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1 GLOWORM-PARA: a flexible framework to simulate the population

2 dynamics of the parasitic phase of gastrointestinal nematodes infecting

3 grazing livestock

4

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23

24 **ABSTRACT**

25 Gastrointestinal (GI) nematodes are a significant threat to the economic and

26 environmental sustainability of keeping livestock, as adequate control becomes

27 increasingly difficult due to the development of anthelmintic resistance (AR) in some

28 systems and climate-driven changes to infection dynamics. To mitigate any negative

29 impacts of climate on GI nematode epidemiology and slow AR development, there is

30 a need to develop effective, targeted control strategies that minimise the

31 unnecessary use of anthelmintic drugs and incorporate alternative strategies such as

32 vaccination and evasive grazing. However, the impacts climate and GI nematode

33 epidemiology may have on the optimal control strategy are generally not

34 considered, due to lack of available evidence to drive recommendations. Parasite

35 transmission models can support control strategy evaluation to target field trials,

36 thus reducing the resources and lead-time required to develop evidence-based

37 control recommendations incorporating climate stochasticity. GI nematode

38 population dynamics arising from natural infections have been difficult to replicate

39 and model applications have often focussed on the free-living stages. A flexible

40 framework is presented for the parasitic phase of GI nematodes, GLOWORM-PARA,

41 which complements an existing model of the free-living stages, GLOWORM-FL.

42 Longitudinal parasitological data for two species that are of major economic

43 importance in cattle, *Ostertagia ostertagi* and *Cooperia oncophora,* were obtained

44 from seven cattle farms in Belgium for model validation. The framework replicated

45 the observed seasonal dynamics of infection in cattle on these farms and overall,

46 there was no evidence of systematic under- or over-prediction of faecal egg counts

47 (FECs). However, the model under-predicted the FECs observed on one farm with

48 very young calves, highlighting potential areas of uncertainty that may need further

49 investigation if the model is to be applied to young livestock. The model could be

50 used to drive further research into alternative parasite control strategies such as

51 vaccine development and novel treatment approaches, and to understand GI

52 nematode epidemiology under changing climate and host management.

53

54 *Keywords*: *Ostertagia ostertagi*; *Cooperia oncophora*; Model; Parasite; Population

55 dynamics; Transmission; Nematode; Livestock

56

57 **1. Introduction**

58   Gastrointestinal (GI) nematodes are increasingly recognised as an important

59 threat to the future sustainability of keeping livestock for food production and

60 leisure. At a policy level, livestock make a significant contribution to agricultural

61 greenhouse gas (GHG) emissions, which may be exacerbated by GI nematode

62 infections (Fox et al., 2018). In 2013, methane emissions from cattle and sheep were

63 responsible for 47% of agricultural GHG emissions in England, and approaching 90%

64 of agricultural GHG emissions in Wales, Scotland and Northern Ireland (Salisbury et

65 al., 2015). GI nematodes also threaten food security and the economic sustainability

66 of livestock farming as they cause significant production losses in ruminants

67 (Nieuwhof and Bishop, 2005; Charlier et al., 2009). For example, a meta-analysis of

68 88 studies found that lambs infected with GI nematodes experienced a 25%

69 reduction in weight gain (Mavrot et al., 2015). Similarly, in cattle, GI nematodes

70 cause significant reductions in weight gain and milk yield (Verschave et al., 2014b).

71 Finally, the pathogenic implications of GI nematode infections (e.g. Besier et al.,

72 2016) on host welfare are clear, however the impact of subclinical and chronic

73 infections remains an understudied but important question in livestock helminth

74 research (Morgan et al., 2018).

75   Currently, the control of GI nematodes in livestock is primarily based on the

76 chemotherapeutic use of anthelmintic substances (Charlier et al., 2014). However,

77 both the influence of climate change and, in some places, the development of AR on

78 farm management and parasite epidemiology are expected to challenge the future

79 control of these infections (Morgan and van Dijk, 2012; Skuce et al., 2013). Progress

80 has been made towards targeted, sustainable control strategies that are

81 economically sound (Charlier et al., 2014) but the need for adequate decision-

82 support tools to aid in the implementation of these strategies remains (Morgan,

83 2013). Multiple initiatives promoting the sustainable control of parasites in livestock

84 have been developed worldwide, such as SCOPS (Sustainable Control of Parasites in

85 Sheep; scops.org.uk), COWS (Control of Worms Sustainably; cattleparasites.org.uk),

86 the UK-VET guidelines on parasite control in horses (Rendle et al., 2019) in the UK,

87 and ASKBILL (Kahn et al., 2017) in Australia. These initiatives provide flexibility to

88 adapt their guidelines to different livestock management systems and, in the case of

89 SCOPS, resource-intensive longitudinal studies evaluating the efficacy of their

90 guidelines in a range of systems are ongoing (e.g. Learmount et al., 2018).

91 However, the epidemiology of GI nematode infections is a result of complex

92 interactions between parasite, host, climate, farm management and historic control

93 strategies. The efficacy of these guidelines in the diversity of management systems

94 practiced by cattle, sheep, goat and horse keepers worldwide, and their

95 sustainability in the face of climate change and AR cannot be studied empirically

96 without significant resource input and multi-year studies to incorporate inter-annual

97 weather variability and extreme weather events.

98 Parasite transmission models are useful as they provide the potential to include a

99 variety of processes on different levels and extrapolate current knowledge to

100 alternative scenarios at large temporal scales (Rose et al., 2015). In doing so, model

101 simulations can be used to target resources for empirical research where they are

102 needed most, and guide the development of evidence-based parasite control

103 strategies and tools. The development of mathematical models to simulate the

104 transmission dynamics of GI nematode infections in ruminants dates back several

105 decades. The majority of the existing models were developed specifically for GI

106 nematode infections in sheep (Verschave et al., 2016a lists 32 models). Fewer

107 models exist for cattle nematodes (Verschave et al., 2016a lists seven models for

108 *Ostertagia ostertagi*), and model development for equine nematode species dates

109 back only a few years (Leathwick et al., 2015, 2016, 2017). Generic models that

110 provide a framework for GI nematode infections that can be applied to a range of

111 host and nematode species are also scarce (Smith, 2011), while their development is

112 of great interest in identifying emerging patterns of change (Molnár et al., 2013;

113 Rose et al., 2014).

114 Recently, a generic model framework for the free-living phase of GI nematodes,

115 which has important modifications on behaviour and development of the larvae on

116 pasture, was developed (GLOWORM-FL, Rose et al., 2015). This model was initially

117 applied to three species of importance in cattle (*O. ostertagi*) and small ruminants

118 (*Haemonchus contortus* and *Teladorsagia circumcincta*), and additional published

119 parameters and data are available to adapt the model to equine cyathostomins

120 (Leathwick et al., 2015), *Cooperia oncophora* in cattle (Sauermann and Leathwick,

121 2018) and *Marshallagia marshalli* in small ruminants (Carlsson et al., 2013). To fully

122 explore the consequences of different control and management approaches on

123 parasite epidemiology, however, a complementary model for the parasitic phase is

124 needed as host-parasite interactions and host acquired immunity play crucial parts in

125 the transmission dynamics of GI nematodes (Claerebout and Vercruysse, 2000).

126 The aim of the current study was to develop a conceptual model framework for

127 the parasitic phase of GI nematodes, GLOWORM-PARA, that can be applied to a

128 range of host and parasite species. Here, the model is parameterised and validated

129   for two species that are of major economic importance in cattle, i.e. *O. ostertagi* and

130   *C. oncophora.* Previous cattle models have tended to only focus on one nematode

131   species, i.e. *O. ostertagi*, perhaps due to its pathogenic significance compared with

132   *C. oncophora*, against which cattle develop an effective immune response. No single-

133   species model exists for *C. oncophora,* despite its increasing importance in the

134   context of anthelmintic resistance and treatment failure (Sutherland and Leathwick,

135   2011). The development of acquired immunity against GI nematodes was modelled

136   and parameterised in a heuristic but data-driven manner, to provide a transparent

137   and replicable approach. An extensive set of field observations of first season grazing

138   cattle was used for model validation.

