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Optimal control analysis of a transmission interruption model for the soil-transmitted helminth infections in Kenya

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ABSTRACT

Kenya is among the countries endemic for soil-transmitted helminthiasis (STH) with over 66 subcounties and over 6 million individuals being at-risk of infection. Currently, the country is implementing mass drug administration (MDA) to all the at-risk groups as the mainstay control strategy. This study aimed to develop and analyze an optimal control (OC) model, from a transmission interruption model, to obtain an optimal control strategy from a mix of three strategies evaluated. The study used the Pontryagin's maximum principle to solve, numerically, the OC model. The analysis results clearly demonstrated that water and sanitation when implemented together with the MDA programme offer the best chances of eliminating these tenacious and damaging parasites. Thus, we advocate for optimal implementation of the combined mix of the two interventions in order to achieve STH elimination in Kenya, and globally, in a short implementation period of less than eight years.

1. Introduction

Soil-transmitted helminthiasis (STH) mainly comprising of *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and *Necator americanus* and *Ancylostoma duodenale* (collectively, hookworms), are part of a group of diseases classified by the World Health Organization (WHO) as neglected tropical diseases (NTDs) (Savioli and Albonico, 2004). These intestinal helminths (worms) are estimated to be endemic in 166 countries and affect over 1.5 billion people globally (Montresor et al., 2020). Currently, these worms account for approximately 1.9 million number of disability-adjusted life years (DALYs) lost due to STH (Montresor et al., 2022). The people most affected are among the poorest and live in resource-constrained conditions where safe drinking water, proper sanitation and hygiene are inadequate (WHO, 2011). Further, it is estimated that over 267 million preschool-aged children (PSAC) and over 568 million school-aged children (SAC) live in areas endemic with these parasites and transmission is highly occurring (Pullan et al., 2014). In Kenya, it is estimated that over 66 subcounties and over 6 million individuals are at risk of infection (Okoyo et al., 2020).

These worms are transmitted mainly through ingestion of eggs in unwashed undercooked vegetables or unpeeled fruits (for the case of *A. lumbricoides* and *T. trichiura*), or penetration of the skin by adult worms (for the case of hookworms) (WHO, 2011). These worms can be effectively controlled through the provision of mass drug administration (MDA) without prior diagnosis to all at-risk groups using the WHO approved drugs such as albendazole, mebendazole, levamisole, or pyrantel (Farrell et al., 2018). Sustainable control can also be achieved through the integration of the provision of improved water, sanitation, and hygiene (WASH) within the MDA programmes (WHO, 2011). However, the majority of the STH control programmes, especially those in the low- and middle income countries (LMICs), have not structurally integrated WASH interventions within their MDA programmes citing high cost of WASH implementation, lack of proper coordination framework and information sharing with the WASH sector alliance, lack of clear research evidence on the WASH benefits, differing programmatic objectives in the two sectors, easy and inexpensive implementation of MDA campaigns, and differences in the scale of funding coupled with siloed funding for each sector (Johnston et al., 2015). Generally, helminth elimination is possible by employing interventions that reduce

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the number of worms in a host, and interventions that reduce the density of parasites from the contaminated environment (Ásbjörnsdóttir et al., 2017). Following these identified challenges in STH and WASH integration, this study was designed to provide the necessary clear evidence, using mathematical modeling, that selected WASH interventions if implemented together with MDA programmes would optimally accelerate the attainment of STH elimination in Kenya and other STH endemic countries.

The application of mathematical modeling to study STH, and other parasitic and infectious diseases, has helped in refining our understanding of the worm and host population dynamics, transmission patterns, and feasible control strategies (Isham and Medley, 1996). These models provide tools for the assessment and evaluation of the many control programmes being implemented today (Coffeng et al., 2018). Deterministic models with ordinary differential equations (ODEs) formulation are the most convenient and commonly used model structures to represent the helminth infection dynamics at large scales (Anderson and May 1982; Truscott et al., 2014). The model outputs defined as ODE solution over a time interval, provide a dynamic representation of the transmission process (Anderson and May 1991). The parameters used to compute model solutions are usually estimated from observational or experimental studies (Grassly and Fraser, 2008). However, only a few STH modeling analysis (Lambura et al., 2020; Oguntolu et al., 2023), have applied optimal control analysis to an STH transmission model in formulating public health control strategies targeting elimination. Optimization of the existing interventions and tools is necessary as a priority research area in order to maximize the intervention impact and sustainability (Gwayi-Chore et al., 2022). Thus, the study on the practical implementation of these public health control measures and their optimal delivery is of great importance.

In this study, we formulated and analyzed an optimal control (OC) model of an STH transmission interruption model. The developed OC model considered two controls, provision of improved water and sanitation ($u_1(t)$) alongside provision of MDA ($u_2(t)$). The analysis aimed to demonstrate, through numerical analysis of the OC model, the optimal control strategy to be implemented in order to achieve effective helminth control and elimination in Kenya. The transmission interruption model parameterization used studies (epidemiological or model) conducted in Kenya, and other geographies with similar infection endemicity and host age group characteristics.

2. Materials and methods

2.1. Public health programmes for STH control

Public health preventive intervention measures for STH are based on (i) periodical deworming with approved anthelminthic medicines to eliminate infecting worms, (ii) improved water and sanitation to reduce soil contamination with infective eggs, and (iii) health and hygiene education to prevent reinfection, among other interventions including environmental management and modification.

