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6. A mathematical model for the eradication of Guinea Worm Disease

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Abstract. Guinea Worm Disease is one of humanity's oldest diseases. Parasites that live in the drinking water are ingested, eventually producing a worm that bursts from the extremities (usually the foot) and deposits larvae in the drinking water. Although the disease does not kill its host, it is severely disabling and has an incubation period of approximately 12 months. However, we stand on the brink of eradicating Guinea Worm Disease, thanks to a combination of education (teaching people not to put their infected limbs into the drinking water for relief), filtration of infected water (before human consumption) and chlorination (which kills the parasite in the water). Here, we develop the first mathematical model of this disease. We use impulsive differential equations to evaluate the effectiveness of chlorination. We derive thresholds for the frequency of both fixed

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and non-fixed chlorination. We then use Latin Hypercube Sampling to determine the practical effectiveness of our three control parameters. We show that, despite the theoretical potential of chlorination to complete eradication of the disease, education is far more effective. While a combination of intervention techniques is most desirable, eradication efforts must focus on educating infected individuals in the remaining endemic countries of the world.

1. Introduction

Guinea Worm Disease (GWD), also known as Dracunculiasis, is one of humanity's ancient scourges [31]. Individuals are infected by drinking water contaminated with water fleas, which act as an intermediate host and carrier of nematode larvae [24]. These nematodes affect the subcutaneous tissue as the adult female migrates through the human body, generally residing in the foot. If left untreated, the nematode will eject larvae when exposed to fresh water, which the host will do to alleviate the burning and itching caused by the worm; the lesion may also acquire a secondary infection if improperly cared for [19, 24]. The pain from GWD can be disabling, which is of great concern as outbreaks tend to occur at times of agricultural importance [21, 24].

Europeans first saw the disease on the Guinea Coast of West Africa in the 17th century [20]. During the 19th and 20th centuries, it was common in much of southern Asia, and in North, West and East Africa. It is estimated that in the 1950s there were 50 million cases [34]. In 1986, the Carter Center, the national Guinea worm eradication programs, the Center for Disease Control and Prevention (CDC), UNICEF and the World Health Organization (WHO) began a concerted eradication program [34]. In 1989, there were 892,000 reported cases [38]. In 1999, there were an estimated 96,000 cases in 13 countries (none of which were in Asia) [34]. In 2009, fewer than 3,500 cases of the disease remained, in four African countries: Sudan, Ghana, Mali and Ethiopia [12]. If successfully eradicated, it will be the first parasitic disease to be eradicated and also the first disease to be eradicated using behaviour changes alone [5].

GWD is the only disease to be solely transmitted via drinking water [34]. When larvae are released into the water, microscopic copepods (water fleas) swallow the larvae. As people drink the water, the copepods are digested by the human digestive system, but the larvae remain intact, resisting the acids in the stomach, and find their way into the small intestine and penetrate it to enter the body cavity. The female larvae grow into full-size adults, approximately 60 to 100 centimetres in length and 0.1 to 0.2 centimetres in width. This takes approximately 10 to 14 months. These worms then migrate to extremities such as the feet, although they can be found elsewhere in the body. A blister appears at the location where the worm will try to break

through. This blister will cause a painful burning sensation and will burst after 24 to 72 hours.

Submerging the wound in water will bring relief but also releases a milky white liquid into the water which contains hundreds of thousands of larvae, contaminating the water supply and restarting the cycle. See Figure 1. There is no vaccine or curative drug and infected individuals do not develop immunity. However, the worm can be removed by surgery or by physically pulling the worm out, often by wrapping it around a stick. This process can take up to two months to complete, as worms can grow up to a metre in length and only 1-2cm can be removed per day [23, 34]. Indeed, the medical symbol of the Staff of Asclepius is based upon the stick used to extract Guinea worms in ancient times [27].

Prevention includes drinking water from underground sources such as a borehole or hand-dug wells, although this is not always possible. Infected individuals should be prevented from submerging wounds in drinking water. Cloth filters that fit over pots and pans can be distributed to local villages, whereas nomadic people have received personal-use cloths fitted over pipes that can be worn around the neck. Boiling water is also effective, where possible [10]. Alternatively, chemical larvicides such as ABATE can be added to stagnant water supplies [34].