139

140   **2. Materials and methods**

141   *2.1. Model framework*

142   The model framework (Fig. 1), tracks the mean number of GI nematodes and level

143   of acquired immunity in a group of hosts (i.e. is a population-based mean-field

144   model). State variables and model parameters are defined in Table 1.

145   Infective L3 are ingested with herbage (*L3i*) and enter the pool of pre-adult

146   parasitic nematodes (*P*). Pre-adult nematodes either develop to adult nematodes (*A*)

147   or arrest their development as larvae (*Pa*) before developing to the adult stage.

148   Although the model is developed and validated for trichostrongylid nematodes in

149   the present study, it could also be applied to other strongylid species with a broadly

150   similar life cycle (e.g. equine cyathostomins) as all pre-adult stages are modelled as a

151   single state variable and the pre-adult stage involved in arrested development is not

152   specified. This basic representation of the GI nematode life cycle is similar to

7

153   numerous previous models, as reviewed by Verschave et al. (2016a) and Smith

154   (2011).

$$\frac{dP}{dt} = L3i - \delta P - \mu_1 P \tag{1}$$

$$\frac{dPa}{dt} = -h_2\mu_2 Pa + \delta h_1 P \tag{2}$$

$$\frac{dA}{dt} = \delta(1 - h_1)P + h_2 Pa - \mu_3 A \tag{3}$$

155   Acquired immunity (*r*) increases in response to exposure to infection (Claerebout

156   and Vercruysse, 2000), in this case the L3 ingestion rate (*L3i*), and decays with time,

157   similar to previous models e.g. Roberts and Grenfell (1991). However, the present

158   framework differs from previous models in its representation of *r* as a logistic growth

159   function to facilitate modelling interactions between the host immune response and

160   parasite life-history parameters (Section 2.3.3).

$$\frac{dr}{dt} = \rho(L3i)(1 - r) - \sigma r \tag{4}$$

161

162   *2.2. Model integration*

163   The model was implemented in R v 3.5.1 "Feather Spray" (R Core Team, 2018. R:

164   A language and environment for statistical computing. R Foundation for Statistical

165   Computing, Vienna, Austria) using the *lsoda* function of the *deSolve* package v 1.24

166   (Soetaert et al., 2010) for solving differential equations. The model returns daily

167   output. Anthelmintic treatments (if applicable) are implemented using the *events*

168   argument of the *lsoda* function to reduce the worm burden by a representative

169   percentage for the duration of the residual activity of the product used. For example,

170 an effective moxidectin pour-on treatment for cattle would trigger a reduction in

171 total worm burden of 99% for 35 days. The percentage of reduction could be

172 modified, if necessary, to represent vaccination strategies or reduced anthelmintic

173 efficacies observed in the field. Model output is the mean stage-specific worm

174 burden and egg output per host, which can be used to estimate the faecal egg count

175 (FEC; eggs per gram of faeces (epg)) if the amount of faeces produced is known.

176

177 *2.3. Parameter estimates*

178   Parameterisation of the framework for multiple species is demonstrated using

179 two species infecting cattle that are currently the focus of vaccine development

180 programmes (Matthews et al., 2016): the abomasal nematode *O. ostertagi* and the

181 intestinal nematode *C. oncophora* (Table 2).

182

183 *2.3.1. Seasonally variable parameters*

184   *Arrested development.* There is currently no consensus on the mechanisms of

185 arrested (hypobiosis) and subsequent resumed development in trichostrongylid

186 nematodes, and numerous confounding factors in available data prevent the

187 development of robust mechanistic models of arrest (Smith, 1974; Michel et al.,

188 1976; Frank et al., 1986; 1988; Eysker, 1993; Fernández et al., 1999; Langrova and

189 Jankovska, 2004; Lützelschwab et al., 2005; Langrova et al., 2008). As the numerous

190 potential drivers of arrest are correlated and seasonal (e.g. the age structure of host

191 populations, host immunity, temperature, moisture and photoperiod), a simplified

192 seasonal approach was taken to estimate seasonal variations in the factor driving

193 arrest rates *(d)* which is used to simulate the proportion of developing pre-adult

194 nematodes that enter a state of arrested development (h_1).

195   For *C. oncophora* and *O. ostertagi* this arrest rate (h_1) was assumed to be related

196 to the development success of eggs and larvae on pasture. *d* was approximated as a

197 7 day moving average, determined by the temperature-dependent development

198 rate (using the *na.ma* function in the *imputeTS* R package v 3.0 (Moritz and Bartz-

199 Beielstein, 2017) and the *ma* function in the *forecast* package v 8.9 (Hyndman and

200 Khandakar, 2008)), whereby the minimum arrest rate is assumed to coincide with

201 the period where development success is at its maximum and the maximum arrest

202 rate is assumed to coincide with the period where development success is at its

203 minimum. Thus, the arrest rate at the current time point, *t,* is a function of the

204 species-specific minimum and maximum arrest rates (h_{min} *and* h_{max}), annual

205 minimum and maximum predicted development success at the study site (d_{min} *and*

206 d_{max}), and predicted development success at the current timestep *(d_t)*.

207

$$h_1 = h_{(max)} - \left(\frac{h_{(max)} - h_{(min)}}{d_{(max)}} \right) \times d_t \qquad (5)$$

208

209   The temperature-dependent development rate of eggs and larvae on pasture for

210 *O. ostertagi* was as described in Rose et al. (2015). For *C. oncophora,* development

211 rate data presented in Sauermann and Leathwick (2018) were extracted using Plot

212 Digitizer v2.6.8 (http://plotdigitizer.sourceforge.net/), and a linear model applied to

213 the data using the *lm()* function in R.

214   The proportion of arrested larvae resuming development (h_2) was assumed to be

215   an inverse function of the driver of arrest (i.e. development success for *O. ostertagi*

216   and *C. oncophora)*:

217

$$h_2 = \left(\frac{1}{d_{(max)} - d_{(min)}}\right) \times (d_t - d_{(min)}) \tag{6}$$

218

219   *L3 ingestion rate and dry matter intake.* To calculate the L3 ingestion rate (*L3i*) the

220   average daily dry matter intake (DMI) by grazing cattle was estimated using the

221   equations of MAFF (1975) based on bodyweight (estimated from the bodyweight at

222   turn out using standard age-related growth curves for dairy cattle; Cue et al., 2012,

223   Verschave et al., 2014a). The equations for growing young stock and adult cattle

224   were used for animals with a bodyweight of less than and more than 400 kg,

225   respectively. The rate of ingestion of dry matter was estimated as a proportion of

226   the total available herbage consumed (*kgDM*; standing biomass, i.e. kilograms of dry

227   matter per hectare). From this, the L3 ingestion rate was estimated as follows

228   (parameter and state variables are defined in Table 1):

$$L3i = -ln\left(1 - \frac{DMI}{kgDM}\right) \times L3h \tag{7}$$

229

230   *Faeces production and faecal egg counts.* The average daily faeces production

231   was estimated based on host body weight using the formula of Nennich et al. (2005).

232   Mean FECs (epg) for the group of hosts can be estimated from the number of adults

233   (*A*), per adult fecundity rate (*λ*) and expected daily faeces production (*f*).

$$\text{FEC} = \frac{Ae^{\lambda}}{f} \tag{8}$$

234

235   *2.3.2. Constant rates*

236   The development rate (δ) from ingested L3 to mature adult was estimated from a

237   prepatent period of 17 days for both *O. ostertagi* and *C. oncophora;* (Table 2; Powers

238   et al., 1982).

239   No data were available in the literature to estimate the mortality rates of arrested

240   larvae due to the confounding effects of resumed development. Therefore, the

241   mortality rate of arrested L4s for both *O. ostertagi* and *C. oncophora* was set at 0.002

242   after Grenfell et al. (1987). Mortality rates of all other pre-adult and adult

243   nematodes were a function of immunity (section 2.3.3).

244

245   *2.3.3. Immunity and dependent parameters*

246   *Immune response and decay rate.* No data were available to formally estimate

247   immunity decay rates (σ) for *O. ostertagi* nor *C. oncophora*, therefore three experts

248   in the area of cattle GI nematodes and vaccine development (J. Vercruysse, E.