2.1.1. Deworming

The WHO recommends periodic medicinal treatment (i.e. deworming or preventive chemotherapy) (WHO, 2011). The treatment is offered without a prior individual diagnosis to all the people at-risk and living in endemic areas. This intervention aims to reduce the morbidity associated with the worm burden and keep it low through repeated treatments. Deworming is the widely applied public health intervention by endemic countries because the medicines used are inexpensive, easy to administer, safe, effective, and efficacious for most of the STH species (Clarke et al., 2019). Additionally, deworming improves child growth, nutritional status, cognition, school attendance, and physical fitness (Taylor-Robinson et al., 2012). The current deworming approach includes both community and school-based programmes. The school-based deworming is currently the most widely implemented in over 60 endemic countries (Taylor-Robinson et al., 2019), including Kenya where it is augmented with a community-based approach (Okoyo et al., 2020; Kepha et al., 2023).

2.1.2. Improved water and sanitation

The provision of adequate and safe water and sanitation is an important public health intervention measure to reduce the contamination of the soil with STH infective eggs. However, this kind of intervention requires large infrastructural changes and development which is not always possible in resource-poor settings typical of LMICs. The main advantage of providing improved water and sanitation is due to its broad-range preventive measures for not only STH but many other diseases that have a fecal-oral route of transmission. In cognizant of this advantage, WHO recommends the implementation of improvements to basic sanitation and adequate access to safe water alongside MDA programmes (WHO, 2011). Whereas some few countries especially the high-income nations have successfully implemented water and sanitation intervention to interrupt STH transmission (Nery et al., 2019), this intervention in LMICs has shown impacts that are lower than expected (Garn et al., 2022). There is a need for more rigorous and targeted implementation of adequate water and sanitation in order to provide benefits to at-risk individuals.

2.1.3. Health and hygiene education

This intervention aims to reduce STH transmission and reinfection by encouraging healthy behaviors. In this intervention, individuals are educated on ways to improve clean and healthy living behaviors, effects of helminthiasis, e.g. anaemia, and transmission pathways (Puspita et al., 2020). However, in this modeling study, we did not evaluate the impact of this intervention in reducing worm burden and elimination period.

2.2. The STH transmission interruption model

In this study, we are referring to and extending an STH transmission interruption model that was earlier developed by Okoyo et al. (2021). Specifically, we are extending the analysis of this model to perform an optimal control analysis.

Briefly, the transmission interruption model employed a compartmental approach to examine the STH transmission and elimination dynamics by dividing the human population into three age groups: PSAC (2–4 years), SAC (5–14 years) and adults (above 14 years). The model also included the dynamics of the infectious materials (i.e. STH eggs or larvae) in the environment. In the model, the helminth life-cycle was represented as a population of mature worms in the human host (M_i) and the population of free-living infectious materials in the environment (L). The hosts are assumed to acquire infections from the environment and subsequently contaminate the environment at distinctively different rates, $\beta_i(1-\varphi)$ and $\lambda_i(1-\varphi)$, respectively. The mortality rates of the mature worms in the host and the infectious materials in the environment are denoted by μ and μ_L, respectively. The STH transmission interruption model considered in this study is shown below:

$$\left.\begin{aligned}
\frac{dM_p}{dt} &= \beta_p(1-\varphi)L-(\mu+c_p)M_p \\
\frac{dM_c}{dt} &= \beta_c(1-\varphi)L-(\mu+c_c)M_c \\
\frac{dM_a}{dt} &= \beta_a(1-\varphi)L-(\mu+c_a)M_a \\
\frac{dL}{dt} &= \left[(1-\varphi)\sum_i f(M_i;k,\gamma)n_i\lambda_i\right]-\left[\mu_L+(1-\varphi)\sum_i \beta_i n_i\right]L; for\, i=p,c,a
\end{aligned}\right\} \quad (1)$$

where, M_i are the mean worm burdens of each of the three age groups, β_i are the transmission rate of each of the three age groups, μ is the mor-

tality rate of the mature worms in the hosts, μ_L is the mortality rate of the infectious materials in the environment, L describes the per capita infectiousness of the shared reservoir, λ_i is the contamination rate of the environment by each of the three age groups, n_i is the proportion of the population for each of the three age groups, φ for $0 \leq \varphi \geq 1$ is the simulated combined effect of the availability and use of improved water source and sanitation (i.e. WASH) by the hosts, $c_i = \frac{-\ln(1-g_i h)}{\tau}$ for $i = p, c, a$ is the function describing the treatment effect (i.e. impact of MDA) on the mean worm burden and egg production output for each of the three age groups, and the function $f(M_i; k, \gamma) = \frac{M_i}{\left[1+\frac{M_i}{k}(1-e^{-\gamma})\right]^{k+1}}$ for $i = p, c, a$ describes the mean egg production rate for each of the three age groups.

2.3. Model parameters

The default parameter values used in this analysis are shown in Table 1. The parameters were estimated mainly for *Ascaris lumbricoides* and generalized for any of the three worms since it is considered the most widespread worm. The parameters were mainly obtained from data collected in Kenya through school-based or community-based deworming programmes. The epidemiology data for the two programmes are routinely collected by the Kenya Medical Research Institute (KEMRI) and the Division of Vector-Borne and Neglected Tropical Diseases (DVBNTD) within the Kenyan Ministry of Health, respectively. Some of the parameters were either obtained from the past modeling and epidemiological studies conducted in Kenya, and other geographies with similar age group characteristics, or were simulated.

Table 1
Parameters and their corresponding values used in the analysis. The values are typical of *Ascaris lumbricoides* and used to generalize for any of the three STH.