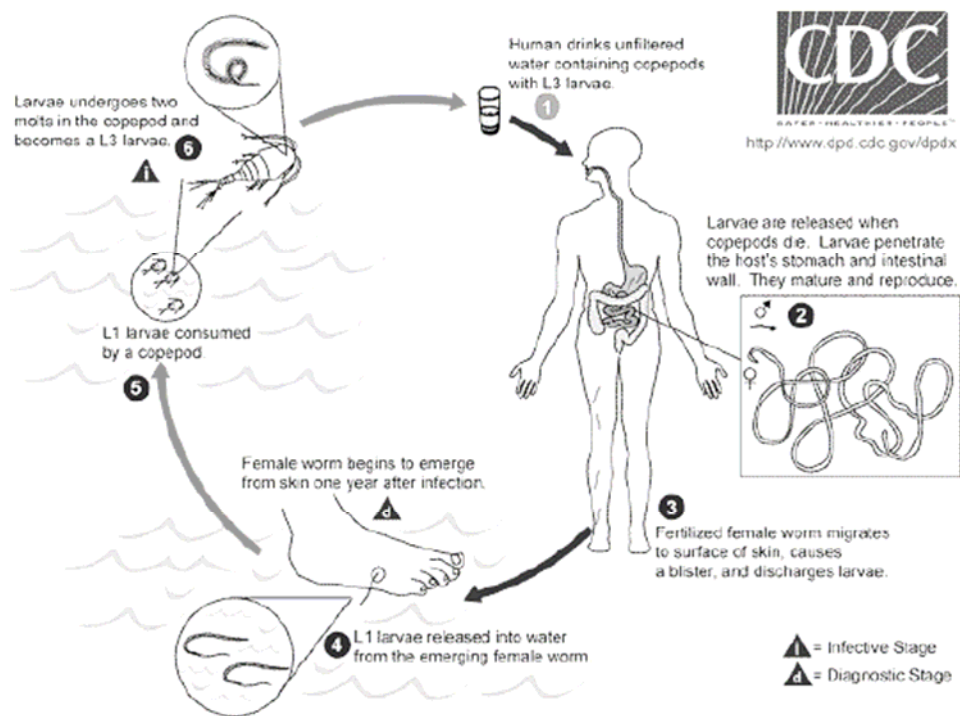


Figure 1. The life cycle of Guinea worm disease. Image copyright the United States Centers for Disease Control and Prevention.

To the best of our knowledge, this is the first mathematical model of GWD [25]. Our aim in this paper is to examine the theoretical likelihood of eradication of the disease using existing intervention techniques in resource-constrained settings.

2. The model

Denote susceptible individuals by S , exposed individuals by E and infected individuals by I . The number of larvae in the water is denoted W . The human birth rate is Π , the infection rate is β , the rate of worm emergence is α , the recovery rate is κ and the death rate is μ . Infected individuals produce new larvae at rate γ and the larvae are naturally cleared from the water at rate μ_W . Although water fleas act as an intermediate host, carrying the nematode until human digestion, we conflate the larvae and the fleas, in order to keep the model tractable.

Interventions include filtration, education or chlorination of the water supply. Although “education” is a complex term, encompassing a multitude of interventions, we consider education to refer directly to teaching people not to put their infected limbs in the water supply, in line with established behaviour-change programs for tackling GWD. Thus, we consider that an increase in education will have the direct effect of reducing the parasite birth rate, hence reducing γ . Likewise, by “filtration”, we mean a method that reduces the ability of the parasite to infect a human host, thus reducing β . Chlorination has the effect of increasing the death rate of the parasite, thus increasing μ_W .

However, continuous chlorination is neither possible nor desirable, so we shall assume chlorination occurs at distinct (not necessarily fixed) times t_k . At these times, the number of larvae in the water are reduced by some proportion r . This results in a system of impulsive differential equations [6, 7, 8, 26]. This is related to the use of pulse vaccinations [1], seasonal skipping in recurrent epidemics [39], antiretroviral drug treatment [29] and birth pulses in animals [33].

Our mathematical model is thus

$$\begin{aligned}
 S' &= \Pi - \beta SW - \mu S + \kappa I & t \neq t_k \\
 E' &= \beta SW - \alpha E - \mu E & t \neq t_k \\
 I' &= \alpha E - \kappa I - \mu I & t \neq t_k \\
 W' &= \gamma I - \mu_W W & t \neq t_k \\
 \Delta W &= -rW & t = t_k.
 \end{aligned}$$