249   Claerebout (both co-authors on this study) and P. Dorny, Ghent University, Belgium)

250   were consulted in order to estimate the percentage of decay in immunity over a

251   typical housing period.

252   To estimate the response rate (*ρ*), it was assumed that protective immunity (*r*=1)

253   was typically acquired after 1.5 grazing seasons (9 months of exposure punctuated

254   by a 6 month housing period during which immunity is assumed to decay as

255   described above) for *O. ostertagi* and one grazing season (6 months) for *C.*

256   *oncophora* (Armour, 1989; Ploeger et al., 1995; Claerebout et al., 1998; Ravinet et

257   al., 2014). Species-specific field observations of L3 density on pasture (*L3h*) over the

258   course of a grazing season were extracted from the raw data from field trials across

259   Europe summarised by Shaw et al. (1998). The data concerned pasture larval counts

260   from both 'clinical' and 'subclinical' pastures (i.e. pastures on which an outbreak of

261   parasitic gastroenteritis in the untreated first season grazers was observed, or not,

262   respectively) and included a mixture of calves that were treated with anthelmintics

263   and untreated controls (Shaw et al., 1998). Using these data, equation 4, the decay

264   rate (σ) and the method described in section 2.3.1 for estimating L3 intake rates, the

265   *optimise* function in R was used to find the response rate that minimised the sum of

266   square error (SSE) for each dataset, given the expectation that *r* should equal 0.4 and

267   0.6 after 3 months of grazing, and 0.7 and 1 after 6 months of grazing for *O. ostertagi*

268   and *C. oncophora,* respectively.

269

270   *Immunity-mediated regulation of the parasite population.* Host acquired

271   immunity is assumed to regulate the parasite population in three ways: (i) by

272   exclusion of ingested larvae (increased pre-adult mortality rate); (ii) by decreasing

273   the survival of established (adult) nematodes; and (iii) by decreasing the fecundity of

274   adult nematodes (Barger et al., 1985; Smith and Grenfell, 1985; Coyne and Smith,

275   1992; Smith, 1994; Stear et al., 1995; Claerebout and Vercruysse, 2000; Garnier et

276   al., 2016). Thus immunity-mediated regulation of the parasite population was

277   incorporated by increasing the mortality rates of pre-adult (μ_1) and adult nematodes

278   (μ_3), and decreasing fecundity (λ) with increasing acquired immunity. As acquired

279   immunity cannot be measured directly (Claerebout and Vercruysse, 2000), little is

280 known about the functional relationship between acquired immunity and these

281 parameters. Therefore, a linear relationship was assumed, whereby mortality

282 increases between the minimum and maximum values, and fecundity decreases

283 between the maximum and minimum values as acquired immunity increases

284 between 0 and 1:

285

$$\mu_i = \mu_{i(min)} + (\mu_{i(max)} - \mu_{i(min)})r \qquad (9)$$

$$\lambda = \lambda_{(max)} - (\lambda_{(max)} - \lambda_{(min)})r \qquad (10)$$

286

287

288 *2.4. Model validation*

289

290 *2.4.1. Longitudinal data*

291 The model was validated using independent datasets containing longitudinal

292 parasitological data collected during 2012 and 2013 (described in detail in

293 Verschave, S.H., 2015. Development of a transmission model for gastro-intestinal

294 nematode infections in cattle. PhD thesis. Ghent University, Belgium) and

295 summarised in Supplementary Table S1. The sampled herds consisted of first season

296 grazers located on seven commercial dairy farms in Flanders (Belgium). The herds

297 were visited monthly from turn out in Spring (April, May or June) until housing in

298 Autumn (September, October or November).

299 FECs of all animals were performed each month using a modified McMaster

300 technique with a sensitivity of 10 epg (MAFF, 1986) and the mean and 95%

301 confidence interval estimated for each month. For this, the *sample* and *replicate*

14

302 functions in R were used to generate 10,000 replicates sampling with replacement.

303 The *quantiles* function was then used with probabilities of 0.025 and 0.975 to obtain

304 the bootstrapped 95% confidence limits for the means of these replicates.

305 For nematode species identification, the positive faecal samples were mixed per

306 herd, cultured and identified according to Borgsteede and Hendriks (1973). Pasture

307 infectivity (density of L3 on herbage; *L3h*) was measured as described in Verschave

308 et al. (2015) each month and every 2 months, respectively, in 2012 and 2013 using

309 the modified technique of Taylor (1939).

310

311 *2.4.2. Validation simulations*

312 Mean FECs and 95% confidence intervals reported by Verschave (Verschave, S.H.,

313 2015. PhD thesis, cited earlier) were corrected for incomplete egg recovery (recovery

314 rate of 55%; Paras et al., 2018). Corresponding daily pasture contamination values

315 for the entire period of each trial were obtained by interpolation of the monthly

316 pasture contamination values using the *approxfun* function in R. The data collected

317 from each herd formed a separate validation dataset.

318 Daily mean air temperature data used to estimate daily values for development

319 success to estimate arrest rates (equations 5 and 6) were obtained for each herd

320 from the E-OBS gridded dataset (Haylock et al., 2008; dataset available to download

321 from https://www.ecad.eu/download/ensembles/download.php) based on the

322 location of the village where each herd was located (Supplementary Table S1) using

323 the *ncdf4* function v 1.17 in R (Pierce, D. 2019. ncdf4: Interface to Unidata netCDF

324 (Version 4 or Earlier) Format Data Files. R package version 1.17. https://CRAN.R-

325 project.org/package=ncdf4).

326   The longitudinal field observations were used to validate species-specific

327   deterministic model simulations. Daily L3 intake rates were estimated from the

328   interpolated field data as described in equation 7. Dry matter intake and faeces

329   production were estimated as described in section 2.3.1. No data were available for

330   standing biomass, therefore, 2000 kg of DM per hectare was assumed. Although the

331   individuals in the longitudinal datasets were first season grazers (i.e. had never had

332   exposure to *O. ostertagi* nor *C. oncophora*), there is potential for age-related

333   immunity due to the maturation of the immune system (see discussion in Vercruysse

334   and Claerebout, 1997, and Smith et al., 1985). Therefore, host immunity (*r*) was set

335   at an initial value between 0.1 and 0.5, dependent on age at the start of the grazing

336   period (i.e. 6 months of age, r = 0.1; 21 months of age, r = 0.5).

337

338   *2.4.3. Statistical validation: deterministic simulations*

339   Model goodness of fit was assessed using a linear regression through the origin of

340   observed and predicted FECs as described by Rose et al. (2015). The first FEC for

341   each herd was excluded from statistical validation as this FEC was simply to confirm

342   the absence of infection at turn out. A statistically significant regression with low

343   residual error indicates that the model reproduces the seasonal patterns of the

344   observed FECs. However, statistical significance does not validate the ability of the

345   model to reproduce the magnitude of FECs observed. For this, the slope estimate

346   was used. A perfect linear fit between model predictions and field observations

347   implies an intercept of zero and a slope of 1. A regression through the origin with a

348   slope that is not significantly different from 1, and therefore included in the 95%

349   confidence interval, indicates that the model reproduces the magnitude of observed

350   FECs over the course of the season, with values significantly less than 1 indicating

351   underestimation of FECs and values significantly greater than 1 indicating

352   overestimation of FECs. A high R^2 value indicates that the model captures a

353   significant proportion of the variance in the observed FECs. Due to the relatively

354   small number of individuals in each herd, the potential for considerable individual

355   variation in FECs (Levecke et al., 2011), and the limitations of the McMaster's faecal

356   egg counting method and other flotation techniques (Egwang and Slocombe, 1981),

357   visual comparison of observed and predicted values were incorporated into the

358   evaluation to mitigate against this variability undermining statistical validation.