No.	Name of the parameter	Symbol	Value	Source
1	PSAC infection transmission rate	β_p	0.9100	Estimated from Kenyan deworming data
2	SAC infection transmission rate	β_c	0.9800	Anderson et al. (2017)
3	Adults infection transmission rate	β_a	0.7700	Truscott et al. (2014)
4	PSAC environmental contamination rate	λ_p	2.5000	Estimated from Kenyan deworming data
5	SAC environmental contamination rate	λ_c	4.0000	Estimated from Kenyan deworming data
6	Adults environmental contamination rate	λ_a	3.5000	Estimated from Kenyan deworming data
7	PSAC proportion in the population	n_p	0.0500	KNBS (2019)
8	SAC proportion in the population	n_c	0.2500	KNBS (2019)
9	Adults proportion in the population	n_a	0.7000	KNBS (2019)
10	PSAC proportion reached with MDA (treated)	g_p	0.7500	Estimated from Kenyan deworming data
11	SAC proportion reached with MDA (treated)	g_c	0.7500	Estimated from Kenyan deworming data
12	Adults proportion reached with MDA (treated)	g_a	0.7500	Estimated from Kenyan deworming data
13	Mortality rate of the mature worms in the host	μ	1 year	Anderson and May (1991)
14	Mortality rate of infectious materials in environment	μ_L	84 days	Anderson and May (1982)
15	Combined effect of WASH	φ	0.7500	WHO (2011)
16	Interval between treatment rounds per year	τ	1 round	Estimated from Kenyan deworming data
17	Strength of density dependence of worm egg production	γ	0.0035	Truscott et al. (2016)
18	Overdispersion (aggregation) parameter	k	0.5700	Anderson et al. (2013)
19	Drug efficacy	h	0.8000	WHO (2011)

2.4. The basic reproduction number

The basic reproduction number (R_o) indicates the average number of new parasite offspring caused by one typical parasite from one generation to the next. If $R_o > 1$, then on average each parasite infecting an individual is expected to produce more than one other case, resulting in a chain reaction of new cases thus an epidemic outbreak. If $R_o < 1$, then a parasite infecting an individual is expected not even to replace itself in the infected population, thus the parasite is lost from the population (i.e. the infection will die off).

From model (1), we obtain the following, with the assumption that $f(M_i; k, \gamma) = M_i$;

$$\frac{d}{dt}\begin{bmatrix} M_p \\ M_a \\ M_a \\ L \end{bmatrix} = (\mu + c_i)\begin{bmatrix} -1 & 0 & 0 & A \\ 0 & -1 & 0 & B \\ 0 & 0 & -1 & C \\ D & E & F & -G \end{bmatrix}\begin{bmatrix} M_p \\ M_a \\ M_a \\ L \end{bmatrix} \tag{2}$$

where $A = \frac{\beta_p(1-\varphi)}{(\mu+c_p)}$, $B = \frac{\beta_c(1-\varphi)}{(\mu+c_c)}$, $C = \frac{\beta_c(1-\varphi)}{(\mu+c_a)}$, $D = \frac{n_p\lambda_p(1-\varphi)}{(\mu+c_p)}$, $E = \frac{n_c\lambda_c(1-\varphi)}{(\mu+c_c)}$, $F = \frac{n_a\lambda_a(1-\varphi)}{(\mu+c_a)}$, and $G = \frac{[\sum_i n_i\lambda_i(1-\varphi)]+\mu_L}{(\mu+\sum_i c_i)}$ for $i = p, c, a$.

From equation (2), we then extract the next generation matrix (NGM) as follows:

$$\begin{bmatrix} -1 & 0 & 0 & A \\ 0 & -1 & 0 & B \\ 0 & 0 & -1 & C \\ D & E & F & -G \end{bmatrix} \tag{3}$$

Solving the eigenvalues of equation (3) using $det(NGM - uI) = 0$ gives the following eigenvalues:

$$\left.\begin{array}{c} u_1 = 1, \\ u_2 = -1, \\ u_3 = -1, and \\ u_4 = (G - FC - EB - DA), \end{array}\right\} \tag{4}$$

Therefore, the spectral radius of equation (3) is $(G - FC - EB - DA)$, which we then use to derive R_o as;

$$\frac{1}{(\mu + \sum_i c_i)}\left[(1-\varphi)\left(\sum_i \beta_i n_i\right) + \mu_L - \frac{(1-\varphi)^2}{(\mu+\sum_i c_i)}\left(\sum_i \beta_i n_i \lambda_i\right)\right]$$
$$\frac{(1-\varphi)^2\left(\sum_i \beta_i n_i \lambda_i\right)}{(\mu+\sum_i c_i)\left[\mu_L + (1-\varphi)\left(\sum_i \beta_i n_i\right)\right]}; \text{ for } i = p, c, a$$

Thus, the overall R_o for model (1) is given by:

$$R_o = \frac{(1-\varphi)^2\left(\sum_i \beta_i n_i \lambda_i\right)}{(\mu+\sum_i c_i)\left[\mu_L + (1-\varphi)\left(\sum_i \beta_i n_i\right)\right]} \text{ for } i = p, c, a \text{ and } 0 \leq \varphi \geq 1 \tag{5}$$

The reproduction number apportioned to each age group (R_{oi}) can be obtained from this overall R_o as appropriately.

2.5. The equilibrium values

Equilibrium values indicate the solution of a dynamical system where the state variables do not change with time. From model (1), we obtained the relevant equilibrium values by solving the generalized equations when the left-hand side (LHS) is equated to zero.