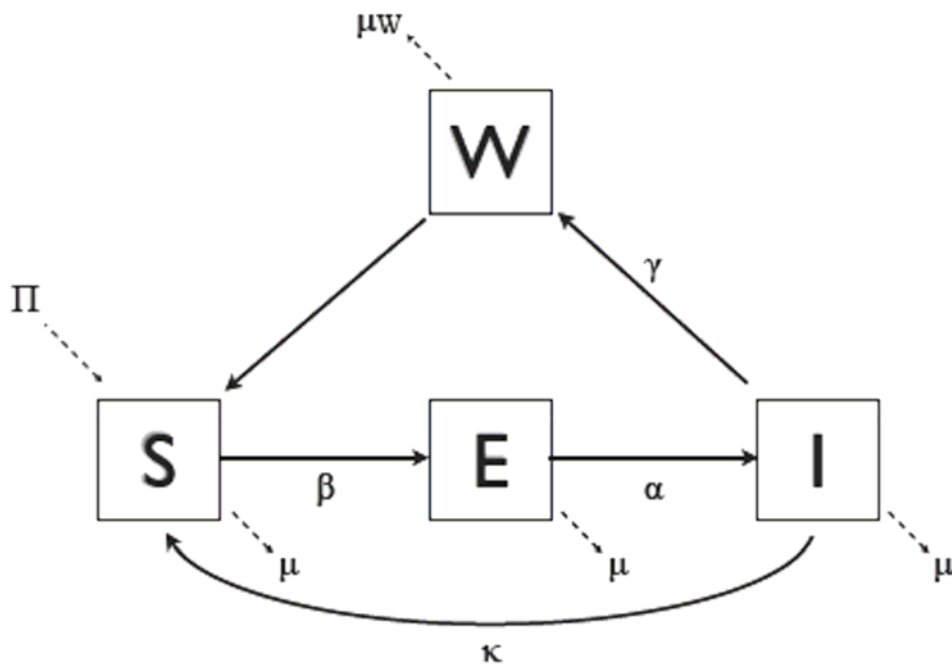


Figure 2. The model. Humans can be susceptible (S), exposed (E) or infected (I). Once infected, they release parasites (W) into the drinking water. The infection rate is β , the rate of developing infection is α , the recovery rate is κ and the parasite birth rate is γ . The human birth and death rates are Π and μ . The parasite death rate is μ_W .

See Figure 2. Note that S , E , I and W are nonnegative. Furthermore, since these quantities are averages, we do not assume that individuals are necessarily infected with only one worm at a time.

We use mass-action transmission since the interaction between parasites in the water and humans involves drinking parasite-laden water. Thus, since everyone in the village usually drinks from a single source, each human has roughly equal chance of encountering the parasite.

3. The system without impulses

First, we shall analyse the corresponding system of ODEs. Note that

$$S' + E' + I' = \Pi - \mu(S + E + I).$$

Thus,

$$S + E + I \leq \frac{\Pi}{\mu}.$$

Hence,

$$I' \leq \frac{\alpha\Pi}{\mu} - (\kappa + \mu)I$$

$$I \leq \frac{\alpha\Pi}{\mu(\kappa + \mu)} + \left[I(0) - \frac{\alpha\Pi}{\mu(\kappa + \mu)} \right] e^{-(\kappa + \mu)t}.$$

Since κ is large, we have

$$I \leq \frac{\alpha\Pi}{\mu(\kappa + \mu)}.$$

It follows that

$$W' \leq \frac{\alpha\Pi\gamma}{\mu(\kappa + \mu)} - \mu_W W \quad (3.1)$$

and thus

$$W \leq \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}. \quad (3.2)$$

These inequalities overestimate the parasite levels in the water, but they allow us to estimate these levels without solving the original system of differential equations. This will be useful in the next section.

The disease-free equilibrium satisfies

$$(\bar{S}, \bar{E}, \bar{I}, \bar{W}) = \left(\frac{\Pi}{\mu}, 0, 0, 0 \right).$$

The endemic equilibrium satisfies

$$\hat{S} = \frac{\mu_W}{\beta\gamma} \left(\kappa + \mu + \frac{\kappa\mu}{\alpha} + \frac{\mu^2}{\alpha} \right)$$

$$\hat{E} = \frac{\kappa + \mu}{\alpha} \hat{I}$$

$$\hat{W} = \frac{\gamma}{\mu_W} \hat{I}$$

$$\hat{I} = \frac{\Pi\beta\gamma\alpha - \mu\mu_W(\kappa\alpha + \mu\alpha + \kappa\mu + \kappa\mu^2)}{(\alpha + \kappa + \mu)\beta\gamma\mu}.$$

The Jacobian matrix is

$$J = \begin{bmatrix} -\beta W - \mu & 0 & \kappa & -\beta S \\ \beta W & -\alpha - \mu & 0 & \beta S \\ 0 & \alpha & -k - \mu & 0 \\ 0 & 0 & \gamma & -\mu W \end{bmatrix}$$

$$J \Big|_{(\Pi/\mu, 0, 0, 0)} = \begin{bmatrix} -\mu & 0 & \kappa & -\beta \bar{S} \\ 0 & -\alpha - \mu & 0 & \beta \bar{S} \\ 0 & \alpha & -k - \mu & 0 \\ 0 & 0 & \gamma & -\mu W \end{bmatrix}.$$

The characteristic polynomial satisfies

$$(-\mu - \lambda) \det \begin{bmatrix} -\alpha - \mu - \lambda & 0 & \beta \bar{S} \\ \alpha & -\kappa - \mu - \lambda & 0 \\ 0 & \gamma & -\mu W - \lambda \end{bmatrix} = 0.$$

Thus

$$0 = \lambda^3 + \lambda^2(\alpha + 2\mu + \kappa + \mu W) + \lambda[(\alpha + \mu)(\kappa + \mu) + (\alpha + \mu)\mu W + (\kappa + \mu)\mu W] + (\alpha + \mu)(\kappa + \mu)\mu W - \alpha\gamma\beta\bar{S}.$$

Since the non-constant coefficients of powers of λ are all positive, the threshold condition will be solely determined by the sign of the constant term. It follows that

$$R_0 = \frac{\Pi\alpha\gamma\beta}{\mu(\alpha + \mu)(\kappa + \mu)\mu W},$$

where R_0 is a threshold predicting disease invasion or eradication [18].

