Journal of Theoretical Biology 354 (2014) 1–11

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

Control strategies for a stochastic model of host–parasite interaction in a seasonal environment

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HIGHLIGHTS

- We present a nonlinear stochastic model for the parasite load of a single host.
- Nonhomogeneous Poisson patterns allow us to incorporate seasonal fluctuations in time.
- Control strategies based on isolation of the host and anthelmintic drugs are considered.
- We analyze control criteria that appropriately balance efficiency and cost of intervention.
- Control criteria are applied to the gastrointestinal nematode burden in growing lambs.

ARTICLE INFO

Article history:
Received 11 February 2013
Received in revised form
11 March 2014
Accepted 12 March 2014
Available online 20 March 2014

Keywords:
Host survival
Nonhomogeneous Poisson process
Parasite-induced host mortality
Parasitism
Time-dependent fluctuation

ABSTRACT

We examine a nonlinear stochastic model for the parasite load of a single host over a predetermined time interval. We use nonhomogeneous Poisson processes to model the acquisition of parasites, the parasite-induced host mortality, the natural (no parasite-induced) host mortality, and the reproduction and death of parasites within the host. Algebraic results are first obtained on the age-dependent distribution of the number of parasites infesting the host at an arbitrary time t. The interest is in control strategies based on isolation of the host and the use of an anthelmintic at a certain intervention instant t_0. This means that the host is free living in a seasonal environment, and it is transferred to a uninfected area at age t_0. In the uninfected area, the host does not acquire new parasites, undergoes a treatment to decrease the parasite load, and its natural and parasite-induced mortality are altered. For a suitable selection of t_0, we present two control criteria that appropriately balance effectiveness and cost of intervention. Our approach is based on simple probabilistic principles, and it allows us to examine seasonal fluctuations of gastrointestinal nematode burden in growing lambs.

1. Introduction

Recently, Herbert and Isham (2000) contribute to the discussion of causes and effects of aggregation of macroparasite counts, with special emphasis on clumped infections and parasite-induced host mortality. Herbert and Isham (2000) use a fully stochastic approach enabling the investigation of a wide range of distributional properties of interest, in a nonlinear stochastic model for the evolution of the parasite load of a single host. A simpler version of such a model was previously investigated by Isham (1995). In Herbert and Isham (2000), the model of Isham (1995) is extended to incorporate three parasite stages (larval, mature and offspring), general clumped infections, parasite-induced host mortality, and to allow durations of the parasite stages to be non-exponentially distributed. Between-host heterogeneities and disease control are also discussed in Herbert and Isham (2000). Exact algebraic results are obtained in Herbert and Isham (2000) and Isham (1995) on the distribution of parasite load and on host survival. In the setting of macroparasites coexisting in individual hosts, important results have been obtained by Anderson et al. (1989), Bottomley et al. (2007), and Rosa et al. (2003); as a related work, see Anderson and May (1992). The paper by Cornell (2010) is an excellent reference where stochastic helminth population models are discussed.

The aim of this paper is to present a nonlinear stochastic model that incorporates host–parasite interactions, for a single host infected by parasites in a seasonal environment. The stochastic model under consideration allows us to examine seasonal changes

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http://dx.doi.org/10.1016/j.jtbi.2014.03.021
0022-5193/

of gastrointestinal (GI) nematode burden in growing lambs. GI nematodes are arguably (see Sutherland and Scott, 2010; Taylor et al., 2007) the major cause for ill health and poor productivity in grazing sheep worldwide, especially in young stock; see e.g. the references Bailey et al. (2009), Boa et al. (2001), and Eysker et al. (2005), which are related to studies on epidemiology and seasonal dynamics of GI nematode infections in New South Wales, Denmark and Netherlands, respectively. Specifically, our interest is in the parasite *Nematodirus* spp.; see Sutherland and Scott (2010) for an overview of GI nematodes, including parasite biology, pathophysiology and epidemiology. Results herein are related to the study conducted by Uriarte et al. (2003), which is designed to describe monthly fluctuations of nematode burden in sheep (Rasa Aragonesa female lambs) raised under irrigated conditions in Ebro Valley, Spain, by using worm-free tracer lambs and monitoring the fecal excretion of eggs by ewes. We focus on two grazing strategies, which are defined in terms of an intervention instant t_0 that, under concrete specifications, implies a move of the host to an uninfected area and anthelmintic treatment. Empirical data in Uriarte et al. (2003, Fig. 2) are combined with those data in Nasreen et al. (2007) on the clinical efficacy assessment of three anthelmintics (*ivermectin*, *fenbendazole* and *albendazole*) in lambs parasitized with nematode infective larvae. For a suitable selection of t_0, we present two control criteria that appropriately balance efficacy and cost of intervention. On applying these criteria, we make the efficacy and cost of intervention depend on the age-dependent distribution of the GI nematode burden. Our methodology is based on simple stochastic principles and time-dependent continuous-time Markov chains; see the book by Allen (2003) for a review of the main results for deterministic and stochastic models of interacting biological populations.

In modeling GI nematode burden in sheep, we use state-dependent nonhomogeneous Poisson processes to reflect seasonal fluctuations in the acquisition of parasites, the reproduction and death of parasites within the host, and the natural (no parasite-induced) and the parasite-induced host mortality. Seasonal mechanisms in animal populations and plant epidemiology have long been a focus on scientific interest; see e.g. Altizer et al. (2006), Conlan and Grenfell (2007), Dietz (1976), Grassly and Fraser (2006), Moneim (2007), Parham and Michael (2011), and Stone et al. (2007), where seasonal mechanisms are analyzed in a variety of models translating seasonality into time-dependent patterns. In host–parasite models, the effect of parasite aggregation on coexistence is studied by Pugliese (2000), who assumes that the number of parasites in one host may increase because of new infections at a time-dependent rate. In the model of Isham (1995), the host is exposed over its lifetime to parasites at times that form a nonhomogeneous Poisson process, and the death rate of the host depends on its age. Similarly, Herbert and Isham (2000) consider that the host is exposed to parasite larvae at time instants of a nonhomogeneous Poisson process and, during the adult stage, the parasite gives birth to clumps of offspring in a nonhomogeneous Poisson process.

The paper is organized as follows. The formal definition of the model is given in Section 2.1 of the paper, and exact analytical results are derived in Section 2.2 for the number of parasites acquired by the host up to a predetermined age τ when, under concrete grazing assumptions, intervention is prescribed at a certain age $t_0 < \tau$. In the spirit of control systems discussed by Barger (1997), our approach in Section 3 concerns with the role of grazing management in reducing anthelmintic use and improving helminth control. More concretely, in Section 3.1 we comment on the life cycle of nematodes, the presence of infective larvae on the small intestine, and aids to diagnosis of GI nematode infections in sheep. Our comments in Section 3.1 are first used in Section 3.2 to define the mathematical model in terms of levels of infection, and then to identify age-dependent patterns from empirical data (Nasreen et al., 2007; Uriarte et al., 2003) in Section 3.3. We present two control criteria allowing us to find the instant t_0 that appropriately balances efficacy and cost of intervention in the resulting grazing strategy, and we examine seasonal changes of GI nematode burden in growing lambs. Finally, concluding remarks are given in Section 4.

2. The age-dependent host–parasite model

In this section, we define the nonlinear stochastic model of host–parasite interaction in a seasonal environment. We set down a set of equations governing the dynamics of the underlying processes, and we use the resulting age-dependent solution to present two control criteria based on simple probabilistic principles. The random variable to be studied in this section is the number $M(t)$ of parasites acquired by the host up to time instant t. It should be noted that, for practical use, $M(t)$ may be interpreted in a more general manner, such as the *level of infection* at time t used in our application to GI nematode burden in Section 3.

2.1. Mathematical model description

We consider a single host that is born, parasite-free, at time $t=0$ and over its lifetime is exposed to parasites at times that form a nonhomogeneous Poisson process of rate $\lambda(t)$. At an exposure instant, the host acquires a single parasite independently from one exposure to another. The number of parasites within the host may increase due to the parasite reproduction. Let $\lambda_m^*(t)$ be the rate of the underlying nonhomogeneous Poisson process governing parasite reproduction when the number of parasites in the host equals m. Let $\mu(t)$ be the death rate of the host at age t in the absence of any parasite burden, and assume that this rate is increased by an amount $\mu_m^*(t)$, which is related to the parasite-induced host mortality as there are m parasites within the host. For later use, we introduce the *combined* rates $\lambda_m(t) = \lambda(t) + \lambda_m^*(t)$ and $\mu_m(t) = \mu(t) + \mu_m^*(t)$.

At age τ, our interest is in the number $M(\tau)$ of parasites acquired by the host up to time instant τ when the host has been moved to an *uninfected area* at a certain age $t_0 < \tau$. The host enters the uninfected area only if it is alive and infected at age t_0. In the uninfected area, the host lives under noninfectious conditions. This means that the host does not acquire new parasites, undergoes a concrete treatment to decrease the number of parasites acquired up to the *intervention instant* t_0, and its natural and parasite-induced mortality are altered. The treatment implies that the reproduction of parasites within the host is stopped. Let $\eta_m(t)$ be the death rate of parasites when there are m parasites within the host, and $\mu'_m(t)$ denote the combined death rate of the host at time $t \in (t_0, \tau)$.