First, we obtain the equilibrium value of the mean number of infectious materials in the environment (L^*) as:

$$\left[(1-\varphi)\sum_i f(M_i;k,\gamma)n_i\lambda_i\right]-\left[\mu_L+(1-\varphi)\sum_i\beta_i n_i\right]L=0;\ \text{for } i=p,c,a$$

Therefore (L^*) is:

$$L^*=\frac{(1-\varphi)\sum_i f(M_i;k,\gamma)n_i\lambda_i}{\mu_L+(1-\varphi)\sum_i\beta_i n_i}\ \text{for } i=p,c,a \text{ and } 0\leq\varphi\geq 1 \tag{6}$$

Secondly, we obtain the equilibrium value of the mean worm burden (M_i^*) by substituting equations (5) and (6) into model (1):

$$\frac{dM_i}{dt}=\beta_i(1-\varphi)L-(\mu+c_i)M_i$$
$$=\beta_i(1-\varphi)\left[\frac{(1-\varphi)\sum_i f(M_i;k,\gamma)n_i\lambda_i}{\mu_L+(1-\varphi)\sum_i\beta_i n_i}\right]-(\mu+c_i)M_i;\ \text{for } i=p,c,a$$

But,

$$\left[\mu_L+(1-\varphi)\sum_i\beta_i n_i\right]=\frac{(1-\varphi)^2\left(\sum_i\beta_i n_i\lambda_i\right)}{(\mu+c_i)R_{oi}};\ \text{for } i=p,c,a$$

Hence,

$$\frac{dM_i}{dt}=\beta_i(1-\varphi)\left[\frac{(\mu+c_i)R_{oi}(1-\varphi)\sum_i f(M_i;k,\gamma)n_i\lambda_i}{(1-\varphi)^2\sum_i\beta_i n_i\lambda_i}\right]-(\mu+c_i)M_i;\ \text{for } i=p,c,a$$

Therefore, (M_i^*) is given as:

$$M_i^*=\frac{\sum_i R_{oi}f(M_i;k,\gamma)n_i}{\sum_i\beta_i n_i};\ \text{for } i=p,c,a \tag{7}$$

2.6. The sensitivity analysis

Sensitivity analysis (SA) measures the uncertainty in the output of a model or system and assigns this uncertainty to various sources related to its parameters. We calculated the sensitivity indices (SIs) for each parameter indicated in Table 1 using the robust, global variance decomposition-based method, the *extended Fourier Amplitude Sensitivity Test (eFAST)* (Homma and Saltelli, 1996).

We obtained both the first and total-order SIs for each parameter. The first-order SIs (SI_i) contained the single effect of each parameter on the model output, while the total-order SIs (SI_{T_i}) incorporated both the complementary and interaction effects between the parameters.

First, SI_i was calculated by considering a standard statistical variance $s^2=\frac{\sum_{i=1}^{N}(y_i-\bar{y})^2}{N-1}$ algorithm that partitioned the output variance and allocated fractions of the variance to each parameter. The strength of each parameter's frequency (i.e. partial variance allocation) was measured using Fourier analysis (Marino et al., 2008). Applying Ergodic theorem (Moore and Ribet, 2015) to a function, $Y=f(X_1,X_2,\cdots X_n)$, which is an n-dimensional integral $\int_0^1\int_0^1\cdots\int_0^1 f(X_1,X_2,\cdots X_n)dX_1,dX_2,\cdots dX_n$, transforms it to a one-dimensional integral. We then considered a Fourier transformation of the function f that allowed a variance-decomposition of the parameters in the input space, $X_i(s)=G_i(sin(\omega_i s))$. The scalar output Y produced different periodic functions based on different ω_i that enabled us express model $Y=f(s)=f(x_1(s),x_2(s),\cdots,x_n(s))$ as a Fourier series:

$$Y=f(s)=\sum_{p=-\infty}^{\infty}\left(A_p\ cos(p)+B_p\ sin(p)\right)$$

where $A_p=\frac{1}{2\pi}\int_{-\pi}^{\pi}f(s)\ cos(ps)\ ds$ and $B_p=\frac{1}{2\pi}\int_{-\pi}^{\pi}f(s)\ sin(ps)\ ds$. Applying Parseval's theorem (Yu, 2014), we get $Var(Y)\approx 2\sum_{p=1}^{\infty}(A_p^2+B_p^2)$. Thus, the SI_i was obtained as:

$$SI_i=\frac{Var(Y_i)}{Var(Y)}$$
$$=\frac{2\sum_{q=1}^{\infty}\left(A_{q.\omega_i}^2+B_{q.\omega_i}^2\right)}{2\sum_{p=1}^{\infty}\left(A_p^2+B_p^2\right)}$$
$$\approx\frac{\sum_{q=1}^{M}\left(A_{q.\omega_i}^2+B_{q.\omega_i}^2\right)}{\sum_{i=1}^{n}\sum_{q=1}^{M}\left(A_{q.\omega_i}^2+B_{q.\omega_i}^2\right)} \tag{8}$$

SI_i is a value between 0 and 1, a large index of $SI_i>0.1$ indicates a significant first-order effect (Marino et al., 2008).

Secondly, SI_{T_i} was obtained as the summed sensitivity index of the entire set of parameters excluding parameter i using the identification frequencies of the Fourier analysis. Thus, SI_{T_i} was calculated as the remaining variance after the contribution of the complementary set (s_{c_i}) was removed;

$$SI_{T_i}=s_i-s_{i,c_i}$$
$$=s_i(1-s_{c_i})$$
$$=1-s_{c_i} \tag{9}$$

The SI_{T_i} included the higher-order nonlinear interactions between the parameter of interest and complementary set of parameters. A large index of $SI_{T_i}>0.1$ indicates a significant total-order effect (Marino et al., 2008).