Thus, if $R_0 < 1$, then the disease-free equilibrium is stable and is the only equilibrium. If $R_0 > 1$, then the disease-free equilibrium is unstable and the endemic equilibrium exists. Note that R_0 is increasing with Π , α , γ and β , decreasing with μ , μW and κ .

Theorem 3.1. *If $R_0 > 1$, then the endemic equilibrium is asymptotically stable.*

Proof. The characteristic polynomial for the endemic equilibrium satisfies

$$0 = \det \begin{bmatrix} -\beta\hat{W} - \mu - \lambda & 0 & \kappa & -\beta\hat{S} \\ \beta\hat{W} & -\alpha - \mu - \lambda & 0 & \beta\hat{S} \\ 0 & \alpha & -\kappa - \mu - \lambda & 0 \\ 0 & 0 & \gamma & -\mu_W - \lambda \end{bmatrix}.$$

Expanding the first column, we have

$$0 = (-\beta\hat{W} - \mu - \lambda) \left\{ -\lambda^3 - \lambda^2(\alpha + 2\mu + \kappa + \mu_W) - \lambda[(\alpha + \mu)(\kappa + \mu) + (\alpha + \mu)\mu_W + (\kappa + \mu)\mu_W - (\alpha + \mu)(\kappa + \mu)\mu_W + \alpha\gamma\beta\hat{S}] + \beta\hat{W}\alpha(-\mu_W\kappa - \kappa\lambda + \beta\gamma\hat{S}) \right\}.$$

We thus have

$$\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0$$

where

$$a_3 = \beta\hat{W} + 3\mu + \alpha + \kappa + \mu_W > 0$$

$$a_2 = (\beta\hat{W} + \mu)(\alpha + 2\mu + \kappa + \mu_W) + (\alpha + \mu)(\kappa + \mu) + (\alpha + \mu)\mu_W + (\kappa + \mu)\mu_W > 0$$

$$a_1 = (\beta\hat{W} + \mu)(\alpha + \mu)(\kappa + \mu + \mu_W) + (\beta\hat{W} + \mu)(\alpha + \mu)\mu_W + (\beta\hat{W} + \mu)(\kappa + \mu)\mu_W + (\alpha + \mu)(\kappa + \mu)\mu_W - \alpha\gamma\beta\hat{S} - \beta\hat{W}\alpha\kappa$$

$$a_0 = (\beta\hat{W} + \mu)(\alpha + \mu)(\kappa + \mu)\mu_W - (\beta\hat{W} + \mu)\alpha\gamma\beta\hat{S} - \beta\hat{W}\alpha\mu_W\kappa + \beta\hat{W}\alpha\beta\gamma\hat{S}.$$

We have

$$\begin{aligned} a_1 &= (\beta\hat{W} + \mu)(\alpha + \mu)\kappa + (\beta\hat{W} + \mu)(\alpha + \mu)(\mu + \mu_W) + (\beta\hat{W} + \mu)(\alpha + \mu)\mu_W \\ &\quad + (\beta\hat{W} + \mu)(\kappa + \mu)\mu_W + (\alpha + \mu)(\kappa + \mu)\mu_W - \alpha\mu_W \left(\kappa + \mu + \frac{\kappa\mu}{\alpha} + \frac{\mu^2}{\alpha} \right) \\ &\quad - \beta\hat{W}\alpha\kappa \\ &= \beta\hat{W}(\alpha + \mu)\kappa + \mu(\alpha + \mu)\kappa + (\beta\hat{W} + \mu)(\alpha + \mu)(\mu + \mu_W) + (\beta\hat{W} + \mu)(\alpha + \mu)\mu_W \\ &\quad + (\beta\hat{W} + \mu)(\kappa + \mu)\mu_W + (\alpha + \mu)(\kappa + \mu)\mu_W - \alpha\mu_W(\kappa + \mu) - (\kappa + \mu)\mu\mu_W \\ &\quad - \beta\hat{W}\alpha\kappa \\ &= \beta\hat{W}\mu\kappa + \mu(\alpha + \mu)\kappa + (\beta\hat{W} + \mu)(\alpha + \mu)(\mu + \mu_W) + (\beta\hat{W} + \mu)(\alpha + \mu)\mu_W \\ &\quad + (\beta\hat{W} + \mu)(\kappa + \mu)\mu_W > 0. \end{aligned}$$