Often biologists and ecologists assume that there is a critical number M_0 of parasites that do not permit the host to retrieve an acceptable parasite load, that is, isolation of the host and the use of an anthelmintic are ineffective when the number of parasites picked up by the host up to age t_0 is strictly greater than M_0. We make no attempt to incorporate parasite death during the interval $(0, t_0)$ in the model because we implicitly assume that the age τ is comparatively smaller than the expected lifetime of a parasite within the host.

2.2. Model equations

To begin with, we distinguish between the *free-living* interval $[0, t_0)$ and the *isolated-living* interval $[t_0, \tau]$, and we let $\mathcal{X}$ and $\mathcal{Y}$ be the processes $\{M(t) : 0 \le t < t_0\}$ and $\{M(t) : t_0 \le t \le \tau\}$, respectively, which are both defined on the state space $\{-1\} \cup \mathcal{S}$ with $\mathcal{S} = \{0, 1, \ldots, M_0\}$. The state $M(t) = -1$ amounts to the host death or a number of parasites acquired up to age t greater than M_0.

For a host that has survived to age t with $t<t_0$ and $M(t)=m\in\mathcal{S}$, the possible transitions in the free-living interval are as follows (see Fig. 1):

(i) $m\to m+1$ at rate $\lambda_m(t)$, for values $m=0,1,\ldots,M_0-1$;
(ii) $m\to -1$ at rate $\mu_m(t)$, for values $m=0,1,\ldots,M_0-1$;
(iii) $M_0\to -1$ at rate $\mu_{M_0}(t)+\lambda_{M_0}(t)$.

In terms of $\pi_m(t)=P(M(t)=m|M(0)=0)$ for $m\in\{-1\}\cup\mathcal{S}$, the dynamics of the process $\mathcal{X}$ become

$$\frac{d\pi_{-1}(t)}{dt}=\sum_{m=0}^{M_0-1}\mu_m(t)\pi_m(t)+(\mu_{M_0}(t)+\lambda_{M_0}(t))\pi_{M_0}(t), \tag{1}$$

$$\frac{d\pi_m(t)}{dt}=-(\lambda_m(t)+\mu_m(t))\pi_m(t)+(1-\delta_{0,m})\lambda_{m-1}(t)\pi_{m-1}(t),\quad m\in\mathcal{S}, \tag{2}$$

for time instants $t<t_0$, where $\delta_{0,m}$ denotes Kronecker's delta.

Since $\pi_0(0)=1$ and $\pi_{-1}(t)+\sum_{m=0}^{M_0}\pi_m(t)=1$, it is readily seen that the solution of (1) and (2) can be expressed as

$$\pi_{-1}(t)=1-\sum_{m=0}^{M_0}R_m(t)e^{-(\Lambda_m(t)+\Delta_m(t))},$$
$$\pi_m(t)=R_m(t)e^{-(\Lambda_m(t)+\Delta_m(t))},\quad m\in\mathcal{S},$$

where $\Lambda_m(t)=\int_0^t\lambda_m(u)\,du$ and $\Delta_m(t)=\int_0^t\mu_m(u)\,du$. The functions $R_m(t)$ are iteratively computed, starting with $R_0(t)=1$, as

$$R_m(t)=\int_0^t\lambda_{m-1}(u)R_{m-1}(u)e^{\tilde{\Lambda}_m(u)+\tilde{\Delta}_m(u)}\,du,\quad 1\le m\le M_0,$$

with $\tilde{\Lambda}_m(t)=\Lambda_m(t)-\Lambda_{m-1}(t)$ and $\tilde{\Delta}_m(t)=\Delta_m(t)-\Delta_{m-1}(t)$.

At age t_0, the host can be *dead* (i.e., $M(t_0)=-1$), *alive and parasite free* (i.e., $M(t_0)=0$), or *alive and infected* (i.e., $M(t_0)=m$ with $m\in\{1,2,\ldots,M_0\}$); we recall that the state $M(t_0)=-1$ amounts to the physical death of the host or a number of parasites acquired by the host up to the time instant t_0 that is greater than the number M_0. We assume from now on that the host is alive and infected at age t_0, and we let $\overline{\boldsymbol{\pi}}=(\overline{\pi}_m:m\in\{1,2,\ldots,M_0\})$ be a probability distribution defining the intervention rule; for example, in our application in Section 3, we select $\overline{\boldsymbol{\pi}}$ with entries

$$\overline{\pi}_m=\begin{cases}0 & \text{if } 1\le m\le m'-1,\\ \pi_m(t_0) & \text{if } m'\le m\le M_0,\end{cases} \tag{3}$$

where $m'\in\{1,2,\ldots,M_0\}$ is a predetermined threshold. An eventual intervention (i.e., isolation and use of an anthelmintic at age t_0) is therefore prescribed by a minimum number m' of parasites infecting the host.

For a host that has survived to age t with $t_0<t<\tau$ and $M(t)=m\in\mathcal{S}$, the possible transitions are given by (see Fig. 2)

(i) $m\to m-1$ at rate $\eta_m(t)$, for values $m=1,\ldots,M_0$;
(ii) $m\to -1$ at rate $\mu'_m(t)$, for values $m\in\mathcal{S}$.

For a selected rule $\overline{\boldsymbol{\pi}}$, the dynamics of $\mathcal{Y}$ are described in terms of the age-dependent probabilities $\pi_m(t_0;t)=P_{\overline{\boldsymbol{\pi}}}(M(t)=m)$, for $m\in\{-1\}\cup\mathcal{S}$ and $t\in(t_0,\tau]$, and the initial conditions $\pi_{-1}(t_0;t_0)=\pi_0(t_0;t_0)=0$, and $\pi_m(t_0;t_0)=\overline{\pi}_m$ for $m\in\{1,2,\ldots,M_0\}$. It is readily seen that

$$\frac{d\pi_{-1}(t_0;t)}{dt}=\sum_{m=0}^{M_0}\mu'_m(t)\pi_m(t_0;t),$$
$$\frac{d\pi_m(t_0;t)}{dt}=-(\mu'_m(t)+(1-\delta_{0,m})\eta_m(t))\pi_m(t_0;t)+(1-\delta_{m,M_0})\eta_{m+1}(t)\pi_{m+1}(t_0;t),\quad m\in\mathcal{S}.$$

It is straightforward to derive the following expressions for $\pi_m(t_0;t)$ with $m\in\{-1\}\cup\mathcal{S}$ and $t\in(t_0,\tau]$:

$$\pi_{-1}(t_0;t)=1-\sum_{m=0}^{M_0}\pi_m(t_0;t), \tag{4}$$

$$\pi_m(t_0;t)=\left((1-\delta_{0,m})\overline{\pi}_m+(1-\delta_{m,M_0})\sum_{j=0}^{M_0-1-m}\overline{\pi}_{m+1+j}\tilde{R}^j_{m+1}(t_0;t)\right)\times e^{-(\Delta'_m(t_0;t)+H_m(t_0;t))},\quad m\in\mathcal{S}, \tag{5}$$

where $\Delta'_m(t_0;t)=\int_{t_0}^t\mu'_m(u)\,du$, $H_m(t_0;t)=\int_{t_0}^t\eta_m(u)\,du$ (with $H_0(t_0;t)\equiv 0$), $\tilde{\Delta}'_m(t_0;t)=\Delta'_m(t_0;t)-\Delta'_{m-1}(t_0;t)$ and $\tilde{H}_m(t_0;t)=H_m(t_0;t)-H_{m-1}(t_0;t)$. The functions $\tilde{R}^0_m(t_0;t)$ are evaluated from

$$\tilde{R}^0_m(t_0;t)=\int_{t_0}^t\eta_m(u)e^{-(\tilde{\Delta}'_m(t_0;u)+\tilde{H}_m(t_0;u))}\,du,\quad 1\le m\le M_0. \tag{6}$$

For $1\le j\le M_0-m$ and $1\le m\le M_0-1$, the functions $\tilde{R}^j_m(t_0;t)$ are specified by

$$\tilde{R}^j_m(t_0;t)=\int_{t_0}^t\eta_m(u)e^{-(\tilde{\Delta}'_m(t_0;u)+\tilde{H}_m(t_0;u))}\tilde{R}^{j-1}_{m+1}(t_0;u)\,du. \tag{7}$$

2.3. Control criteria

A control strategy is specified by an age t_0 and a probability vector $\overline{\boldsymbol{\pi}}$ defining the intervention rule, which is related to a concrete threshold $m'\in\{1,2,\ldots,M_0\}$ by (3). For a suitable selection of t_0, it is advisable to consider the age-dependent probability $P_{\ge m'}(t)=\sum_{m=m'}^{M_0}\pi_m(t)$ and determine the set $I_{\ge m'}$ of *potential* intervention instants $t\in(0,\tau)$ verifying

$$P_{\ge m'}(t)\ge p,$$

for a predetermined value $p\in(0,1)$, provided that $I_{\ge m'}$ is nonempty for the number m'. This means that the resulting set $I_{\ge m'}$ depends on p and m' (i.e., the vector $\overline{\boldsymbol{\pi}}$ of initial probabilities at age t_0). Time instants $t\in(0,\tau)\backslash I_{\ge m'}$ can be termed as *low-risk* intervention instants and, consequently, they are not considered in subsequent arguments. The value p can be seen as an *index of intervention*; in particular, for a fixed threshold m', less (respectively, more) conservative rules are derived as the index p is close to one (respectively, zero).