359

360   *2.4.4. Qualitative validation: stochastic simulations*

361   Although the framework presented here is a deterministic mean-field model

362   representing a group of hosts, incorporating individual variation is possible and is

363   beneficial for further validation and future evaluation of individual-based parasite

364   control strategies. An additional 50 simulations were run per herd, per nematode

365   species (representing 50 individual hosts) to incorporate the stochastic influences of

366   between-host variation. The aggregation of *L3h* and chance encounters with *L3h*

367   during grazing was incorporated as described in Berk et al. (2016b). The L3 ingestion

368   rate was drawn from a negative binomial distribution using the *rnbinom* function in

369   R, with a mean equal to the observed *L3h* at each time point, and a high level of

370   aggregation, as would be expected for the moderate *L3h* densities observed in this

371   study (k = 1.41; Verschave et al., 2015). For other species or farming systems, the

372   mean and aggregation values could be adapted to reflect the characteristics of the

373   system to be modelled. In addition to stochastic L3 ingestion, between-host

374 variability in immune response was drawn from a negative binomial distribution with

375 a mean equal to ρ and level of aggregation equal to that used for the L3 intake rate,

376 after Stear et al. (2007) suggested that the distribution of the immune response

377 between hosts mirrored that of the parasitological variables.

378   The practical significance of deviations in model predictions from the observed

379 FECs was also considered in the context of the hypothetical use of the simulated

380 FECs to guide further risk assessment (e.g. prompting a FEC or weighing) and

381 potentially trigger anthelmintic treatment in cattle. Fifty to 200 epg is considered a

382 "Medium" to "High" risk egg count (COWS, 2014). Therefore, a deviation of 200 epg

383 in predicted FECs within the range of 0-400 epg could theoretically result in incorrect

384 risk assessment and anthelmintic treatment choices.

385

386 **3. Results**

387 *3.1. Parameter estimates*

388   Linear regression of the development rates reported by Sauermann and

389 Leathwick (2018) against temperature for *C. oncophora* yielded a statistically

390 significant fit (a = -0.04, b = 0.008, R^2 = 0.8166, R^2adjusted = 0.8058, $F_{(1,17)}$ = 75.7, p

391 = 1.142e-07) with a predicted minimum development threshold of 5°C (minimum

392 threshold for development = (0-a)/b).

393   Expert opinion placed the estimated decay rate over an average 6 month housing

394 period (Charlier et al., 2010) at between 10% and 50%. Therefore, a 6 month decay

395 rate of 30% was used to estimate a daily decay rate (Table 2).

396   Using optimisation to fit the response rate (ρ) to data from Shaw et al. (1998)

397 yielded a median response rate for *O. ostertagi* of 0.00006 (inter-quartile range (IQR)

398   0.00024) with a median SSE of 0.03205 (IQR 0.32502). For *C. oncophora* this yielded

399   a median response rate of 0.00013 (IQR 0.00040) with a median SSE of 0.00250 (IQR

400   0.11904). The median fitted response rate was used in all subsequent simulations.

401   All other parameter estimates are provided in Table 2.

402

403   *3.2. Model validation*

404   The R code used for model simulations and validation is provided in

405   Supplementary Data S1. The code can be viewed and run in R software, or viewed in

406   a plain text editor.

407   Daily temperature and rainfall data are shown for the location of each herd in

408   Supplementary Fig. S1. The average age at turn out varied between 6 and 21 months

409   (Verschave, S.H., 2015. PhD Thesis, cited earlier; Supplementary Table S1). With the

410   exception of herd 2, longitudinal FEC data used for model validation (Figs. 2 and 3;

411   Supplementary Data S1) tended to be low throughout the grazing season. Mean

412   pasture larval counts (L3h kg DM^{-1}) were low at turnout, ranging from 0.001 to 176

413   L3h kg DM^{-1} (Supplementary Table S1), potentially accounting for the low FECs.

414   However the FECs used for validation are typical for calves in their first grazing

415   season with subclinical infections (Shaw et al., 1997).

416   Qualitatively, species-specific simulations for *O. ostertagi* and *C. oncophora*

417   reproduced general observed patterns of FECs over the course of a grazing season in

418   first season grazers (Figs. 2 and 3). Overall, the model captured a high proportion of

419   variance in the observed FECs for both *O. ostertagi* (mean R^2 = 0.76) and *C.*

420   *oncophora* (mean R^2 = 0.67), and residual error was low (Table 3). A statistically

421 significant regression through the origin was achieved for 6/7 (*O. ostertagi*) and 3/7

422 (*C. oncophora*) of the validation datasets (Table 3; Fig. 4).

423   For *O. ostertagi,* there were both negative and positive deviations in the slope

424 from 1 (Table 3), indicating under- or over-prediction of FECs, respectively. However,

425 as the model both under- and over-predicted FECs, there was no evidence of

426 systematic bias. Significant deviations in the slope from 1 were estimated for three

427 of the herds (Table 3). Qualitative assessment of model fit against the mean model

428 and 50 individual simulations incorporating individual variation in immune response

429 and the aggregation of L3s on pasture (Fig. 2) suggests that these deviations are of

430 no practical significance (section 2.4.4), with the exception of Herd 2, where high

431 FECs were observed at the end of the grazing season while predicted FECs remained

432 low.

433   For *C. oncophora*, there were predominantly negative deviations in the slope

434 from 1, indicating underprediction of FECs. A significant deviation in the slope from 1

435 was estimated for five of the herds (Table 3). Nevertheless, qualitative assessment as

436 above (Fig. 3) suggests that these deviations, similar to the *O. ostertagi* simulations,

437 are of little practical significance (section 2.4.4). Herd 2 was, again, an exception,

438 with higher FECs observed than predicted.

439

440 **4. Discussion**

441   Smith noted, in 2011, that "*Although it was eventually realised that within each*

442 *class of parasites a single generic model framework with suitably adjusted parameter*

443 *values could satisfactorily represent almost all the infections of interest... most of the*

444 *examples of nematode and trematode models in the literature were constructed on*

20

445 *an ad hoc basis to address issues dealing with control of a specific parasite in a*

446 *specific host in a specific country*". Although many of the models published in recent

447 decades contain important differences in the focus of detail necessary for the

448 specific application of the model (e.g. Cornell et al., 2004; Laurenson et al., 2011),

449 more widely applicable models use proprietary software (e.g. Learmount et al.,

450 2006) or are developed using complex spreadsheets (e.g. Sauermann and Leathwick

451 2018) that can be difficult to reproduce. Furthermore, differences in the structure of

452 the various model frameworks available and their parameters prevent direct

453 comparisons between model outputs.

454 Here, GLOWORM-PARA, a generic model framework for the parasitic phase of GI

455 nematode infections is presented. The model can be adapted to different host and

456 nematode species and was developed to complement a previously published model

457 of the free-living stages (GLOWORM-FL; Rose et al., 2015). The model's flexibility is

458 demonstrated by parameterisation for two economically important trichostrongylid

459 species infecting cattle worldwide, *C. oncophora* and *O. ostertagi,* and validation

460 against multiple independent datasets. To our knowledge, no previous attempt has

461 been made to model *C. oncophora* transmission alone.

462 Aspects of the framework that can be adapted to represent the host-parasite

463 system of interest are highlighted throughout. For example, parameter *d*, the factor

464 driving arrested development, could be adapted to include immunity (e.g. to simulate

465 the periparturient rise in FECs in ewes), or to extend the estimate of development

466 success (used here for *C. oncophora* and *O. ostertagi*) to include the impacts of

467 desiccation to simulate seasonal arrest in arid regions. In addition, reduced weight

468 gain and parasite-induced anorexia are economically important impacts of GI

469 nematode infection that have been the focus of many previous models (e.g.

470 Laurenson et al., 2011; Berk et al., 2016a) but were not considered here.

471   Reduced weight gain could be included in the model by substituting the Cue et al.

472 (2012) equation used here with one that estimates weight gain based on worm

473 burden, and estimating DMI as a function of worm burden to simulate parasite-

474 induced anorexia (e.g. Berk et al., 2016a). The simulations presented here also

475 assumed constant herbage biomass throughout the grazing season due to the lack of

476 data and models to track grass growth. Incorporating models of grass growth, and

477 thus seasonal changes in biomass, may improve predictions by acting on the L3

478 ingestion rate (i.e. rate of infection, which is a function of DMI rates, total L3 on

479 herbage and available standing biomass). Berk et al. (2016b) incorporated mean

480 monthly grass growth rates for England in their model of *O. ostertagi* in calves.