Then

$$\begin{aligned}
a_0 &= (\beta\hat{W} + \mu)(\alpha + \mu)(\kappa + \mu)\mu_W - \mu\alpha\mu_W \left(\kappa + \mu + \frac{\kappa\mu}{\alpha} + \frac{\mu^2}{\alpha} \right) - \beta\hat{W}\alpha\mu_W\kappa \\
&= \beta\hat{W}(\alpha + \mu)(\kappa + \mu)\mu_W + \mu(\alpha + \mu)(\kappa + \mu)\mu_W - \mu\alpha\mu_W(\kappa + \mu) - (\kappa + \mu)\mu^2\mu_W \\
&\quad - \beta\hat{W}\alpha\mu_W\kappa \\
&= \beta\hat{W}\alpha(\kappa + \mu)\mu_W + \beta\hat{W}\mu(\kappa + \mu)\mu_W + \mu\alpha(\kappa + \mu)\mu_W + \mu^2(\kappa + \mu)\mu_W \\
&\quad - \mu\alpha\mu_W(\kappa + \mu) - (\kappa + \mu)\mu^2\mu_W - \beta\hat{W}\alpha\mu_W\kappa \\
&= \beta\hat{W}\alpha\mu\mu_W + \beta\hat{W}\mu(\kappa + \mu)\mu_W > 0.
\end{aligned}$$

Since all the coefficients of the characteristic polynomial are positive, it follows that all the roots have negative real part. Hence, the endemic equilibrium is asymptotically stable.

Education will discourage infected individuals from putting infected limbs into the drinking water. This will decrease γ . Filtration of drinking water using cloth filters will decrease β . Continuous chlorination of the water will increase μ_W . All of these interventions will result in R_0 decreasing. However, continuous water treatment is neither desirable nor feasible, due to environmental and toxicity issues, as well as limited supplies of resources. We will thus consider discrete chlorination.

4. The system with impulses

In this section, we use inequality (3.1) to overestimate the number of larvae in the water. This allows us to solve the corresponding impulsive differential equation, in order to derive sufficient controls.

Suppose we have maximum growth of larvae in the water, so that we have equality in (3.1). Then we have the one-dimensional impulsive differential equation

$$\begin{aligned}
W' &= \frac{\alpha\Pi\gamma}{\mu(\kappa + \mu)} - \mu_W W & t \neq t_k \\
\Delta W &= -rW & t = t_k.
\end{aligned} \tag{4.3}$$

It follows that, for a single impulsive cycle $t_k \leq t \leq t_{k+1}$, the solution is

$$W(t_{k+1}^-) = W(t_k^+)e^{-\mu_W(t_{k+1}-t_k)} + \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \left[1 - e^{-\mu_W(t_{k+1}-t_k)} \right],$$

where $W(t_k^-)$ is the value immediately before the impulse and $W(t_k^+)$ is the value immediately after. For simplicity of notation, we can denote $W_k^+ = W(t_k^+)$ and $W_k^- = W(t_k^-)$. The degree of overestimation in (4.3) is shown in Figure 3.

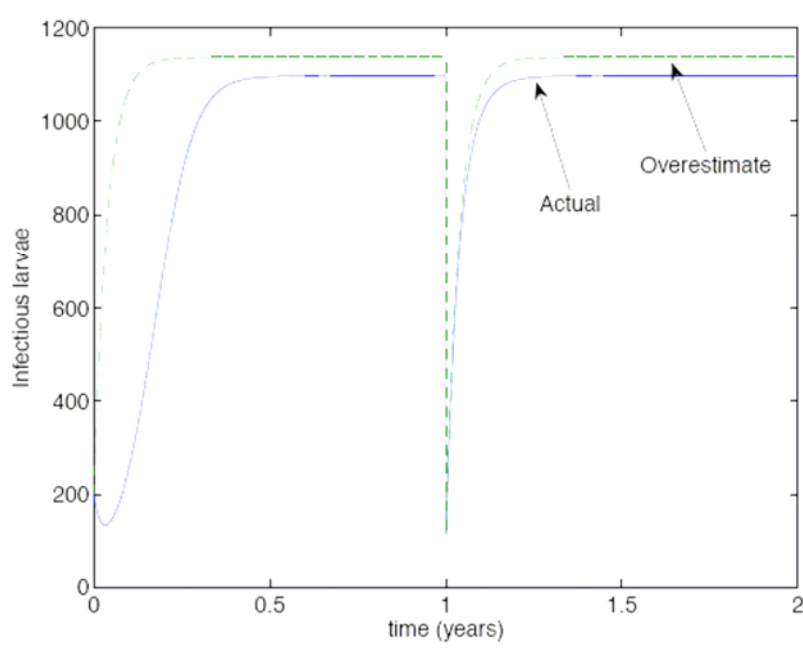


Figure 3. Comparison of the actual W with the overestimate used when the growth rate is assumed to be maximal.