Assume that a fixed pair (m',p) results in the nonempty set $I_{\ge m'}$ of potential intervention instants. Then, the problem is to find a single instant $t_0\in I_{\ge m'}$ that adequately balances the effectiveness and cost of intervention. To this end, we let $\mathit{eff}(t_0;\tau)$ and $\mathit{cost}(t_0;\tau)$ denote the effectiveness and cost of intervention at time

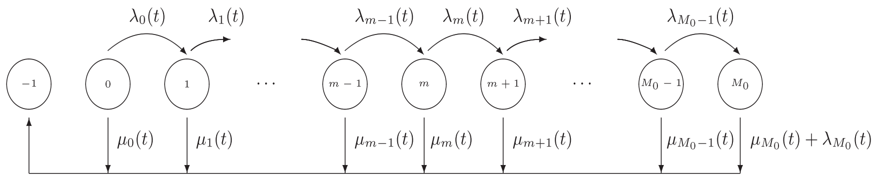

Fig. 1. State space and transitions of the process $\mathcal{X}$.

instant t_0, respectively, and we take $eff(t_0;\tau)$ and $cost(t_0;\tau)$ to depend on the age-dependent solution in (4) and (5). For example, a basic choice for $eff(t_0;\tau)$ is given by the probability $\pi_0(t_0;\tau)$ that the host is alive and parasite free and, in contrast, we may make $cost(t_0;\tau)$ depend on the probability $\pi_{-1}(t_0;\tau)$ that it does not survive at age τ.

In the choice of t_0, there are two lines of reasoning that can be taken to provide a balance between the efficiency and the cost of intervention. They are specified as follows:

Criterion 1: *The objective is to minimize the cost of intervention and to maintain a minimum level of effectiveness*. We thus translate the minimum level of effectiveness into a certain probability $p_1 \in (0,1)$, and determine the subset $J^1_{\geq m'}$ of potential intervention instants $t \in I_{\geq m'}$ satisfying

$$eff(t;\tau) \geq p_1.$$

Then, we suggest to choose the intervention age t_0 verifying $cost(t_0;\tau) = \inf\{cost(t;\tau) : t \in J^1_{\geq m'}\}$.

Criterion 2: *The objective is to maximize the effectiveness and to set an upper bound to the cost of intervention*. For a suitably chosen probability $p_2 \in (0,1)$, we first determine the subset $J^2_{\geq m'}$ of time instants $t \in I_{\geq m'}$ verifying

$$cost(t;\tau) \leq p_2,$$

and then select the intervention age t_0 such that $eff(t_0;\tau) = \sup\{eff(t;\tau) : t \in J^2_{\geq m'}\}$.

One difficulty with both lines of reasoning is that the age t_0 is chosen according to $eff(t;\tau)$ and $cost(t;\tau)$, which requires inverting (4) and (5). An analytical formula for t_0 is not simple, but the solution of this problem is straightforward as concrete specifications for the age-dependent rates $\lambda_m(t)$, $\mu_m(t)$, $\eta_m(t)$ and $\mu'_m(t)$ are assumed.

3. GI nematode burden in growing lambs

In this section we apply Criteria 1 and 2 to the development of GI parasitism in growing lambs. The focus is on the parasite *Nematodirus* spp. with *Nematodirus battus*, *Nematodirus filicollis* and *Nematodirus spathiger* as main species.

For convenience, we first comment on the parasite *Nematodirus* spp., its life cycle and aids to diagnosis of GI nematode infection in sheep. Such comments are then used in Section 3.2 to define the mathematical model in terms of levels of infection, and to identify age-dependent patterns from empirical data in Nasreen et al. (2007) and Uriarte et al. (2003). In Section 3.3, we apply Criteria 1 and 2 to various grazing management strategies.

3.1. Preliminary comments

In nematodes, the sexes are separate, and the males are generally smaller than the females, which lay eggs or larvae. During its development, a nematode moults at intervals, shedding its cuticle. In the complete life cycle of *Nematodirus* spp. there are four moults, the successive larval stages being designated as L_1, L_2, L_3, L_4 and finally L_5, which is the immature adult. Infection occurs by ingestion of the free-living L_3, with establishment proportions of L_3 in susceptible lambs ranging between 45% and 60%; (see e.g. Barger, 1989; Barger et al., 1985; Dobson et al., 1990). Moisture levels, temperature and the availability of oxygen are key drivers, affecting not only how quickly eggs hatch and larvae develop, but also how long larvae and eggs survive on pasture. Thus, the occurrence of nematode infections in sheep is inherently connected with diversities of physiographic and climatic conditions; see Bailey et al. (2009) and Boa et al. (2001). For further details on nematode taxonomy and morphology, and the treatment and control of parasitic gastroenteritis in sheep, we refer the reader

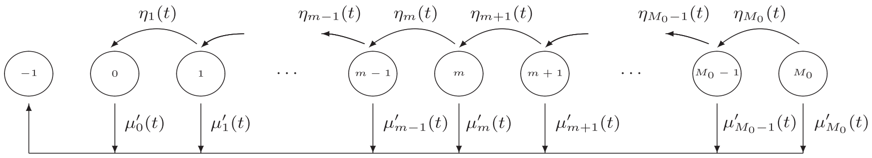

Fig. 2. State space and transitions of the process $\mathcal{Y}$.

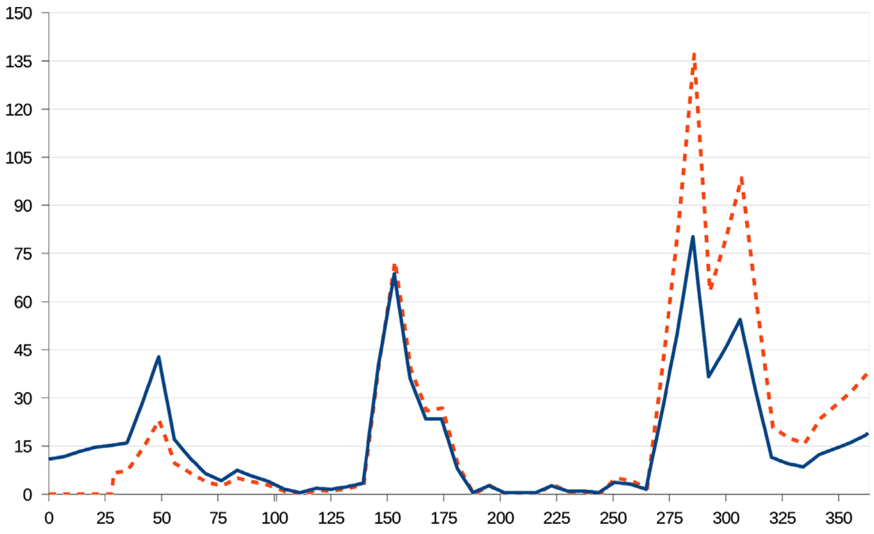

Fig. 3. Numbers of L_3 infective larvae on pasture (solid line), and increments in the number of L_3 infective larvae on the small intestine (broken line). Establishment proportion: 55%.

to the monographs Sutherland and Scott (2010) and Taylor et al. (2007).

Our starting point is the set of data in Uriarte et al. (2003, Fig. 2) recording the number of L_3 infective larvae on herbage samples at weekly intervals from a fixed paddock of the farm. Results are expressed as infective larvae per kilogram of dry matter (L_3 kg^{-1} DM) after drying the herbage overnight at 60 °C. The numbers of L_3 infective larvae on herbage samples in Uriarte et al. (2003, Fig. 2) correspond to *Chabertia ovina* and *Haemonchus* spp. (9.6%), *Nematodirus* spp. (4.0%), *Ostertagia* spp. (71.4%), and *Trichostrongylus* spp. (15.0%). The variation of L_3 infective larvae on herbage over time (Fig. 3, solid line) shows three periods of maximum pasture contamination, with 42.0 L_3 kg^{-1} DM (by mid-February), 68.0 L_3 kg^{-1} DM (by June 2) and 80.0 L_3 kg^{-1} DM (between October and November) as maximum values. Then, the increments in the number of L_3 infective larvae on the small intestine (Fig. 3, broken line) are estimated by fixing the establishment proportion and incorporating specifications for the lamb growth pre-weaning and post-weaning. In our examples, the establishment proportion equals 55%, and we consider a lamb that is born on January 1 (i.e., day 0 in our figures and tables); otherwise, we shall handle the set of data in Uriarte et al. (2003) starting from the day on which the lamb was born. It is assumed that the lamb birth weight equals 5 kg, the pre-weaning period consists of 4 weeks, and the lamb growth rate from birth to weaning is given by 0.3 kg per day. The lamb growth rate on pasture post-weaning is assumed to be equal to 0.15 kg per day, and the daily DM intake amounts to the 6% of body weight (BW). Details on lamb growth rates on pasture may be found, for example, in Grennan (1999).