481 However this, and infection-dependent host growth, was beyond the scope of the

482 current study, which was to develop a minimal, location-independent framework that

483 could be easily parameterised for multiple species and host systems.

484   GLOWORM-PARA is a mean-field model, simulating the mean trajectory of

485 parasite population dynamics and host immunity in a group of hosts. Mean-field

486 models are useful to explore changes in the system under disparate conditions such

487 as current climate and predicted climate change (Rose et al., 2016), and to evaluate

488 the impact of competing management strategies at a herd/flock level (Learmount et

489 al., 2012). However, in an attempt to stem the development of AR, the focus of

490 parasite control has turned from whole-group treatments to targeted selective

491 treatment (TST), where individuals in a flock/herd are treated either based on

492 parasitological indicators (e.g. FECs in horses and sheep; Kenyon and Jackson, 2012;

493   Matthews and Lester, 2015) or based on performance indicators (e.g. liveweight gain

494   in sheep and cattle; Kenyon and Jackson, 2012). The framework can be adapted to

495   incorporate environmental stochasticity, as demonstrated here, to simulate the

496   heterogeneity of intensity of infection between hosts that forms the basis of

497   selection for TST. This was demonstrated by incorporating stochastic L3 intake rate

498   and immune response in the present study.

499   Limitations of previously published detailed mechanistic approaches include an

500   incomplete understanding of the processes and pathways involved in host immunity

501   to GI nematode infection (although this is disputed by some; Roberts, 1999) and the

502   detailed and invasive immunological datasets required to parameterise these

503   models. The latter is a severe impediment to applying these models to understudied

504   systems and necessitates a more simplified approach to modelling acquired

505   immunity, regardless of whether or not there is an adequate understanding of the

506   underlying processes. Complete representation of relevant immunological pathways,

507   supported by sufficient empirical data to estimate parameters, is therefore difficult

508   to achieve for most GI nematode species and is acknowledged as a bottleneck in the

509   production of mathematical models for the population dynamics of GI nematodes

510   (Charlier et al., 2018).

511   Previous models of GI nematode population dynamics and transmission have

512   differed in their approaches to modelling acquired immunity, which increases during

513   the course of an infection (Claerebout and Vercruysse, 2000). For example, some

514   model acquired immunity as a simple increasing function of the time of exposure to

515   infection (Learmount et al., 2006; Berk et al., 2016a), exposure to larvae (Grenfell et

516   al., 1995), host age (Garnier et al., 2016), or worm burden (Cornell et al., 2004), or

517   mechanistically via the impact of exposure to infection on immunological

518   parameters (Singleton et al., 2011; Prada Jiménez de Cisneros et al., 2014). Practical

519   limitations of the former examples include the absence of upper boundaries on the

520   levels of acquired immunity, which subsequently introduces difficulties scaling

521   immune-mediated parasite life-history parameters. Practical limitations of the latter

522   examples involve the need for invasive immunological measurements (plasma IgA)

523   to estimate immune response rates.

524   The model presented here represents immunity as a logistic growth function. This

525   allows an exponential response with cumulative exposure to GI nematodes,

526   mimicking the stronger immune response that would be expected after

527   administration of a challenge infection or a booster vaccination, and limits acquired

528   immunity to values less than 1 to facilitate modelling interactions between host

529   immune response and parasite life-history parameters. This simple approach also

530   facilitates model application in data-sparse systems. To effectively model the

531   development of host acquired immunity to GI nematodes without explicit

532   representation of the complexities of the immune response and the necessary data

533   for parameterisation, the decay and response rates for the logistic function are

534   estimated using a combination of empirical, non-invasive field data, qualitative

535   observational data and expert judgement. This approach requires fewer data for

536   parameterisation than a more detailed mechanistic representation of immunity, and

537   therefore permits application of this framework to a wider range of host-parasite

538   systems than would be possible with a more detailed model. Nevertheless, there is

539   scope to adapt the representation of immunity as more data become available. It

540   would also be possible, with slight adaptation of the model, to apply varying levels of

541   host immunity to the different within-host life cycle stages, for example to simulate

542   the use of vaccines with parasite stage-specific activity.

543   Overall, the mean-field model captured a high proportion of the variability in the

544   observed FECs (*O. ostertagi* mean R^2 = 0.76 and *C. oncophora* mean R^2 = 0.67).

545   Residual error can be attributed to multiple sources, including measurement error in

546   the pasture larval counts used to initiate the model simulations (Couvillion, 1993),

547   multiple sources of variability in the FEC method used in the validation dataset

548   (Levecke et al., 2015), and individual host variability as described above. There was

549   no evidence of systematic bias for *O. ostertagi*, and although the *C. oncophora*

550   model tended to underestimate FECs, the differences in observed and predicted

551   FECs were of no practical significance (section 2.4.4; COWS, 2014). The statistical

552   significance of small deviations in predicted FECs from observed FECs (<25 eggs per

553   gram in herds 1, 2, and 4; Fig. 3) highlights the importance of pragmatic validation

554   methods including statistical, negative binomial models and qualitative appraisal.

555   This is again highlighted by herd 7 which performed poorly in the statistical

556   validation, despite low residual error and high R^2 values (Table 3), and the predicted

557   FECs being within a reasonable range of the observed FECs for both species tested.

558   This was likely due to failure of the model to capture a slight, practically insignificant,

559   increase in FEC for both species mid-August. Despite the overall good performance

560   of the model, there were some exceptions. Herd 1 produced a high *C. oncophora* FEC

561   1 month after turnout which was not predicted by the model and could be of

562   practical significance, as FECs of the level observed would usually require treatment.

563   The FECs observed for herd 2 were significantly higher than predicted for both

564   species, with differences at the end of the grazing season in the order of several

565 hundred epg. One plausible hypothesis for this, given the good performance of the

566 model for most other herds, is that the individuals on this farm were particularly

567 susceptible to GI nematode infection, which could be due to a number of factors

568 such as genetics, nutrition and coinfection (which cannot be interrogated within the

569 current dataset). Alternatively, the underprediction of FECs on this farm may

570 indicate model bias when applied to young cattle – the calves simulated in Herd 2

571 were the youngest of all the farms used for model validation (6 months, cf. 10-21

572 months). Further validation would be required before applying the model to

573 simulate very young calves (<10 months of age), to determine if this discrepancy is

574 due to the susceptibility of the calves on this farm (posited above), an overestimate

575 of immune response in younger calves, or a non-linear relationship between

576 acquired immunity and the parasitological parameters.

577 To conclude, a generic framework to simulate the parasitic phase of GI nematode

578 infections is presented here and its flexibility is demonstrated by simulating *O.*

579 *ostertagi* and *C. oncophora* infections. The model simulations replicated infection

580 patterns of first season grazers for these nematode species. The lead authors have

581 previously developed a complementary framework for the free-living stages of the

582 GI nematode life cycle, which has been applied to several GI nematode species, and

583 has also been successfully adapted to simulate the development and dispersal of

584 cattle lungworm (*Dictyocaulus viviparus;* McCarthy, C.A., 2018. Predicting the

585 unpredictable: the changing epidemiology of *Dictyocaulus viviparus* in Great Britain.

586 PhD Thesis. University of Liverpool, UK). It is hoped that GLOWORM-PARA will drive

587 similar innovation and international collaboration by providing an accessible and

588 transparent framework that can be adapted to multiple species and extended where

589 additional detail is required. Future research will integrate GLOWORM-PARA with

590 GLOWORM-FL and host-parasite interactions (host movements, anthelmintic

591 treatments etc.) to obtain a full lifecycle framework for the evaluation of alternative

592 GI nematode control strategies.

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886

887 **Figure legends**

888

889 Fig. 1. Conceptual framework of the GLOWORM-PARA model. State variable and

890 parameter definitions are given in Table 1. Solid arrows indicate life-cycle transitions

891 (e.g. from ingested L3 (L3i) to pre-adult (P) to adult (A)), mortality (μ_i) or deposition

892 of eggs (λ). Dashed arrows indicate dependencies (e.g. the level of acquired

893 immunity (r) depends on the intake of L3 (L3i)).