If we start on the endemic equilibrium, then the parasite values at the impulse times satisfy

$$\begin{aligned}
 W_1^- &= \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \\
 W_1^+ &= (1-r)\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \\
 W_2^- &= (1-r)\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}e^{-\mu(t_2-t_1)} + \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}\left(1 - e^{-\mu_W(t_2-t_1)}\right) \\
 W_2^+ &= (1-r)^2\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}e^{-\mu(t_2-t_1)} + (1-r)\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}\left(1 - e^{-\mu_W(t_2-t_1)}\right) \\
 W_3^- &= \left[(1-r)^2\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}e^{-\mu(t_2-t_1)} + (1-r)\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}\left(1 - e^{-\mu_W(t_2-t_1)}\right) \right] e^{-\mu(t_3-t_2)} \\
 &\quad + \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}\left(1 - e^{-\mu_W(t_3-t_2)}\right) \\
 &= (1-r)^2\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}e^{-\mu_W(t_3-t_1)} + (1-r)\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}e^{-\mu_W(t_3-t_2)} \\
 &\quad - (1-r)\frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}e^{-\mu_W(t_3-t_1)} + \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} - \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}e^{-\mu_W(t_3-t_2)} \\
 W_3^+ &= \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}\left[(1-r)^3e^{-\mu_W(t_3-t_1)} + (1-r)^2e^{-\mu_W(t_3-t_2)} + 1 - r \right. \\
 &\quad \left. - (1-r)^2e^{-\mu_W(t_3-t_1)} - (1-r)e^{-\mu_W(t_3-t_2)} \right] \\
 W_4^- &= \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}\left[(1-r)^3e^{-\mu_W(t_4-t_1)} + (1-r)^2e^{-\mu_W(t_4-t_2)} + (1-r)e^{-\mu_W(t_4-t_3)} + 1 \right. \\
 &\quad \left. - (1-r)^2e^{-\mu_W(t_4-t_1)} - (1-r)e^{-\mu_W(t_4-t_2)} - e^{-\mu_W(t_4-t_3)} \right].
 \end{aligned}$$

Thus, the general solution satisfies

$$W_n^- = \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \left[(1-r)^{n-1}e^{-\mu_W(t_n-t_1)} + (1-r)^{n-1}e^{-\mu_W(t_n-t_2)} + \dots + (1-r)e^{-\mu_W(t_n-t_{n-1})} + 1 \right. \\ \left. - (1-r)^{n-2}e^{-\mu_W(t_n-t_1)} - (1-r)^{n-3}e^{-\mu_W(t_n-t_2)} - \dots - e^{-\mu_W(t_n-t_{n-1})} \right]. \quad (4.4)$$

We have thus derived a general solution for the maximal number of parasites in the water. This occurs immediately before chlorination is applied and was derived from the overestimate (3.2). Note that this solution does not depend on the time between chlorinations being fixed.

4.1. Fixed chlorination

If chlorination occurs at fixed times, then $t_n - t_{n-1} = \tau$ is constant. We thus have

$$W_n^- = \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \left[1 + (1-r)e^{-\mu_W\tau} + (1-r)^2e^{-2\mu_W\tau} + \dots + (1-r)^{n-1}e^{-(n-1)\mu_W\tau} \right. \\ \left. - e^{-\mu_W\tau} \left(1 + (1-r)e^{-\mu_W\tau} + \dots + (1-r)^{n-2}e^{-(n-2)\mu_W\tau} \right) \right] \\ = \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \left[\frac{1 - (1-r)^ne^{-n\mu_W\tau}}{1 - (1-r)e^{-\mu_W\tau}} - e^{-\mu_W\tau} \frac{1 - (1-r)^{n-1}e^{-(n-1)\mu_W\tau}}{1 - (1-r)e^{-\mu_W\tau}} \right] \\ \lim_{n \rightarrow \infty} W_n^- = \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \left[\frac{1}{1 - (1-r)e^{-\mu_W\tau}} - e^{-\mu_W\tau} \frac{1}{1 - (1-r)e^{-\mu_W\tau}} \right] \\ = \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \left[\frac{1 - e^{-\mu_W\tau}}{1 - (1-r)e^{-\mu_W\tau}} \right].$$

This is the long-term maximum value of the infected water (since the effect of the impulse is to immediately reduce the level of infection). To keep this below a desired threshold \tilde{W} , we thus require

$$\tau < \frac{1}{\mu_W} \ln \left[\frac{\alpha\Pi\gamma - (1-r)\tilde{W}\mu\mu_W(\kappa + \mu)}{\alpha\Pi\gamma - \tilde{W}\mu\mu_W(\kappa + \mu)} \right] \equiv \tau_{\max}(r).$$

This is the maximum period between water treatments required to keep the infection below \tilde{W} .

Note that \tilde{W} must satisfy

$$\tilde{W} < \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} \quad (4.5)$$

from (3.2).

It follows that, in the case of fixed chlorination, we can derive a maximal (fixed) period of chlorination that will keep the parasite level strictly below a threshold of our choosing.