2.7. The STH optimal control model

In the previous subsections, the parameters associated with WASH and MDA interventions were extensively analyzed to determine their impact on worm burden using the transmission interruption model. In this subsection, we formulate an optimal control model to address STH control and elimination based on two time-dependent controls denoted by $u_1(t)$ and $u_2(t)$ and we therefore modified model (1) as appropriate. The two time-dependent controls were analyzed to show the effect of their variation with time on the dynamic of STH elimination. The control variable $u_1(t)$ was used to denote the reduction of worm burden through provision of improved water source and sanitation intervention while $u_2(t)$ denoted the reduction of worm burden through MDA intervention. Thus, the formulated STH control model is as follows:

$$\left.\begin{aligned}\frac{dM_p}{dt}&=\beta_p(1-u_1(t))L-(\mu+u_2(t))M_p\\ \frac{dM_c}{dt}&=\beta_c(1-u_1(t))L-(\mu+u_2(t))M_c\\ \frac{dM_a}{dt}&=\beta_a(1-u_1(t))L-(\mu+u_2(t))M_a\\ \frac{dL}{dt}&=\left[(1-u_1(t))\sum_i f(M_i;k,\gamma)n_i\lambda_i\right]-\left[\mu_L+(1-u_1(t))\sum_i\beta_i n_i\right]L;\\ &\quad for\ i=p,c,a\end{aligned}\right\} \tag{10}$$

We then formulated the cost function associated with STH control as:

$$J(u_1,u_2)=\int_0^{T_f}\left\{A_1M_p+A_2M_c+A_3M_a+A_4L+\frac{1}{2}\left(A_5u_1^2+A_6u_2^2\right)\right\} \tag{11}$$

where the constants A_k for $k=1,\cdots,6$ represent the balancing cost functions, and T_f is the final evaluation time for the model. Thus, the cost function needs to be minimized. We minimized a quadratic objective functional since the intervention equations were nonlinear (Ullah and Khan, 2020). The main objective was to search for optimal control variables u_i^* for $i=1,2$, such that:

$$J(u_1^*,u_2^*) = \max_{\psi}\{J(u_1,u_2)\} \tag{12}$$

where $\psi = \{(u_1,u_2) : [0,T_f] \rightarrow [0,1], (u_1,u_2)\}$ is the associated control set and is *lebesque measurable*.

The Lagrangian and the Hamiltonian related to model (10) are respectively defined as:

$$\mathscr{L} = A_1M_p + A_2M_c + A_3M_a + A_4L + \frac{1}{2}\left(A_5u_1^2 + A_6u_2^2\right) \tag{13}$$

and

$$\begin{aligned}\mathscr{H} = {} & A_1M_p + A_2M_c + A_3M_a + A_4L + \frac{1}{2}\left(A_5u_1^2 + A_6u_2^2\right) \\ & +\lambda_1\left[\beta_p(1-u_1(t))L - (\mu + u_2(t))M_p\right] \\ & +\lambda_2\left[\beta_c(1-u_1(t))L - (\mu + u_2(t))M_c\right] \\ & +\lambda_3\left[\beta_a(1-u_1(t))L - (\mu + u_2(t))M_a\right] \\ & +\lambda_4\left[\left[(1-u_1(t))\sum_i f(M_i;k,\gamma)n_i\lambda_i\right] - \left[\mu_L + (1-u_1(t))\sum_i \beta_i n_i\right]L\right];\ \text{for } i = p,c,a\end{aligned} \tag{14}$$

where λ_k for $k = 1,\cdots,4$ denote the adjoint variables.

Finally, the existence of optimal control solution from model (10) can be obtained by utilizing the Pontryagin's maximum principle (Pontryagin, 2018). Accordingly, the assumed desired optimal solutions are u_1^* and u_2^*. We first set the necessary conditions for the Pontryagin's maximum principle as follows:

$$\left.\begin{aligned}\frac{d\zeta}{dt} &= \frac{\partial}{\partial\lambda_k}\mathscr{H}\left(t,u_j^*,\lambda_k\right) \\ \frac{\partial}{\partial u}\mathscr{H}\left(t,u_j^*,\lambda_k\right) &= 0 \\ \frac{d\lambda_k(t)}{dt} &= -\frac{\partial}{\partial\zeta}\mathscr{H}\left(t,u_j^*,\lambda_k\right)\end{aligned}\right\} \tag{15}$$

Given that the optimal controls u_1^* and u_2^*, and the model (10) solutions M_p^*, M_c^*, M_a^* and L^*, minimize the objective functional $J(u_1,u_2)$ over ψ, then there exists adjoint variables λ_k for $k = 1,\cdots,4$ along with transversality conditions $\lambda_k(T_f) = 0$ such that:

$$\left.\begin{aligned}\frac{d\lambda_1}{dt} &= -A_1 + \beta_p(1-u_1(t))(\lambda_1-\lambda_2)L^* - (\mu+u_2(t))\lambda_1M_p^* \\ \frac{d\lambda_2}{dt} &= -A_2 + \beta_c(1-u_1(t))(\lambda_1-\lambda_2)L^* - (\mu+u_2(t))\lambda_2M_c^* \\ \frac{d\lambda_3}{dt} &= -A_3 + \beta_a(1-u_1(t))(\lambda_1-\lambda_2)L^* - (\mu+u_2(t))\lambda_3M_a^* \\ \frac{d\lambda_4}{dt} &= \left[\left[(1-u_1(t))(\lambda_1-\lambda_2)\sum_i f(M_i;k,\gamma)n_i\lambda_i\right] - \left[\mu_L + (1-u_1(t))\lambda_4\sum_i\beta_i n_i\right]L^*\right]; \\ & \quad for\ i = p,c,a\end{aligned}\right\} \tag{16}$$

Hence, the associated optimal controls u_1^* and u_2^* are given by:

$$\left.\begin{aligned}u_1^* &= min\left\{1, max\left(\left(1 - \frac{A_k + \mu\lambda_kM_i^*}{\beta_i(\lambda_1-\lambda_2)L^*}\right), -1\right)\right\} \\ u_2^* &= min\left\{1, max\left(\left(\frac{\beta_i(\lambda_1-\lambda_2)L^* - A_k - \mu\lambda_iM_i^*}{\lambda_2M_i^*}\right), 0\right)\right\}\end{aligned}\right\} \tag{17}$$

Therefore, the desired results in (16) and the transversality conditions are obtained by using the conditions specified in (15) and with the settings $M_i = M_i^*$ for $i = p,c,a$ and $L = L^*$. Additionally, to obtain the control characterization outlined in equation (17), we use the condition $\frac{\partial\mathscr{H}(t,u_j^*,\lambda_k)}{\partial u_j} = 0$ for $j = 1,2$ as given in (15).