894

895 Fig. 2. Observed and predicted faecal egg counts (FEC) for *Ostertagia ostertagi* in

896 first season grazing animals of dairy herds in Belgium. FECs were monitored for the

897 entire length of the first grazing season. Further information on the background of

898 this data can be found in Supplementary Table S1. Points and error bars show the

899 observed number of eggs per gram of faeces (epg) and the corresponding 95%

900 confidence interval obtained by bootstrapping (10,000 repeats). The dashed black

901 line depicts the predicted FEC for a group of hosts based on a deterministic model

902 simulation. The solid grey lines depict predictions obtained from 50 model

903 simulations representing individual hosts, in which stochastic L3 intake and

904 between-host variability in immune response were incorporated.

905

906 Fig. 3. Observed and predicted faecal egg counts (FEC) for *Cooperia oncophora* in

907 first season grazing animals of dairy herds in Belgium. FECs were monitored for the

908 entire length of the first grazing season. Further information on the background of

909 this data can be found in Supplementary Table S1. Points and error bars show the

910 observed number of eggs per gram of faeces (epg) and the corresponding 95%

911 confidence interval obtained by bootstrapping (10,000 repeats). The dashed black

912 line depicts the predicted FEC for a group of hosts based on a deterministic model

913 simulation. The solid grey lines depict predictions obtained from 50 model

914 simulations representing individual hosts, in which stochastic L3 intake and

915 between-host variability in immune response were incorporated.

916

917 Fig. 4. The observed and simulated faecal egg counts (FECs; points) with 95%

918 confidence intervals (observed = horizontal, simulated = vertical). The diagonal black

919 line indicates hypothetical perfect agreement between the observed and simulated

920 FECs. The grey solid line indicates the predicted slope of the regression, with 95%

921 confidence intervals show as grey dashed lines. Note that the 95% confidence

922 intervals for the simulated data (estimated using the stochastic simulations shown in

923 grey in Figs. 2 and 3) are narrow and may not be easily seen due to the scale of the

924 Y-axes.

925

926 Supplementary Fig. S1. Mean daily temperature (A) and total daily rainfall (B) for the

927 observation period for each herd used for model validation. Data were obtained from

928 the E-OBS gridded dataset (Haylock et al., 2008) based on the village where each herd

929 was located (Supplementary Table S1).