4.2. Non-fixed chlorination

In resource-constrained regions, regular disease control may be difficult, due to limited resources and infrastructure [35]. In particular, chlorinating water at fixed intervals may be difficult or impossible. In order to determine the “next best” chlorination time under these circumstances using (4.4), the entire history of chlorination would need to be known. This is unlikely to be the case, so we assume that only the two most recent chlorination events are known. Specifically, we assume that

$$e^{-\mu W(t_n - t_k)} \approx 0 \text{ for } k > 2$$

We thus have

$$W_n^- \approx \frac{\alpha \Pi \gamma}{\mu \mu W (\kappa + \mu)} \left[(1 - r)^2 e^{-\mu W(t_n - t_{n-2})} + (1 - r) e^{-\mu W(t_n - t_{n-1})} + 1 - (1 - r) e^{-\mu W(t_n - t_{n-2})} - e^{-\mu W(t_n - t_{n-1})} \right].$$

To keep this below \tilde{W} , we thus require

$$1 - r(1 - r)e^{-\mu W(t_n - t_{n-2})} - (2 - r)e^{-\mu W(t_n - t_{n-1})} < \frac{\tilde{W} \mu \mu W (\kappa + \mu)}{\alpha \Pi \gamma}. \quad (4.6)$$

Hence, if the previous two chlorination times are known, then the “next best” chlorination time satisfies

$$t_n < \frac{1}{\mu W} \ln \left[\frac{2 - r^2}{1 - r(1 - r)e^{\mu W t_{n-2}} - (2 - r)e^{\mu W t_{n-1}} - \tilde{W} \mu \mu W (\kappa + \mu) / (\alpha \Pi \gamma)} \right].$$

To compare fixed and non-fixed chlorination, suppose the chlorination times in the non-fixed case are constant, \tilde{T} . For $r = 1$, we have

$$W_n^- \approx \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} [1 - e^{-\mu_W\tilde{\tau}}] < \tilde{W}$$

$$\tilde{\tau} < \frac{1}{\mu_W} \ln \left[\frac{\alpha\Pi\gamma}{\alpha\Pi\gamma - \tilde{W}\mu\mu_W(\kappa + \mu)} \right]$$

$$= \tau_{\max}(1).$$

Thus, when $r = 1$, the two options are equivalent.

Note that $\tau_{\max}(0) = 0$. For non-fixed chlorination, when $r = 0$,

$$W_n^- \approx \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)} [e^{-2\mu_W\tilde{\tau}} + e^{-\mu_W\tilde{\tau}} + 1 - e^{-2\mu_W\tilde{\tau}} - e^{-\mu_W\tilde{\tau}}]$$

$$= \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}.$$

Thus, if $\tilde{W} < W_n^-$ (which we expect), then, from (4.5), there is no solution. Furthermore, from (4.5),

$$\tilde{W} < \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}$$

$$< \frac{\alpha\Pi\gamma}{(1-r)\mu\mu_W(\kappa + \mu)}$$

since $0 < r < 1$. Thus

$$\alpha\Pi\gamma > \mu\mu_W(\kappa + \mu)$$

$$\alpha\Pi\gamma > (1-r)\mu\mu_W(\kappa + \mu)$$

and hence $\tau_{\max}(r)$ is defined for all r .

Define $\tilde{\tau}_{\max}$ to be the constant period in the non-fixed case with equality in (4.6). Then $\tilde{\tau}_{\max}$ satisfies

$$r(r-1)e^{-2\mu_W\tilde{\tau}_{\max}} - re^{-\mu_W\tilde{\tau}_{\max}} + 1 < \frac{\tilde{W}\mu\mu_W(\kappa + \mu)}{\alpha\Pi\gamma}.$$

If $\tilde{\tau}_{\max} = 0$, then

$$\begin{aligned}
 r(r-1) - r + 1 &= \frac{\tilde{W}\mu\mu_W(\kappa + \mu)}{\alpha\Pi\gamma} \\
 (r-1)^2 &= \frac{\tilde{W}\mu\mu_W(\kappa + \mu)}{\alpha\Pi\gamma} \\
 r &= 1 - \sqrt{\frac{\tilde{W}\mu\mu_W(\kappa + \mu)}{\alpha\Pi\gamma}}, 1 + \sqrt{\frac{\tilde{W}\mu\mu_W(\kappa + \mu)}{\alpha\Pi\gamma}}
 \end{aligned}$$

The second root is larger than 1 and can thus be discounted. The first root is greater than zero, since $\tilde{W} < \frac{\alpha\Pi\gamma}{\mu\mu_W(\kappa + \mu)}$. It follows that non-fixed chlorination will only be successful for $r_0 < r \leq 1$, where

$$r_0 \equiv 1 - \sqrt{\frac{\tilde{W}\mu\mu_W(\kappa + \mu)}{\alpha\Pi\gamma}}$$

That is, there is a minimum degree of effectiveness required in the non-fixed case.