3. Results

3.1. Transmission interruption model analysis results

In the absence of any intervention (i.e. no MDA or WASH), the model demonstrated that the STH infections will rise gradually and reach an endemic equilibrium point. The equilibrium points attained by each host will vary slightly mainly influenced by their different interaction rates with the infectious materials in the environment. Figure 1 shows the endemic equilibrium points attained by each host.

Next, we modeled the impact of each intervention on the worm burden and observed the perturbation on the endemic equilibrium. Figure 2 panel A shows the impact of MDA alone, panel B shows the impact of WASH alone and panel C shows the impact of both MDA and WASH interventions. In all the three simulations, the endemic equilibrium was perturbed, and the disease burden was reduced to very low levels after certain evaluation time. The solution to the ODE model (1) indicated that the combined impact of both MDA and WASH interventions was the most effective in achieving near-elimination of the worm burden in a short implementation period. The results indicated that it will take a longer period to achieve the elimination of STHs with annual MDA alone.

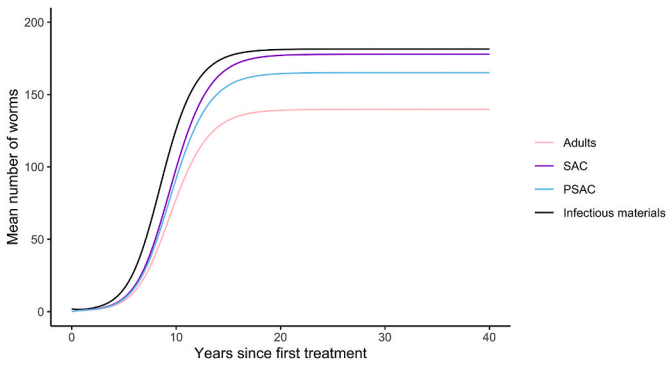

Fig. 1. Equilibrium points attained by each host in the absence of any intervention.

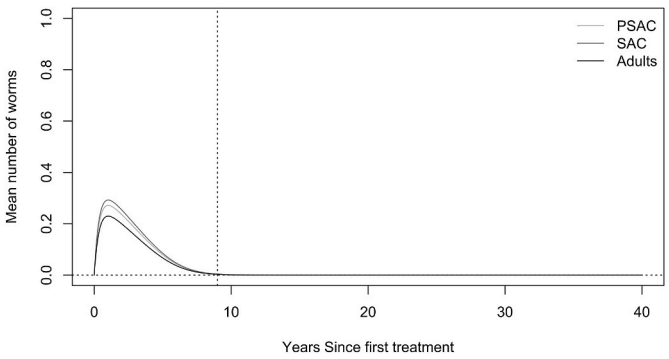

Fig. 4. Strategy A: Prevention of STH using mass drug administration (MDA) as primary intervention. Consistent treatment coverage of 75% among each host group was assumed throughout the control period.

3.2. Sensitivity analysis results

The sensitivity analysis contained in equations (8) and (9) were applied to the transmission interruption model (1) and used the parameters outlined in Table 1. However, the parameters were allowed to range from a minimum value (each parameter divided by 2) to a maximum value (each parameter multiplied by 2) with the exception of intervention-related parameters that were first defaulted at 0.50 before being divided or multiplied by 2. The sensitivity analysis results showed that the WASH parameter (φ) was the most important factor in influencing the STH control dynamics (i.e. host worm burden reduction and elimination), followed by treatment (MDA) related parameters like adult

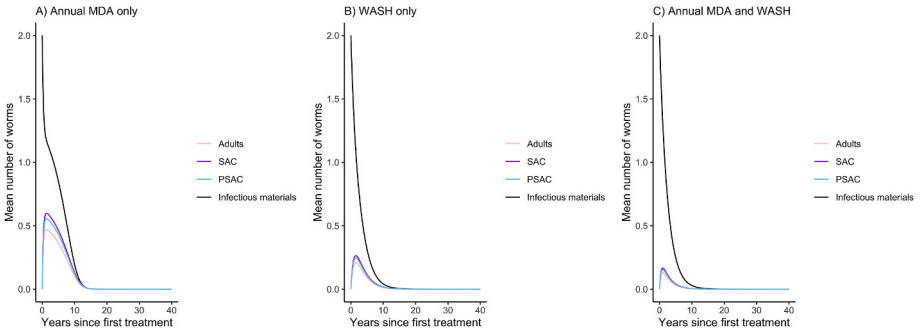

Fig. 2. Impact of the two interventions on the STH infections among each host. We assumed 80% drug efficacy, 75% treatment coverage, and 75% WASH coverage among all the hosts, the assumptions are as per the current WHO guidelines (WHO, 2011).