Fecal examination for the presence of worm eggs or larvae is the most common routine aid to diagnosis employed. In the fecal egg count (FEC) reduction test, animals are allocated to groups of 10 based on pre-treatment FEC, with one group of 10 for each anthelmintic tested and a further untreated control group. For instance, this requires the use of 40 animals in Nasreen et al. (2007), where the efficacy of three anthelmintics (*ivermectin*, *fenbendazole* and *albendazole*) against GI nematodes is investigated. Each animal is periodically sampled for FEC, and bulk samples of feces are cultured for larval differentiation. A full FEC reduction test is understandably expensive and takes a significant length of time before farmers are presented with the results, and accurate larval differentiation also demands a high degree of skill. A *points system* (see Abbott et al., 2012) serves as a crude guide to interpreting worm counts, which is based on the fact that 1 *point* is equivalent to the presence of 4000 worms, a total of 2 *points* in a young sheep is likely to be causing measurable losses of productivity, and clinical signs and deaths are unlikely unless the total exceeds 3 *points*. In Table 1, we summarize the equivalence used here in the identification of degree of infestation, level of infection, eggs per gram (EPG) value, number of L_3 infective larvae on small intestine, and the points system; further details can be found in Abbott et al. (2012) and Taylor et al. (2007).

3.2. Identifying age-dependent patterns

We construct the mathematical model in terms of *levels of infection*. Thus, we let the random variable $M(t)$ record the level of infection at time t. This means that the degree of infestation is *null* if $M(t)=0$, *light* if $M(t)=m$ with $m\in\{1,2,3\}$, *moderate* if $M(t)=m$ with $m\in\{4,5,6,7\}$, *high* if $M(t)=m$ with $m\in\{8,9,10,11\}$, and *heavy* if $M(t)=-1$; see e.g. Abbott et al. (2012) and Taylor et al. (2007).

The first step in studying the development of GI parasitism is to fix appropriate age-dependent rates for acquisition of L_3 infective larvae, and the death of larvae within the host. Since infective larvae cannot reproduce directly within the host, it is assumed that $\lambda^*_m(t)=0$ for every level $m\in\{-1\}\cup\mathcal{S}$. As a result, we have that $\lambda_m(t)=\lambda(t)$ where $\lambda(t)$ is derived from Fig. 3 (broken line) and Table 1 by translating increments in the number of L_3 infective larvae into levels of infection. To be concrete, we first specify the value $\lambda(n)$ at the nth day as

$$\frac{\lambda'(n)\times i(n)\times pr}{l},$$

where $\lambda'(n)$ is the number of L_3 infective larvae of *Nematodirus* spp. on pasture, $i(n)$ is the DM intake at the nth day (i.e., 6% of BW), pr is the establishment proportion (i.e., $pr=0.55$), and l is the interval length used in Table 1 to define infection levels m in terms of numbers of infective larvae; i.e., $l=1000$ for $m\in\mathcal{S}$. The age-dependent rate $\lambda(t)$ for acquisition of L_3 infective larvae is then defined to be the piecewise linear function formed by connecting the points $(n,\lambda(n))$ in order, by line segments.

Table 1
Degree of infestation, level of infection, number of L_3 infective larvae on the small intestine and EPG value. A guide to interpretation for *Nematodirus* spp.

Degree of infestation	Level of infection (m)	Points system	Number of L_3 infective larvae on the small intestine	EPG value (FEC reduction test)
Null	0	0	$[0,1000)$	$[0,50)$
Light	1	0	$[1000,2000)$	$[50,100)$
Light	2	0	$[2000,3000)$	$[100,150)$
Light	3	0	$[3000,4000)$	$[150,200)$
Moderate	4	1	$[4000,5000)$	$[200,250)$
Moderate	5	1	$[5000,6000)$	$[250,300)$
Moderate	6	1	$[6000,7000)$	$[300,350)$
Moderate	7	1	$[7000,8000)$	$[350,400)$
High	8	2	$[8000,9000)$	$[400,450)$
High	9	2	$[9000,10\,000)$	$[450,500)$
High	10	2	$[10\,000,11\,000)$	$[500,550)$
High	11	2	$[11\,000,12\,000)$	$[550,600)$
Heavy	-1	$\{3,4,\ldots\}$	$[12\,000,\infty)$	$[600,\infty)$

A reasonable assumption for the death rates of L_3 infective larvae is given by

$$\eta_m(t)=m\eta(t), \tag{8}$$

for levels m of infection ranging between 1 and $M_0=11$, where $\eta(t)$ reflects the therapeutic efficacy of a concrete anthelmintic over time. We use in Section 3.3 empirical data of Nasreen et al. (2007), where the efficacy of three anthelmintics against GI nematodes is investigated. More concretely, 40 weaner sheep having naturally acquired infestation of GI nematodes were selected for the study in Nasreen et al. (2007), and randomly divided into four groups termed as A, B, C and D, of 10 animals each. Animals of Groups B, C and D were orally administered *ivermectin* (0.2 mg kg^{-1} BW), *fenbendazole* (5.0 mg kg^{-1} BW) and *albendazole* (7.5 mg kg^{-1} BW), respectively, and animals of Group A served as control. Fecal samples were collected from each animal at day 0 immediately before administering the drug, and thereafter on day 3, 7, 14, 21 and 28 (post-treatment), and EPG values of samples were appropriately determined.

In our approach, the intervention instant t_0 corresponds to the day 0 in Nasreen et al. (2007) and, for a concrete anthelmintic treatment (termed as B, C and D), the underlying age-dependent function $\eta(t)$ in (8) is defined as the polyline connecting the points $(t_n,\eta(t_n))$ where instants t_n are given by t_0, $t_1=t_0+3$, $t_2=t_0+7$, $t_3=t_0+14$, $t_4=t_0+21$ and $t_5=t_0+28$. Values $\eta(t_n)$ with $n\in\{0,\ldots,4\}$ are derived from Nasreen et al. (2007, Table 1) as

$$\frac{1}{lev(t_n)}\times\frac{1}{t_{n+1}-t_n}\left(\frac{\lambda''(t_n)}{l'}\left(1+\frac{\lambda''_A(t_{n+1})-\lambda''_A(t_n)}{\lambda''_A(t_n)}\right)-\frac{\lambda''(t_{n+1})}{l'}\right), \tag{9}$$

where $\lambda''(t)$ and $lev(t)$ record the EPG value and the infection level at time t, respectively, and l' is the interval length used in Table 1 to define levels of infection in terms of EPG values. Since $l'=50$ for

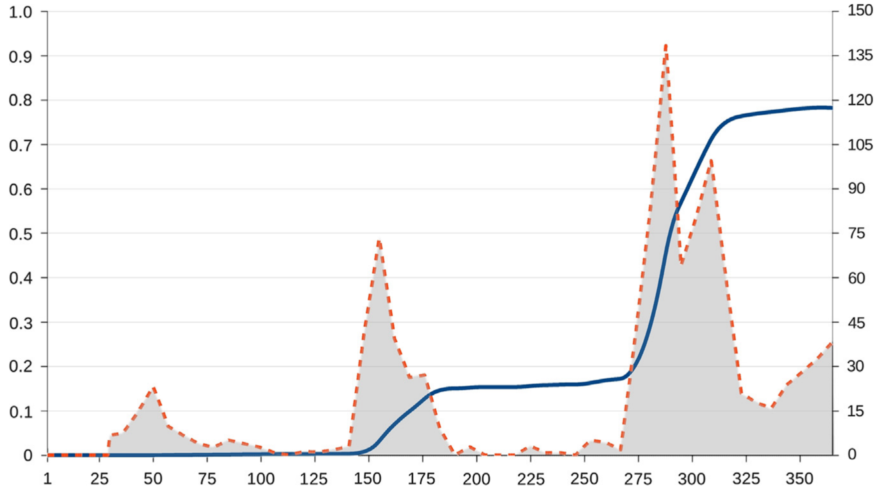

Fig. 4. The age-dependent probability $P_{\geq 4}(t)$ (solid line) as a function of $t \in (0, \tau)$ with $\tau = 1$ year, and increments in the number of L_3 infective larvae on the small intestine (shaded area, right vertical axis).