930 **Reference**

931 Haylock, M.R., Hofstra, N., Klein Tank, A. M. G., Klok, E. J., Jones, P. D., New, M., 2008. A

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934
935 **Highlights**
936

937 • The transmission of gastrointestinal nematode parasitic stages was modelled
938 • The generic model was parameterised for *Cooperia oncophora* and *Ostertagia*
939 *ostertagi* in cattle
940 • Extensive validation using field data demonstrated good model performance
941 • A pragmatic approach to modelling data-sparse systems (immunity) is
942 demonstrated
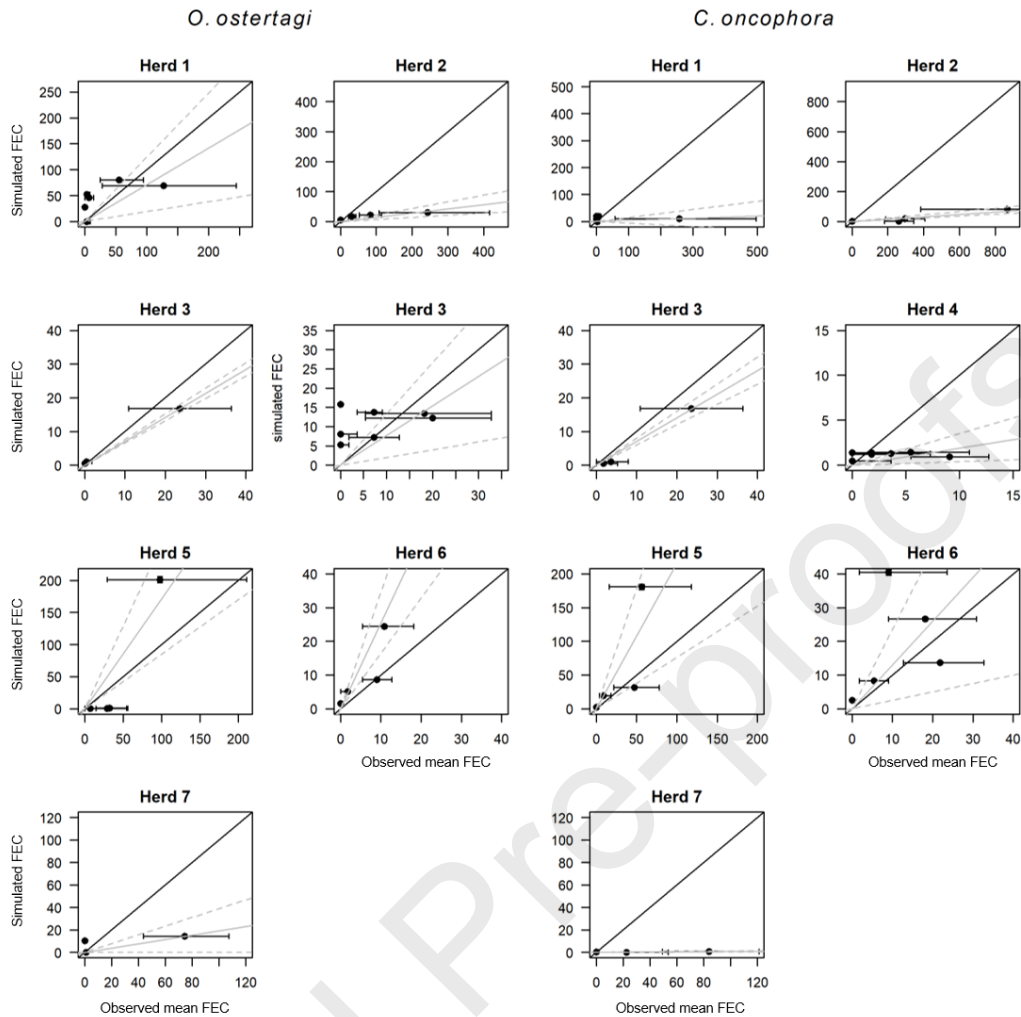943 • Stochastic parameters can be introduced to incorporate host variability
944
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O. ostertagi   C. oncophora
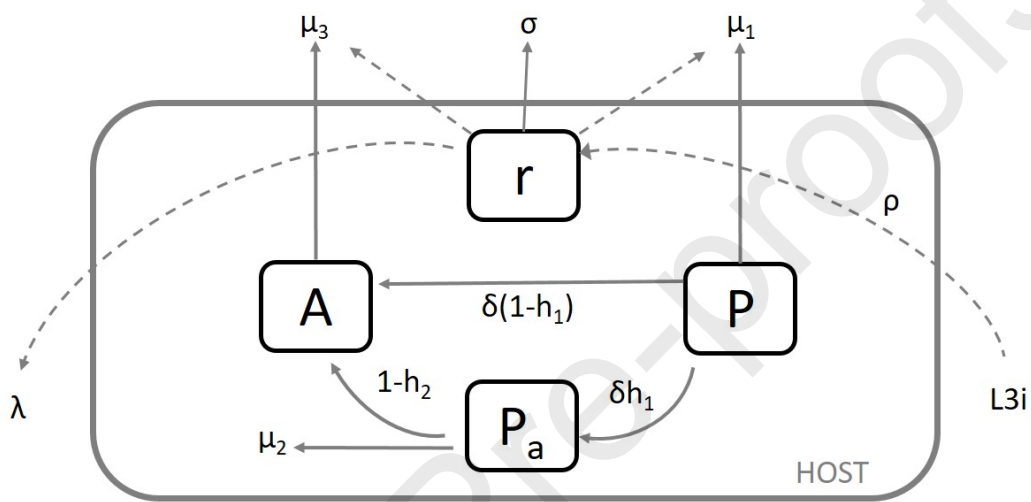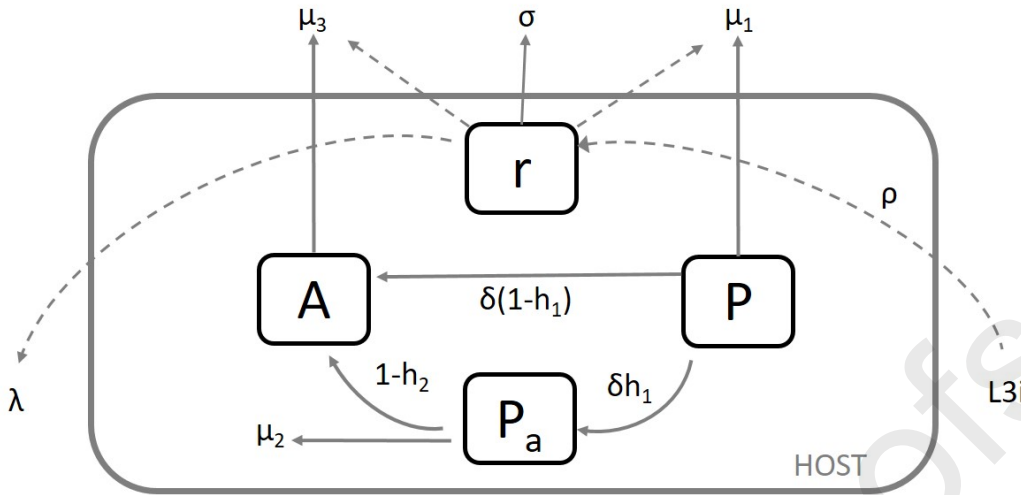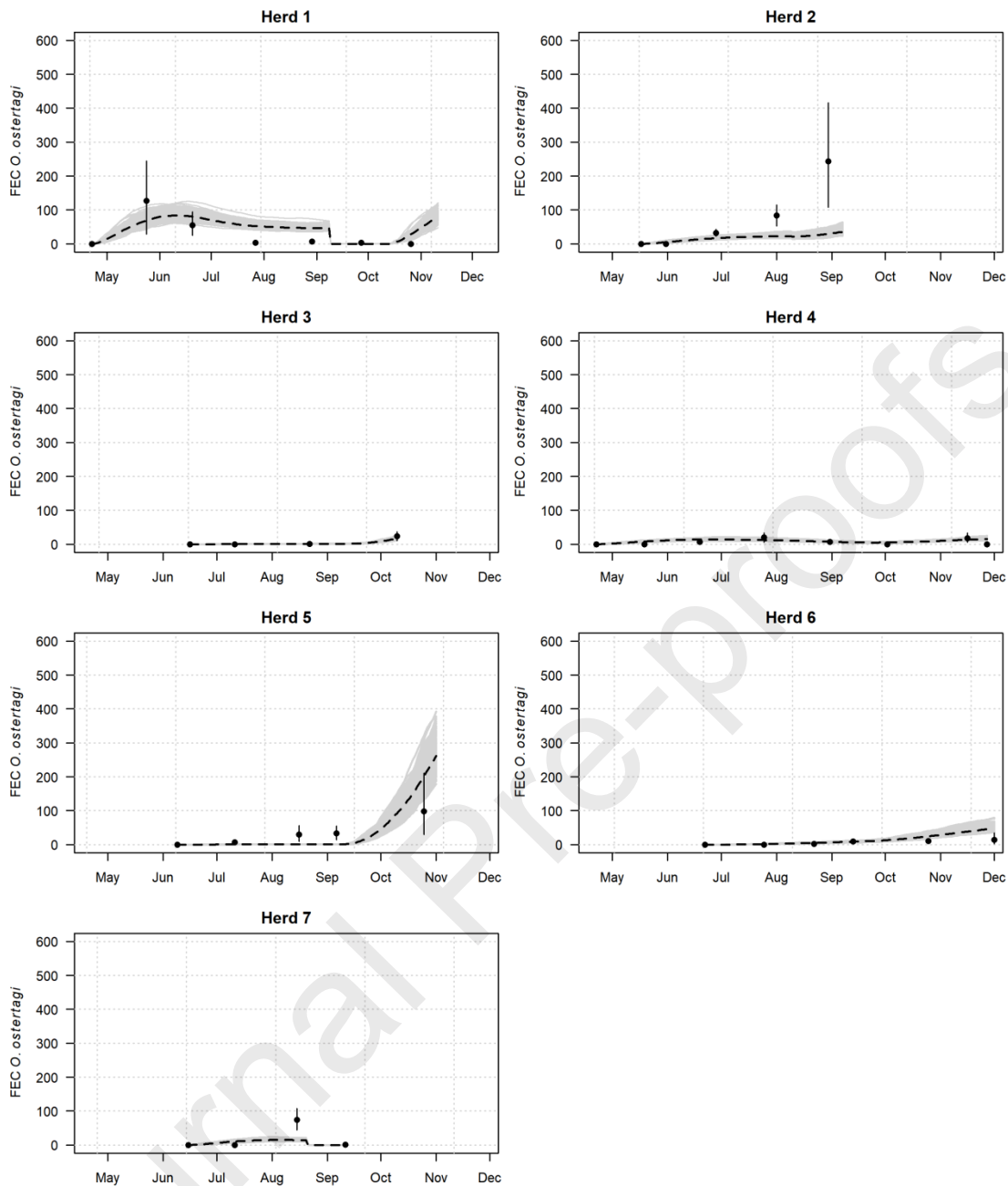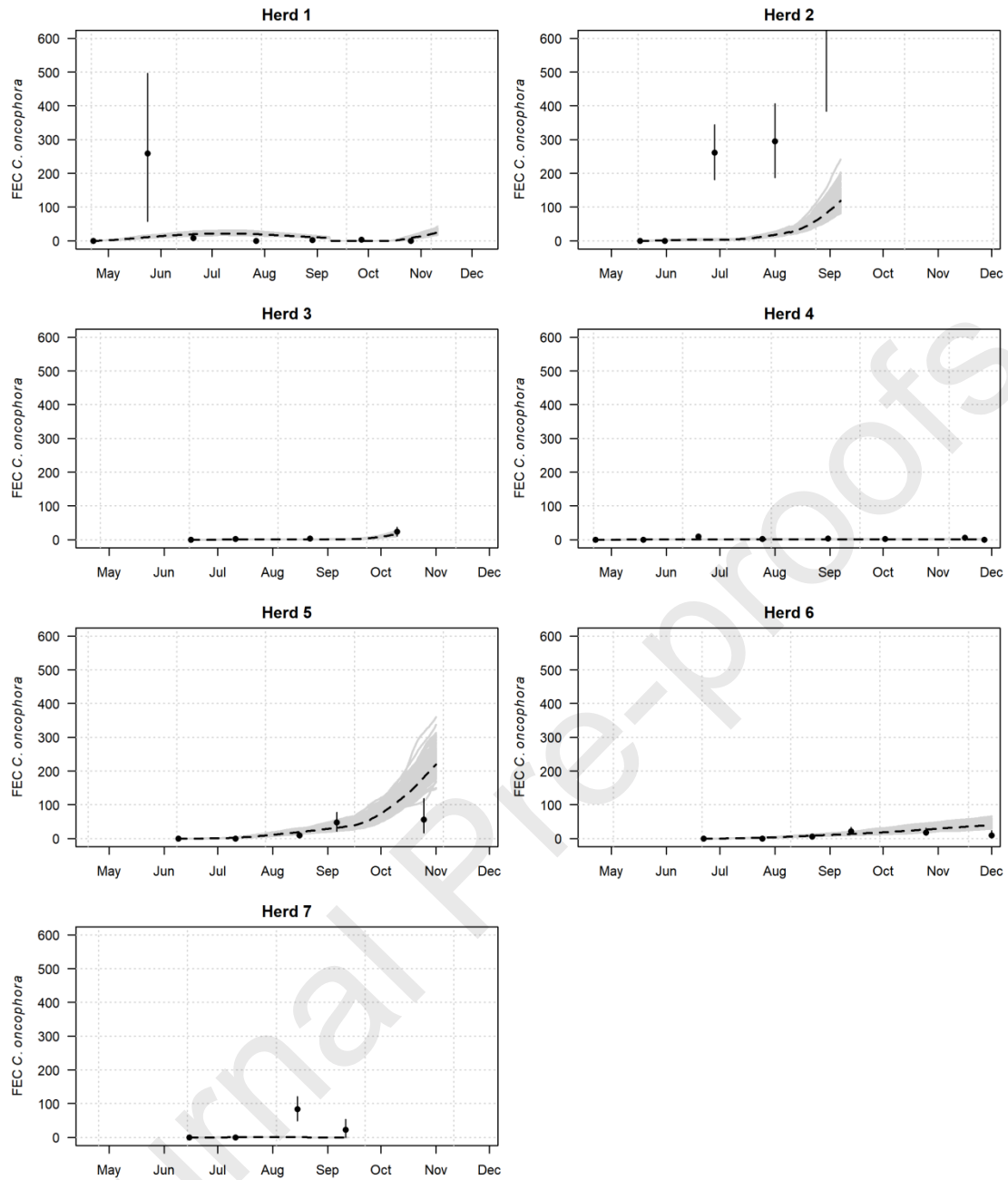
950