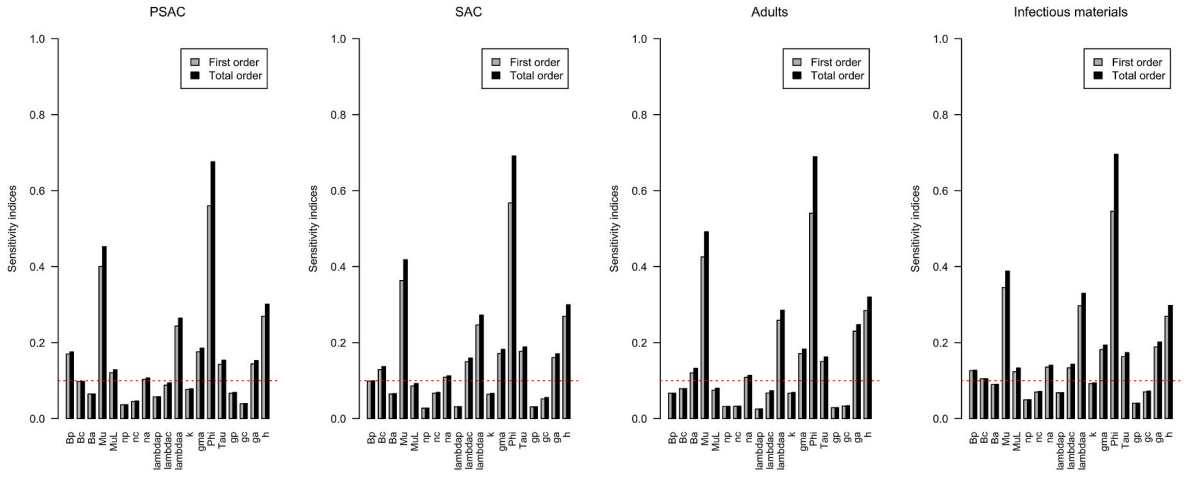

Fig. 3. Sensitivity analysis results of each parameter among the hosts computed using the eFAST method as outlined in equations (8) and (9) and applied to model (1). The cut-off value above which a parameter was considered significant was 0.1 (denoted by the horizontal red dotted line). The further up a parameter span, the greater the influence it has on the model dynamics. *Abbreviations*: *Bp*, PSAC infection transmission rate; *Bc*, SAC infection transmission rate; *Ba*, adults infection transmission rate; *Mu*, mature worm mortality rate; *MuL*, infectious materials mortality rate; *np*, PSAC population proportion; *nc*, SAC population proportion; *na*, adults population proportion; *lambdap*, relative contributions by PSAC; *lambdac*, relative contributions by SAC; *lambdaa*, relative contributions by adults; *k*, over-dispersion parameter; *gma*, strength of density dependence of worm egg production; *Phi*, WASH effect; *Tau*, interval between treatment rounds per year; *gp*, proportion of PSAC treated; *gc*, proportion of SAC treated; *ga*, proportion of adults treated; *h*, drug efficacy.

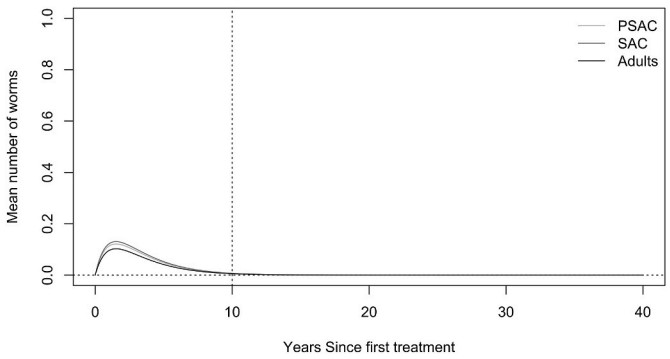

Fig. 5. Strategy B: Prevention of STH using provision of improved water and sanitation (WASH) as primary intervention. Consistent coverage of 75% for provision of improved WASH among each host group was assumed throughout the control period.

worm death rate (μ) and drug efficacy (h) (Fig. 3).

3.3. Optimal control model analysis results

Here, we performed the numerical simulations of the OC model (10) using the parameter values outlined in Table 1. We simulated the impact of three control strategies in controlling the burden of STH infections in the community and the projected elimination period (i.e. the point at which the mean number of worms in the host will reduce to zero at the final control period). Starting with an initial guess for the optimal controls $u_1(t)$ and $u_2(t)$, the ODE state system (10) was solved numerically forward in time using the fourth-order Runge-Kutta method (Tan and Chen, 2012). The initial conditions were; $M_p = 0$, $M_c = 0$, and $M_a = 0$. Additionally, the adjoint system (16) was solved numerically backward in time using the fourth-order Runge-Kutta method using the supplied state variables and the initial guess of the controls obtained earlier.

3.3.1. Strategy A: Prevention with mass drug administration

In this strategy, we used the optimal control $u_2(t)$ i.e., provision of MDA as the primary intervention to optimize the objective functional J while setting the optimal control $u_1(t)$ i.e., provision of improved water and sanitation to zero. The analysis showed that with this strategy, the elimination point (i.e. point at which mean number of worms is reduced to zero) of STH infections will be after 9 years since the onset of treatment. This imply that the mean number of worms in the host will peak at 0.3 worms before being reduced to zero worms after 9 years at the final control period (Fig. 4). In this strategy, we assumed that 75% of the population (each host group) was consistently reached with MDA throughout the control period.