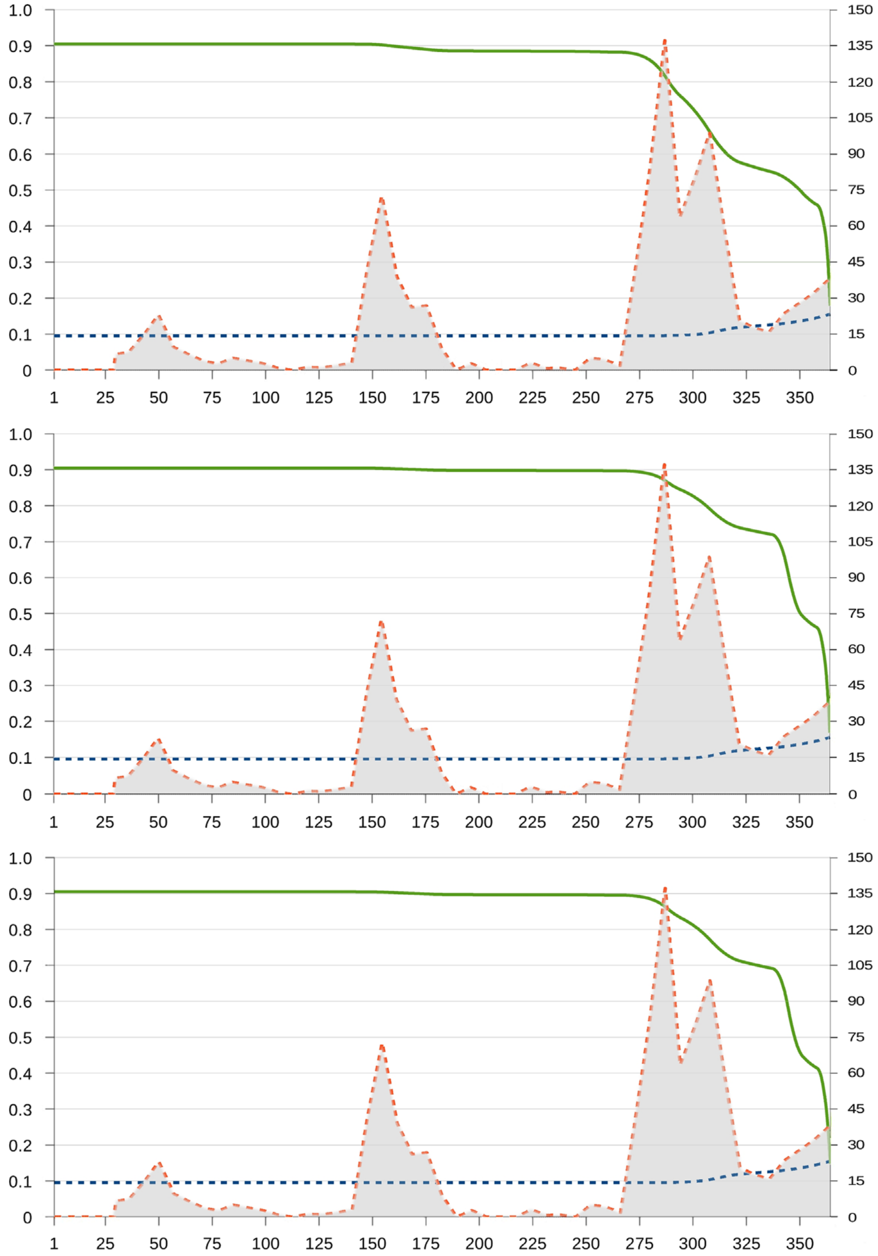

Fig. 5. Effectiveness (solid line) and cost (broken line) of intervention versus the intervention instant t_0, and increments in the number of L_3 infective larvae on the small intestine (shaded area, right vertical axis). Strategy TI with the anthelmintics *ivermectin*, *fenbendazole* and *albendazole* (from top to bottom).

levels $m \in \mathcal{S}$, $lev(t_n)$ is given by $[(l')^{-1}\lambda''(t_n)]$ where $[x]$ denotes integer part of x. Note that EPG values in Group A, denoted by $\lambda''_A(\cdot)$ in (9), allow us to estimate the effect of larvae established on the small intestine in the interval $(t_n, t_{n+1}]$. In order to reflect the end of the therapeutic period, it is assumed that $\eta(t) = 0$ if $t \geq t_5$, that is, the therapeutic period consists of 28 days. As the reader may readily verify, the functions $\tilde{R}^j_m(t_0;t)$ in (6) and (7) can be evaluated from

$$\tilde{R}^j_{m-j}(t_0;t) = \binom{m}{j+1}(1-e^{-H(t_0;t)})^{j+1},$$

where $H(t_0;t) = \int_{t_0}^{t} \eta(u)\,du$. Values for $H(t_0;t)$, which are related to the area under the polyline, can be computed as a function of the length $t - t_0$.

We conclude the model construction with the selection $\mu_m(t) = \mu'_m(t) = \mu(t)$ for every $m \in \mathcal{S}$. In accordance with the points system (Table 1), this implies that the parasite-induced death of the host is negligible, except as the total exceeds 3 points (i.e., $m = -1$). Then, with the specification $\mu(t) = e^{-10.0t}$ used in Section 3.3, the conditional probability that the host death occurs within the first 24 h, given that it dies in the interval $(0, \tau)$ with $\tau = 1$ year, is equal to 99.995%.

3.3. Discussion

The interest is in the grazing management strategy, termed as *strategy TI*, which is defined in the following manner:

Strategy TI: *The host is treated with an anthelmintic drug and isolated* (*that is*, *moved to an uninfected area*) *at age* t_0.

From an analytical point of view, the process $\mathcal{X}$ results in an age-dependent pure birth process with killing, where the birth and killing rates are respectively given by $\lambda_m(t) = \lambda(t)$ for values $m = 0, 1, \ldots, M_0 - 1$, and $\mu(t) + \delta_{m,M_0}\lambda_{M_0}(t)$ for values $m = 0, 1, \ldots, M_0$, at time instants $t < t_0$. Similarly, the process $\mathcal{Y}$ can be seen as an age-dependent pure death process with killing, where the death and killing rates are respectively given by $\eta_m(t) = m\eta(t)$ for values $m = 1, 2, \ldots, M_0$, and $\mu(t)$ for values $m = 0, 1, \ldots, M_0$, at time instants $t_0 \leq t \leq \tau$. Such processes $\mathcal{X}$ and $\mathcal{Y}$ are both defined on the set of infection levels $\{-1, 0, 1, \ldots, M_0\}$ with $M_0 = 11$ as the critical level, and functions $\lambda(t)$ and $\eta(t)$ are connected, by Section 3.2, to the empirical data in Nasreen et al. (2007) and Uriarte et al. (2003).

In applying Criteria 1 and 2 to strategy TI, we measure the effectiveness and cost of intervention at age t_0 in terms of

$$eff(t_0;\tau) = \sum_{m=0}^{3} \pi_m(t_0;\tau), \tag{10}$$

$$cost(t_0;\tau) = \pi_{-1}(t_0;\tau), \tag{11}$$

with $\tau = 1$ year, and determine the set $I_{\geq m'}$ of potential intervention instants with threshold $m' = 4$ and a predetermined index $p \in (0,1)$. In the terminology of veterinary parasitology, the effectiveness in (10) reflects a degree of infestation that is either null or light, and the cost of intervention in (11) amounts to a degree of infestation that is heavy. In accordance with the points system, the selection of $m' = 4$ is related to measurable presence of L_3 infective larvae on the small intestine.

Table 2
Intervention instants t_0 versus the index p and the lower bound p_1 for effectiveness. Strategy TI with the anthelmintics *ivermectin* (Group B), *fenbendazole* (Group C) and *albendazole* (Group D). Application of Criterion 1.

p	$I_{\geq 4}$	p_1	$J^{1,B}_{\geq 4}$	t^B_0	$J^{1,C}_{\geq 4}$	t^C_0	$J^{1,D}_{\geq 4}$	t^D_0
0.1	[170,365)	0.75	[170,295]	170	[170,317]	170	[170,311]	170
		0.70	[170,303]	170	[170,340]	170	[170,330]	170
		0.65	[170,308]	170	[170,343]	170	[170,341]	170
0.2	[274,365)	0.75	[274,295]	274	[274,317]	274	[274,311]	274
		0.70	[274,303]	274	[274,340]	274	[274,330]	274
		0.65	[274,308]	274	[274,343]	274	[274,341]	274
0.3	[281,365)	0.75	[281,295]	281	[281,317]	281	[281,311]	281
		0.70	[281,303]	281	[281,340]	281	[281,330]	281
		0.65	[281,308]	281	[281,343]	281	[281,341]	281
0.4	[286,365)	0.75	[286,295]	286	[286,317]	286	[286,311]	286
		0.70	[286,303]	286	[286,340]	286	[286,330]	286
		0.65	[286,308]	286	[286,343]	286	[286,341]	286
0.5	[290,365)	0.75	[290,295]	290	[290,317]	290	[290,311]	290
		0.70	[290,303]	290	[290,340]	290	[290,330]	290
		0.65	[290,308]	290	[290,343]	290	[290,341]	290
0.6	[298,365)	0.75	–	–	[298,317]	298	[298,311]	298
		0.70	[298,303]	298	[298,340]	298	[298,330]	298
		0.65	[298,308]	298	[298,343]	298	[298,341]	298
0.7	[308,365)	0.75	–	–	[308,317]	308	[308,311]	308
		0.70	–	–	[308,340]	308	[308,330]	308
		0.65	[308,308]	308	[308,343]	308	[308,341]	308

Table 3
Intervention instants t_0 versus the index p and the upper bound p_2 for the cost of intervention. Strategy TI with the anthelmintics *ivermectin* (Group B), *fenbendazole* (Group C) and *albendazole* (Group D). Application of Criterion 2.

