L3s on herbage, in the empirical studies that report them, are uncertain; their potential effect could have been evaluated by generating distributions of predictions based on an assumed range of input values; these would be expected to include the data in the validation exercise. Sensitivity to uncertainty in other input parameters could be tackled similarly. Taking such an approach would have added an extra layer of complexity to the results, while sensitivity to such factors can be assessed from the results of the model behaviour study.

Finally, as we already discussed extensively, the model was designed for infection by a single-parasite, i.e. *O. ostertagi*, although it was applied to co-infections for reasons explained. This is the case with most models developed for specific GIN infections. Our results, however, supported the application to co-infections by *O.*

ostertagi and *C. oncophora* in the empirical studies considered here. A future challenge is to extend such non-linear models to account explicitly for co-infection. Generic models investigating the implications of parasite co-infection have, for tractability, assumed unspecific host responses to parasite burdens and thus that parasite species did not interact directly (Dobson and Roberts, 1994), but there have been theoretical attempts at including such effects (Bottomley et al., 2005). However, currently, there is little knowledge about which responses would be interacting and how; therefore, more empirical study on GIN co-infection is needed.

4.5. Conclusions

We developed a model of the full life cycle of *O. ostertagi* that, to our knowledge for the first time, also incorporates grass and animal growth, and data-driven environmental effects on infective larval availability, in addition to host immunity. The model was able to reproduce expected patterns and scales of host growth and parasite dynamics in first season grazing cattle, and closely matched observed results in published studies without the need for model fitting. Exploration of initial pasture conditions, stocking density and treatment scenarios showed that the model can be used to predict the effects of management and climate on infection patterns. Future application could include optimisation of intervention strategies under a rapidly changing climate and advancing anthelmintic resistance.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpara.2022.11.009.

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