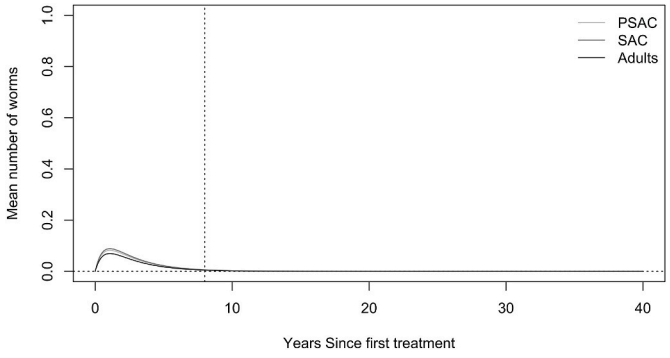

Fig. 6. Strategy C: Prevention of STH using both mass drug administration (MDA) and improved water and sanitation (WASH) as primary interventions. Consistent coverage of 75% for both MDA and WASH was assumed among each host group throughout the control period.

3.3.2. Strategy B: Prevention with the provision of improved water and sanitation

In this strategy, we used the optimal control $u_1(t)$ i.e., provision of improved water and sanitation as the primary intervention to optimize the objective functional J while setting the optimal control $u_2(t)$ i.e., provision of MDA to zero. With this strategy, we demonstrated that WASH (i.e. provision of improved water and sanitation) was effective in reducing the peak of the mean number of worms in the host to *circa* 0.18, which is much lower than what was observed in strategy A. However, this peak took *circa* 10 years to reduce to zero at the final control period (Fig. 5). The evaluation took a little longer to reach zero (elimination) because WASH does not have an immediate impact like a drug therapy but it has a sustained impact on reducing worm burden. In this strategy, we assumed that 75% of the population (each host group) was consistently reached with improved water and sanitation throughout the control period.

3.3.3. Strategy C: Prevention with both MDA and WASH

In this strategy, we used a combination of all the two optimal controls $u_1(t)$ and $u_2(t)$ as primary interventions to optimize the objective functional J. When the optimal combination of both controls was in place, we observed that the peak of the mean number of worms reduced to below 0.1 worms and the elimination point reduced to 8 years (Fig. 6).

4. Discussion

In this paper, we formulated and analyzed an OC model for STH infections in Kenya. The OC model followed from the robust analysis of the transmission interruption model, analysis of the basic reproduction number, analysis of the equilibrium values, and sensitivity analysis. The results from these forgoing analyses informed the development of an efficient and effective OC model, and the selection of suitable optimal controls $u_1(t)$ and $u_2(t)$. This is the first application of optimal control analysis specific to the Kenya STH transmission dynamics setting. The results from this study will be helpful in advocating and informing policy implementation of WASH and NTD integration in Kenya.

The analyses of both the transmission interruption model, sensitivity model, and the OC model all revealed that WASH when implemented along with MDA gives effective optimal control for helminth infection. Specifically, for the OC model, we considered three strategies: implementation of MDA only as the primary intervention (strategy A); provision of water and sanitation only as the mainstay intervention (strategy B); and implementation of both MDA, and water and sanitation (strategy C). The OC model was then solved to obtain the optimal controls $u_1(t)$ and $u_2(t)$ using the Pontryagin's maximum principle by first obtaining the objective functional, Lagrangian and Hamiltonian functions, and the adjoint variables along with their transversality conditions.

Though, applying single-control measures (i.e. either MDA or WASH) alone was shown to be equally effective in controlling helminth infection as has been reported with other modeling studies (Coffeng et al., 2018; Chong et al., 2021), using a combination of the two control measures to optimize the objective functional J was shown to increase the effectiveness. Thus, the two interventions when applied together were the most optimal control intervention that assured elimination within a short time (less than 8 years).

This study is among the few modeling works that has considered a mix of key STH interventions with an optimal control analysis (Lambura et al., 2020; Oguntolu et al., 2023). The findings of this modeling work are in line with other modeling studies (Coffeng et al., 2018), and epidemiological studies (Campbell et al., 2014; Strunz et al., 2014), that have clearly demonstrated the importance of WASH in accelerating the attainment of helminth elimination when implemented alongside MDA intervention.

The findings from this study add to the evidence base, from the modeling perspective, that complementing MDA programmes with

WASH-related interventions will be the key necessary to unlock the 2030 STH elimination target set by WHO for endemic countries. Additionally, WASH is also a proven sustainable way of controlling these parasites without posing the risk of disease resurgence, drug resistance, and drug "fatigue" among individuals.

5. Conclusion

In this paper, we have modeled the transmission dynamics and interventions at a high level, but spatial heterogeneity and variation in programme implementation will mean that these results are not predictions. In particular, elimination programmes are always challenged by local "pockets" of transmission that are hardest to reach. Nonetheless, our results demonstrate that simultaneous implementation of WASH and MDA offers the best chances of eliminating these tenacious and damaging parasites in Kenya, and globally, within the current WHO elimination target of 2030.

CRediT authorship contribution statement

Collins Okoyo: Conceptualization, Methodology, Software, Formal analysis, Visualization, Data Curation, Funding acquisition, Writing - original draft, Writing - review & editing. **Idah Orowe:** Validation, Investigation, Resources, Supervision, Writing - review & editing. **Nelson Onyango:** Validation, Investigation, Resources, Supervision, Writing - review & editing. **Antonio Montresor:** Validation, Resources, Writing - review & editing. **Charles Mwandawiro:** Validation, Investigation, Resources, Supervision, Project administration, Writing - review & editing. **Graham F. Medley:** Validation, Resources, Supervision, Writing - review & editing.

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Ethical approval

The studies involving human participants were reviewed and approved by Kenya Medical Research Institute (KEMRI)'s Scientific and Ethics Review Unit (SSC Number 2206). Written informed consent to participate in this study was provided by the participant's legal guardian/next of kin.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author. R codes used in the analysis are available at: https://github.com/mancollo/OCmodel.

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