p	$I_{\geq 4}$	p_2	$J^{2,B}_{\geq 4}$	t^B_0	$J^{2,C}_{\geq 4}$	t^C_0	$J^{2,D}_{\geq 4}$	t^D_0
0.1	[170,365)	0.25	[170,365)	170	[170,365)	170	[170,365)	170
		0.20	[170,365)	170	[170,365)	170	[170,365)	170
		0.15	[170,360]	170	[170,360]	170	[170,360]	170
0.2	[274,365)	0.25	[274,365)	274	[274,365)	274	[274,365)	274
		0.20	[274,365)	274	[274,365)	274	[274,365)	274
		0.15	[274,360]	274	[274,360]	274	[274,360]	274
0.3	[281,365)	0.25	[281,365)	281	[281,365)	281	[281,365)	281
		0.20	[281,365)	281	[281,365)	281	[281,365)	281
		0.15	[281,360]	281	[281,360]	281	[281,360]	281
0.4	[286,365)	0.25	[286,365)	286	[286,365)	286	[286,365)	286
		0.20	[286,365)	286	[286,365)	286	[286,365)	286
		0.15	[286,360]	286	[286,360]	286	[286,360]	286
0.5	[290,365)	0.25	[290,365)	290	[290,365)	290	[290,365)	290
		0.20	[290,365)	290	[290,365)	290	[290,365)	290
		0.15	[290,360]	290	[290,360]	290	[290,360]	290
0.6	[298,365)	0.25	[298,365)	298	[298,365)	298	[298,365)	298
		0.20	[298,365)	298	[298,365)	298	[298,365)	298
		0.15	[298,360]	298	[298,360]	298	[298,360]	298
0.7	[308,365)	0.25	[308,365)	308	[308,365)	308	[308,365)	308
		0.20	[308,365)	308	[308,365)	308	[308,365)	308
		0.15	[308,360]	308	[308,360]	308	[308,360]	308

Table 4
Effectiveness and cost of intervention versus the intervention instant t_0. Strategy TI with anthelmintics *ivermectin*, *fenbendazole* and *albendazole*.

t_0	Anthelmintic	Cost	Effectiveness
170	*Ivermectin*	0.09516	0.89296
	Fenbendazole	0.09516	0.90104
	Albendazole	0.09516	0.89999
274	*Ivermectin*	0.09517	0.87534
	Fenbendazole	0.09517	0.89480
	Albendazole	0.09517	0.89218
281	*Ivermectin*	0.09521	0.85437
	Fenbendazole	0.09521	0.88681
	Albendazole	0.09521	0.88230
286	*Ivermectin*	0.09540	0.82248
	Fenbendazole	0.09540	0.87372
	Albendazole	0.09540	0.86636
290	*Ivermectin*	0.09592	0.78717
	Fenbendazole	0.09592	0.85808
	Albendazole	0.09592	0.84758
298	*Ivermectin*	0.09763	0.73694
	Fenbendazole	0.09763	0.83380
	Albendazole	0.09763	0.81895
308	*Ivermectin*	0.10415	0.65801
	Fenbendazole	0.10415	0.79063
	Albendazole	0.10415	0.76935

We may note that, by Fig. 4, only values of the index p of intervention ranging between 0 and $P_{\geq 4}(\tau)$ lead us to non-empty sets $I_{\geq 4}$, since $P_{\geq 4}(t)$ appears to be a non-decreasing function of $t \in (0, \tau)$. Thus, we next determine sets $I_{\geq 4}$ for values $p \in \{0.1, 0.2, \ldots, 0.7\}$. In any host–parasite model like this, because of the seasonal conditions, a preliminary analysis of the effectiveness and cost of intervention is frequently required in order to determine concrete values of the lower bound p_1 for effectiveness (Criterion 1) and the upper bound p_2 for the cost of intervention (Criterion 2) so that Criteria 1 and 2 result in nonempty subsets $J^1_{\geq m'}$ and $J^2_{\geq m'}$. For practical use, a graphical representation of $eff(t_0; \tau)$ and $cost(t_0; \tau)$ can help in measuring allowable values for the minimum level of effectiveness and the maximum cost of intervention in terms of p_1 and p_2, respectively. In our case, Fig. 5 shows how $eff(t_0; \tau)$ and $cost(t_0; \tau)$ behave in terms of the intervention instant t_0, and leads us to apply Criteria 1 and 2 with lower bounds $p_1 \in \{0.65, 0.7, 0.75\}$ and upper bounds $p_2 \in \{0.15, 0.2, 0.25\}$, respectively.

Values of the intervention instant t_0 are listed in Tables 2 and 3 for the anthelmintics *ivermectin* (administered to animals of Group B), *fenbendazole* (Group C) and *albendazole* (Group D), and they are denoted by t_0^B, t_0^C and t_0^D, respectively. An examination of the resulting instants t_0 reveals three important observations:

(i) For every anthelmintic treatment and fixed index p, Criteria 1 and 2 yield identical intervention instants with the exception of the pairs $(p, p_1) \in \{(0.6, 0.75), (0.7, 0.7), (0.7, 0.75)\}$ for the anthelmintic *ivermectin*.

(ii) For every anthelmintic treatment, the intervention instant t_0 increases with increasing values of the index p of intervention, regardless of the control criterion.

(iii) On applying Criterion 1 (respectively, Criterion 2), values of the lower bound $p_1 \in \{0.65, 0.7, 0.75\}$ (respectively, values of the upper bound $p_2 \in \{0.15, 0.2, 0.25\}$) result in identical intervention instants t_0, irrespective of the anthelmintic drug.

These consequences can be easily explained from the monotone behaviors of the effectiveness $eff(t_0; \tau)$ and cost $cost(t_0; \tau)$ of intervention shown in Fig. 5. On the one hand, it is shown in Fig. 5 that the cost of intervention appears to behave as a constant function for intervention instants t_0 ranging between 0 and 300, and it becomes an increasing function for instants t_0 ranging between 300 and 365. On the other hand, it is seen that the effectiveness essentially behaves as a constant function within the interval (0,275), with only a small decrease at day 175. The variability of $eff(t_0; \tau)$ is very significant for instants t_0 ranging between 275 and 365, which is closely related to the occurrence of maximum increments in the number of L_3 infective larvae on the small intestine; such as maximum increments are registered at days 287 and 308, that is, by October–November. It is also remarkable to observe that, by Table 4, *fenbendazole* administered to animals of Group C is found to be the most effective drug since the highest values of $eff(t_0; \tau)$ are associated with Group C for every intervention instant t_0 in Tables 2 and 3.

4. Conclusions

An intervention at age $t_0^C = 170$ (Table 4) results simultaneously in the minimum cost of intervention, $cost(t_0^C; \tau) = 0.09516$, and the maximum effectiveness, $eff(t_0^C; \tau) = 0.90104$, and consequently it can be taken as *optimal* for our purposes. In applying Criteria 1 and 2, the

Table 5
Intervention instants t_0 versus the index p and the lower bound p_1 for effectiveness. Strategy TI+S with the anthelmintics *ivermectin* (Group B), *fenbendazole* (Group C) and *albendazole* (Group D).

p	$I_{\geq 4}$	p_1	$J^{1,B}_{\geq 4}$	$\bar{t}_0^B$	$\hat{t}_0^B$	$J^{1,C}_{\geq 4}$	$\bar{t}_0^C$	$\hat{t}_0^C$	$J^{1,D}_{\geq 4}$	$\bar{t}_0^D$	$\hat{t}_0^D$
0.1	[170,365)	0.75	–	–		–	–		–	–	
		0.70	–	–		[334,340]	334	334	–	–	
		0.65	–	–		[284,306]∪[323,343]	284	287	[287,297]∪[330,341]	287	287
		0.60	–	–		[280,345]	280	287	[281,343]	281	287
		0.55	[282,296]	282	286	[276,347]	280	287	[277,345]	280	287
0.2	[274,365)	0.75	–	–		–	–		–	–	
		0.70	–	–		[334,340]	334	334	–	–	
		0.65	–	–		[284,306]∪[323,343]	284	287	[287,297]∪[330,341]	287	287
		0.60	–	–		[280,345]	280	287	[281,343]	281	287
		0.55	[282,296]	282	286	[276,347]	280	287	[277,345]	280	287
0.3	[281,365)	0.75	–	–		–	–		–	–	
		0.70	–	–		[334,340]	334	334	–	–	
		0.65	–	–		[284,306]∪[323,343]	284	287	[287,297]∪[330,341]	287	287
		0.60	–	–		[281,345]	281	287	[281,343]	281	287
		0.55	[282,296]	282	286	[281,347]	281	287	[281,345]	281	287
0.4	[286,365)	0.75	–	–		–	–		–	–	
		0.70	–	–		[334,340]	334	334	–	–	
		0.65	–	–		[286,306]∪[323,343]	286	287	[287,297]∪[330,341]	287	287
		0.60	–	–		[286,345]	286	287	[286,343]	286	287
		0.55	[286,296]	286	286	[286,347]	286	287	[286,345]	286	287
0.5	[290,365)	0.75	–	–		–	–		–	–	
		0.70	–	–		[334,340]	334	334	–	–	
		0.65	–	–		[290,306]∪[323,343]	290	290	[290,297]∪[330,341]	290	290
		0.60	–	–		[290,345]	290	290	[290,343]	290	290
		0.55	[290,296]	290	290	[290,347]	290	290	[290,345]	290	290
0.6	[298,365)	0.75	–	–		–	–		–	–	
		0.70	–	–		[334,340]	334	334	–	–	
		0.65	–	–		[298,306]∪[323,343]	298	298	[330,341]	330	330
		0.60	–	–		[298,345]	298	298	[298,343]	298	298
		0.55	–	–		[298,347]	298	298	[298,345]	298	298
0.7	[308,365)	0.75	–	–		–	–		–	–	
		0.70	–	–		[334,340]	334	334	–	–	
		0.65	–	–		[323,343]	323	323	[330,341]	330	330
		0.60	–	–		[308,345]	308	308	[308,343]	308	308
		0.55	–	–		[308,347]	308	308	[308,345]	308	308

selection $t_0^C = 170$ is derived with the index of intervention $p = 0.1$, which leads us to the most conservative intervention rule in our examples. Moreover, we may observe that $t_0^C = 170$ is also related to the longest isolated-living interval $[t_0^C, \tau]$. It is important to recognize that, for practical use, $t_0^C = 170$ might be unsustainable since the maintenance of noninfectious conditions for a long period of time is highly expensive. Thus, in Tables 5–8 and Fig. 6, we investigate a modified grazing strategy, which is specified as follows:

Strategy TI+S: *The host is first treated with an anthelmintic drug and isolated at age t_0, and it is then moved to its original paddock (set-stocking) after living for 28 days under noninfectious conditions.*

Table 6
Intervention instants t_0 versus the index p and the upper bound p_2 for the cost of intervention. Strategy TI+S with the anthelmintics *ivermectin* (Group B), *fenbendazole* (Group C) and *albendazole* (Group D). Application of Criterion 2 with the cost of intervention defined as $cost(t;\tau) = \pi_{-1}(t;\tau)$.

p	$I_{\geq 4}$	p_2	$J_{\geq 4}^{2,B}$	$\bar{t}_0^B$	$J_{\geq 4}^{2,C}$	$\bar{t}_0^C$	$J_{\geq 4}^{2,D}$	$\bar{t}_0^D$
0.1	[170,365)	0.25	[170,365)	286	[170,365)	337	[170,365)	337
		0.20	[170,365)	286	[170,365)	337	[170,365)	337
		0.15	[170,360]	286	[170,360]	337	[170,360]	337
0.2	[274,365)	0.25	[274,365)	286	[274,365)	337	[274,365)	337
		0.20	[274,365)	286	[274,365)	337	[274,365)	337
		0.15	[274,360]	286	[274,360]	337	[274,360]	337
0.3	[281,365)	0.25	[281,365)	286	[281,365)	337	[281,365)	337
		0.20	[281,365)	286	[281,365)	337	[281,365)	337
		0.15	[281,360]	286	[281,360]	337	[281,360]	337
0.4	[286,365)	0.25	[286,365)	286	[286,365)	337	[286,365)	337
		0.20	[286,365)	286	[286,365)	337	[286,365)	337
		0.15	[286,360]	286	[286,360]	337	[286,360]	337
0.5	[290,365)	0.25	[290,365)	290	[290,365)	337	[290,365)	337
		0.20	[290,365)	290	[290,365)	337	[290,365)	337
		0.15	[290,360]	290	[290,360]	337	[290,360]	337
0.6	[298,365)	0.25	[298,365)	337	[298,365)	337	[298,365)	337
		0.20	[298,365)	337	[298,365)	337	[298,365)	337
		0.15	[298,360]	337	[298,360]	337	[298,360]	337
0.7	[308,365)	0.25	[308,365)	337	[308,365)	337	[308,365)	337
		0.20	[308,365)	337	[308,365)	337	[308,365)	337
		0.15	[308,360]	337	[308,360]	337	[308,360]	337

Table 7
Intervention instants t_0 versus the index p and the upper bound p_2 for the cost of intervention. Strategy TI+S with the anthelmintics *ivermectin* (Group B), *fenbendazole* (Group C) and *albendazole* (Group D). Application of Criterion 2 with the cost of intervention defined as $cost(t;\tau) = \sum_{m=8}^{11} \pi_m(t;\tau) + \pi_{-1}(t;\tau)$.

p	$I_{\geq 4}$	p_2	$J_{\geq 4}^{2,B}$	$\hat{t}_0^B$	$J_{\geq 4}^{2,C}$	$\hat{t}_0^C$	$J_{\geq 4}^{2,D}$	$\hat{t}_0^D$
0.1	[170,365)	0.25	[255,363]	286	[251,363]	337	[252,363]	337
		0.20	[259,362]	286	[257,362]	337	[257,362]	337
		0.15	[266,352]	286	[262,352]	337	[263,349]	337
0.2	[274,365)	0.25	[274,363]	286	[274,363]	337	[274,363]	337
		0.20	[274,362]	286	[274,362]	337	[274,362]	337
		0.15	[274,352]	286	[274,352]	337	[274,349]	337
0.3	[281,365)	0.25	[281,363]	286	[281,363]	337	[281,363]	337
		0.20	[281,362]	286	[281,362]	337	[281,362]	337
		0.15	[281,352]	286	[281,352]	337	[281,349]	337
0.4	[286,365)	0.25	[286,363]	286	[286,363]	337	[286,363]	337
		0.20	[286,362]	286	[286,362]	337	[286,362]	337
		0.15	[286,352]	286	[286,352]	337	[286,349]	337
0.5	[290,365)	0.25	[290,363]	290	[290,363]	337	[290,363]	337
		0.20	[290,362]	290	[290,362]	337	[290,362]	337
		0.15	[290,352]	290	[290,352]	337	[290,349]	337
0.6	[298,365)	0.25	[298,363]	337	[298,363]	337	[298,363]	337
		0.20	[298,362]	337	[298,362]	337	[298,362]	337
		0.15	[298,352]	337	[298,352]	337	[298,349]	337
0.7	[308,365)	0.25	[308,363]	337	[308,363]	337	[308,363]	337
		0.20	[308,362]	337	[308,362]	337	[308,362]	337
		0.15	[308,352]	337	[308,352]	337	[308,349]	337

This means to distinguish between two free-living intervals $[0, t_0)$ and $[t_5, \tau]$, and an intermediate isolated-living interval $[t_0, t_5)$ with $t_5 = t_0 + 28$; see Nasreen et al. (2007). In applying Criteria 1 and 2 under the grazing assumptions yielding strategy TI+S, we use $\sum_{m=0}^{3} \pi_m(t;\tau)$ to measure the effectiveness, whereas the cost of intervention is measured by $\pi_{-1}(t;\tau)$ (i.e., the degree of infestation is heavy) and, alternatively, by $\sum_{m=8}^{11} \pi_m(t;\tau) + \pi_{-1}(t;\tau)$ (i.e., the degree of infestation is high or heavy), with the resulting intervention instants denoted by $\bar{t}_0$ and $\hat{t}_0$, respectively. In contrast to Fig. 5, the effectiveness and cost of intervention (under both definitions) for strategy TI+S exhibit in Fig. 6 non-monotone behaviors over time.

Tables 5–8 are themselves explanatory, whence we comment only on three remarkable observations. First, we emphasize that there is no optimal intervention instant t_0 under strategy TI+S; see, for example, entries in Table 8 for $eff(t_0;\tau)$ and $cost(t_0\tau) = \pi_{-1}(t_0;\tau)$ at ages $t_0 = 280$ and 337 and the anthelmintic drug *fenbendazole* administered to animals of Group C. Second, *fenbendazole* is also found to be the most effective drug as the length of 28 days is assumed for the isolated-living interval. Third, an interesting feature in applying Criteria 1 and 2 is that the intervention by anthelmintics is mostly prescribed at age 337, thus

Table 8
Effectiveness and cost of intervention. Strategy TI+S with the anthelmintics *ivermectin*, *fenbendazole* and *albendazole*.

t_0	Anthelmintic	$\pi_{-1}(t_0;\tau)$	$\sum_{m=8}^{11} \pi_m(t_0;\tau) + \pi_{-1}(t_0;\tau)$	Effectiveness
280	*Ivermectin*	–	–	–
	Fenbendazole	0.09524	–	0.61241
	Albendazole	0.09525	–	0.59796
281	*Ivermectin*	–	–	–
	Fenbendazole	0.09524	–	0.62559
	Albendazole	0.09525	–	0.61074
282	*Ivermectin*	0.09533	–	0.55290
	Fenbendazole	–	–	–
	Albendazole	–	–	–
284	*Ivermectin*	–	–	–
	Fenbendazole	0.09530	–	0.65477
	Albendazole	–	–	–
286	*Ivermectin*	0.09547	0.10772	0.56927
	Fenbendazole	0.09541	–	0.66563
	Albendazole	0.09542	–	0.64831
287	*Ivermectin*	–	–	–
	Fenbendazole	–	0.10012	0.66852
	Albendazole	0.09551	0.10113	0.65056
290	*Ivermectin*	0.09600	0.10869	0.56314
	Fenbendazole	0.09594	0.10024	0.67312
	Albendazole	0.09594	0.10131	0.65342
292	*Ivermectin*	–	–	–
	Fenbendazole	–	–	–
	Albendazole	0.09631	–	0.65392
293	*Ivermectin*	–	–	–
	Fenbendazole	0.09649	–	0.67475
	Albendazole	–	–	–
298	*Ivermectin*	0.09770	–	0.54469
	Fenbendazole	0.09764	0.10181	0.67148
	Albendazole	0.09765	0.10301	0.64877
308	*Ivermectin*	–	–	–
	Fenbendazole	0.10416	0.10899	0.64554
	Albendazole	0.10416	0.11057	0.61845
323	*Ivermectin*	–	–	–
	Fenbendazole	0.11948	0.12269	0.65152
	Albendazole	–	–	–
330	*Ivermectin*	–	–	–
	Fenbendazole	–	–	–
	Albendazole	0.12295	0.12561	0.65263
334	*Ivermectin*	–	–	–
	Fenbendazole	0.12485	0.12598	0.70327
	Albendazole	–	–	–
337	*Ivermectin*	0.12629	0.13310	0.54949
	Fenbendazole	0.12629	0.12700	0.71988
	Albendazole	0.12629	0.12745	0.69110