951 **Table 1.** Model state variable and parameter definitions

State variable (bold) or Parameter	Definition	Units
P	Pre-adult nematodes in the host (L3, L4 and immature adult)	-
Pa	Arrested L4	-
A	Mature adult	-
r	Acquired immunity	-
$L3h$	L3 density on herbage	L3 kg dry matter^{-1}
$L3i$	L3 ingestion rate	L3 day^{-1} host^{-1}
δ	Development rate from ingested L3 to mature adult	P^{-1} day^{-1}
μ_1	Pre-adult mortality rate	P^{-1} day^{-1}

47

μ_2	Arrested L4 mortality rate	$Pa^{-1} day^{-1}$
μ_3	Adult mortality rate	$A^{-1} day^{-1}$
h_1	Rate of developing pre-adult nematodes entering arrested development	$P^{-1} day^{-1}$
h_2	Rate of arrested larvae resuming development	$Pa^{-1} day^{-1}$
ρ	Immune response	$L3i^{-1}$
σ	Immune decay	Day^{-1}
λ	Daily fecundity (eggs produced)	$Eggs\ worm^{-1} day^{-1}$
f	Daily faeces production	$Grams\ (wet\ weight)\ day^{-1}$
d	Driver of arrest	N/A[a]
DMI	Daily herbage dry matter intake	$Grams\ day^{-1}$
$kgDM$	Standing biomass (herbage) on pasture	$kg\ dry\ matter\ hectare^{-1}$
FEC	Faecal egg count	$Eggs\ gram^{-1}$

952   [a] As this parameter is used to scale the immune-dependent parameters, the unit need not be
953   fixed. In the present study, the temperature-dependent development rate of *Ostertagia ostertagi*
954   or *Cooperia oncophora* has been used as an indicator of development success. However other,
955   more complex, indicators can be used where sufficient data exist for parameterisation, such as Q_0
956   estimates or the proportion of eggs surviving to L3 on pasture, or this parameter can be adapted
957   to incorporate immunity-driven arrested development.

958

959

960   **Table 2.** Parameter estimates for *Ostertagia ostertagi* (*Oo*) and *Cooperia*

961   *oncophora* (*Co*).

Parameter	Species	Estimate	Source
$\boldsymbol{\delta}$	*Oo, Co*	-ln(0.5)/17= 0.041	Powers et al. (1982)
$\boldsymbol{\mu_{1(min)}}$	*Oo*	0.054	Mean in Verschave et al. (2014a)
	Co	0.044	Mean in Verschave et al. (2016b)
$\boldsymbol{\mu_{1(max)}}$	*Oo*	0.062	Upper 95% CI in Verschave et al. (2014a)
	Co	0.052	Upper 95% CI in Verschave et al. (2016b)
$\boldsymbol{\mu_2}$	*Oo, Co*	0.002	Grenfell et al. (1987)
$\boldsymbol{\mu_{3(min)}}$	*Oo*	0.028	Mean in Verschave et al. (2014a)
	Co	0.039	Mean in Verschave et al. (2016b)
$\boldsymbol{\mu_{3(max)}}$	*Oo*	0.032	Upper 95% CI in Verschave et al. (2014a)

48

	Co	0.048	Upper 95% CI in Verschave et al. (2016b)
$h_{(min)}$	*Oo*	0.02	Lower 95% CI in Verschave et al. (2014a)
	Co	0.004	Lower 95% CI in Verschave et al., (2016b)
$h_{(max)}$	*Oo*	0.06	Upper 95% CI in Verschave et al. (2014a)
	Co	0.011	Upper 95% CI in Verschave et al. (2016b)
ρ	*Oo*	5.981×10^{-5}	Current study (fitted to data from Shaw et al. (1998), see main text for assumptions)
	Co	1.316×10^{-4}	Current study (fitted to data from Shaw et al. (1998), see section 2.3.3. for assumptions)
σ	*Oo, Co*	$-\ln(0.7)/(6*30) = 0.002$	Current study (expert opinion)
$\lambda_{(min)}$	*Oo*	$\ln(196/2) = 4.58$	Lower 95% CI in Verschave et al. (2014a)
	Co	$\ln(1253/2) = 6.44$	Lower 95% CI in Verschave et al. (2016b)
$\lambda_{(max)}$	*Oo*	$\ln(284/2) = 4.96$	Mean in Verschave et al. (2014a), assuming a 1:1 sex ratio
	Co	$\ln(2968/2) = 7.30$	Mean in Verschave et al. (2016b); assuming a 1:1 sex ratio
d	*Oo*	$-0.07258 + 0.00976T$[a]	Rose et al. (2015)
	Co	$-0.0401 + 0.00821T$[a]	Current study (fitted to data from Sauermann and Leathwick (2018))

962   [a]T = daily mean air temperature (°C)

963   CI, Confidence Interval.

964

965   **Table 3.** Validation of simulations for faecal egg counts (FECs) of *Ostertagia*

966   *ostertagi* and *Cooperia oncophora* using parasitological data of first season

967   grazing animals on seven commercial dairy herds in Belgium.

49

Data set	Ostertagia ostertagi				Cooperia oncophora			
	Error (residual sum of squares)	Linear regression	R^2 (R^2 adjusted)	Slope (95% CI)	Error (residual sum of squares)	Linear regression	R^2 (R^2 adjusted)	Slope (95% CI)
Herd 1	37.69	$F_{1,5}$ =6.89, P=0.047	0.58 (0.50)	0.71 (0.19 – 1.24)	13.75	$F_{1,5}$ =0.69, P=0.445	0.12 (-0.06)	0.04 (-0.06 – 0.15)
Herd 2	10.11	$F_{1,3}$ =13.35, P=0.035	0.82 (0.76)	0.14 (0.07 – 0.22)	12.62	$F_{1,3}$ =41.06, P=0.008	0.93 (0.91)	0.08 (0.06 – 0.11)
Herd 3	0.61	$F_{1,2}$ =766.7, P=0.001	1 (1)	0.71 (0.66 – 0.76)	1.21	$F_{1,2}$ =191.3, P=0.005	0.99 (0.98)	0.70 (0.60 – 0.80)
Herd 4	8.38	$F_{1,6}$ =7.00, P=0.038	0.54 (0.46)	0.77 (0.20 – 1.33)	0.92	$F_{1,6}$ =5.90, P=0.051	0.50 (0.41)	0.19 (0.04 – 0.35)
Herd 5	47.31	$F_{1,3}$ =15.1, P=0.030	0.83 (0.78)	1.71 (0.85 – 2.57)	53.02	$F_{1,3}$ =9.12, P=0.057	0.75 (0.67)	2.16 (0.76 – 3.56)
Herd 6	9.42	$F_{1,4}$ =30.35, P=0.005	0.88 (0.85)	2.54 (1.64 – 3.45)	16.25	$F_{1,4}$ =5.9, P=0.07	0.60 (0.50)	1.30 (0.25 – 2.35)
Herd 7	7.39	$F_{1,2}$ =3.84, P=0.189	0.66 (0.49)	0.19 (-0.0002 – 0.39)	0.24	$F_{1,2}$=6.48, P=0.126	0.76 (0.65)	0.007 (0.002 – 0.013)

968   CI, Confidence Interval.

969