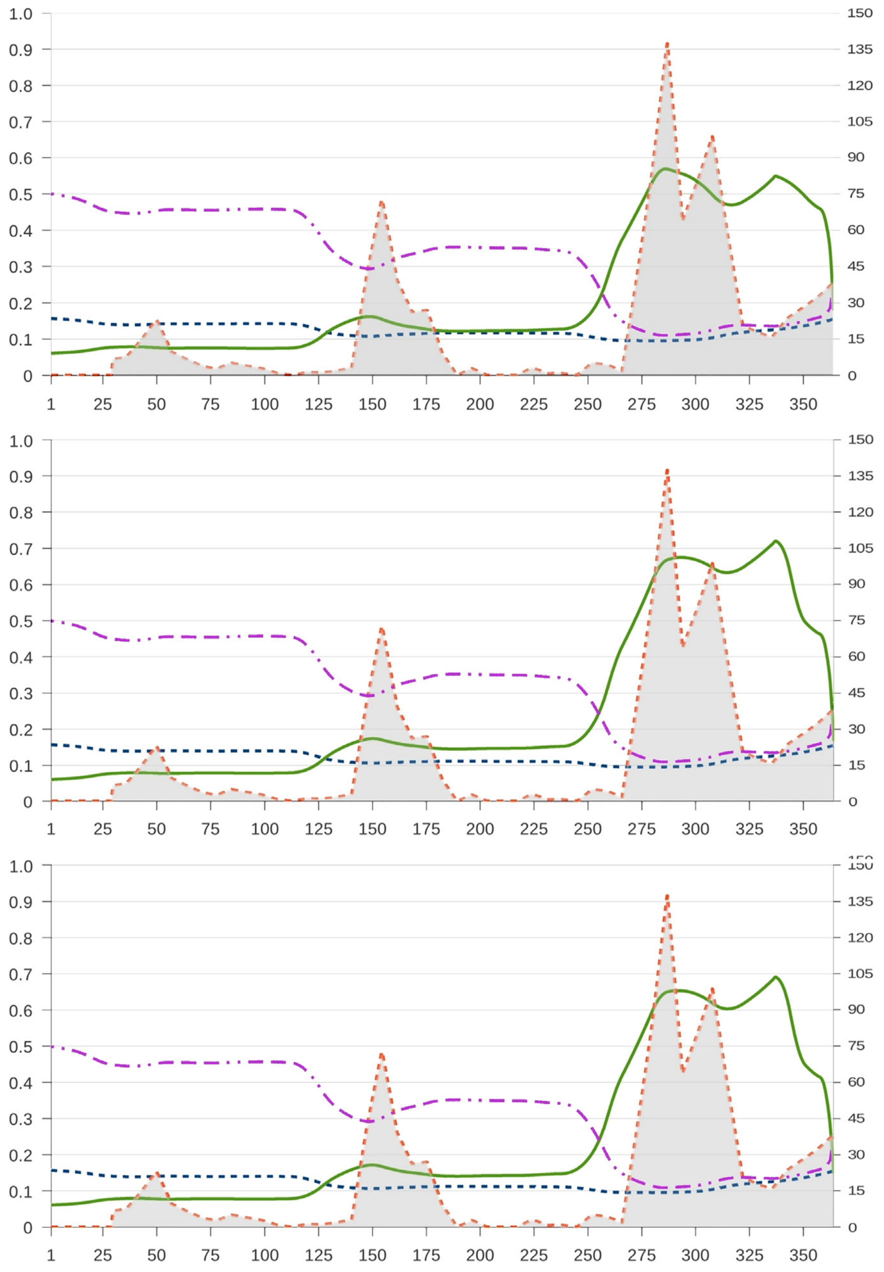

Fig. 6. Effectiveness (solid line) and cost of intervention measured in terms of $\pi_{-1}(t_0;\tau)$ (broken line) and $\sum_{m=8}^{11}\pi_m(t_0;\tau)+\pi_{-1}(t_0;\tau)$ (dashed line) versus the intervention instant t_0, and increments in the number of L_3 infective larvae on the small intestine (shaded area, right vertical axis). Strategy TI+S with the anthelmintics *ivermectin*, *fenbendazole* and *albendazole* (from top to bottom).

Table 9
Effectiveness and cost of intervention at day $t_0=170$, 280 and 337.

Strategy	Anthelmintic	t_0	Effectiveness	$\pi_{-1}(t_0;\tau)$	$\sum_{m=8}^{11}\pi_m(t_0;\tau)+\pi_{-1}(t_0;\tau)$
US	*Fenbendazole*		0.06072	0.15708	0.49951
TI	*Fenbendazole*	170	0.90104 (1483.93% improvement)	0.09516 (165.07% reduction)	0.09516 (524.92% reduction)
TI+S	*Fenbendazole*	280	0.61241 (1008.58% improvement)	0.09524 (164.93% reduction)	0.10359 (482.20% reduction)
TI+S	*Fenbendazole*	337	0.71988 (1185.57% improvement)	0.12629 (124.38% reduction)	0.12700 (393.32% reduction)

implying that the second free-living interval $[t_5,\tau]$ becomes empty in strategy TI+S. It should be noted that the selection $t_0=337$ in strategy TI+S does not contradict those conclusions derived from Table 3 for strategy TI. More concretely, we may first observe that, for the index $p=0.7$ and upper bound $p_2\in\{0.15,0.2,0.25\}$, the sub-sets $J^{2,B}_{\geq 4}$, $J^{2,C}_{\geq 4}$ and $J^{2,D}_{\geq 4}$ of potential intervention instants in Table 3 are identical to their counterparts in Table 6. However, though the values of the effectiveness $\mathit{eff}(t_0;\tau)$ in Figs. 5 and 6 are clearly identical for intervention instants t_0 ranging between 337 and 365, the differences among values of the effectiveness in

Figs. 5 and 6 are significant for time instants $t_0 < 337$, and particularly it is seen that $eff(308;\tau) < eff(337;\tau)$ under strategy TI+S.

The anthelmintic drug *fenbendazole* orally administered to animals of Group C at day $t_0^C = 170$ (under strategy TI), 280 (strategy TI+S) and 337 (strategy TI+S) shows a markedly improved effectiveness and a notable reduction in the cost of intervention; see Table 9, where we use the term *strategy US* to reflect no intervention (i.e., the host is left untreated, and it stays at its original paddock). As intuition tells us, the maintenance of noninfectious conditions at post-intervention instants (i.e., intervention at day $t_0^C = 170$ under strategy TI) is accompanied by a significant increase in effectiveness compared to the use of a 28-day isolated-living period (i.e., intervention at day $t_0^C = 280$ under strategy TI+S), but the reduction in cost is not significant if we make the cost of intervention depend on the probability $\pi_{-1}(t_0;\tau)$ that either the host does not survive at age $\tau = 1$ year or its level of infection does not permit it to retrieve an acceptable GI nematode burden. It is difficult to judge whether an intervention at day $t_0^C = 280$ followed by a 28-day isolated-living interval does result in a more favorable response to treatment than at day $t_0^C = 337$. A plausible choice of the intervention age $t_0^C \in \{280, 337\}$ may be based on the fact that an early intervention at day $t_0^C = 280$ is related to a conservative intervention rule, whereas a late intervention at day $t_0^C = 337$ yields the less conservative rule in our examples; i.e., the index p of intervention at day $t_0^C = 280$ equals 0.2 by Table 5, and its value at day $t_0^C = 337$ equals 0.7 by Tables 6 and 7.

There are several directions in which the work reported in this paper may be developed. It is important to compare strategies TI and TI+S with other worm control strategies in grazing sheep, related to pasture management in organic production systems. Concrete specifications for these grazing management strategies can be found in Boa et al. (2001), which are based on strategic treatments and setstocking, (termed as TS in Boa et al., 2001), strategic treatments and move to clean pastures (termed TM), and treatment and move to clean pastures (termed UM). The host–parasite model in Section 2.1 can also be extended further by allowing parasites to exist in various forms within the host (such as larvae, mature parasites and parasite offspring), and the acquisition of a random number of infective larvae at an exposure instant. In these modifications of our model, the resulting processes $\mathcal{X}$ and $\mathcal{Y}$ will be no longer formulated as pure birth/death processes with killing. Current research on these modifications will be reported shortly.

Acknowledgments

Financial support for this work was provided by the Government of Spain (Ministry of Economy and Competitiveness) and the European Commission through the project MTM-2011-23864, and the Grant BES-2009-018747.

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