It follows that, when chlorination is not fixed, we can derive the “next best” chlorination time, assuming the previous two chlorination times are known. We have also demonstrated that non-fixed chlorination is always inferior to fixed chlorination (and has an additional requirement of minimum efficacy), but that both can control the disease.

5. Numerical simulations

We used Latin Hypercube Sampling and partial rank correlation coefficients (PRCCs) to explore the sensitivity of R_0 to parameter variations. Latin Hypercube Sampling is a statistical sampling method that allows for an efficient analysis of parameter variations across simultaneous uncertainty ranges in each parameter [9]. PRCCs rank each parameter by the effect it has on the outcome when all other parameters are kept at median values. We used 1000 simulations per run.

Figure 4 illustrates the degree of sensitivity of each parameter on R_0 , using ranges in the table. Parameters with PRCCs > 0 will increase R_0 when they are increased, while parameters with PRCCs < 0 will decrease R_0 when they are increased. The three parameters we have the most control over are the parasite death rate μ_w , the transmissibility β and the parasite birth rate γ due to chlorination, filtration and education, respectively. From Figure 4, we

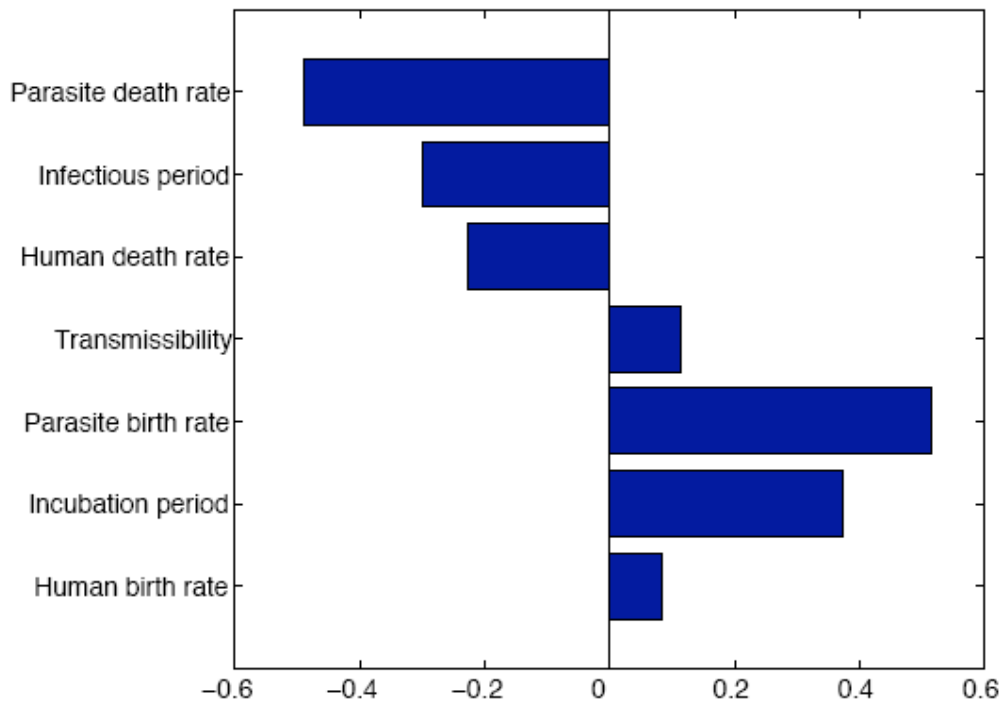


Figure 4. Tornado plots of partial rank correlation coefficients (PRCCs) of all seven parameters that influence R_0 . Parameters with $\text{PRCC} > 0$ will increase R_0 as they are increased, whereas parameters with $\text{PRCC} < 0$ will decrease R_0 as they are increased. Variations in the parasite death rate μ_W and the parasite birth rate γ will have the greatest effect on the outcome.

see that two of these – the parasite birth and death rates – are the parameters that have the largest impact on the outcome.

Figure 5 illustrates the effect of the three parameters we have the greatest control over on R_0 as all parameters are varied simultaneously. This shows that increasing the parasite death rate is unlikely to lead to eradication, even if the death rate is quite high. Conversely, decreasing the parasite birth rate or the transmissibility to very low levels is likely to lead to eradication.

To examine the three crucial control parameters in more detail, we fixed all other parameters at their sample values and set $R_0 = 1$. The resulting surface is plotted in Figure 6. Parameter combinations under the surface will lead to eradication, while those above will maintain disease persistence. The outcome is significantly dependent on changes in γ . Even if μ_W were increased tenfold, it is still unlikely to lead to eradication, while β would have to be reduced to extremely low levels.

In order to determine the relative utility of the three interventions, we considered the effect of reducing the parasite birth rate and transmissibility to 1% while increasing the parasite death rate by a factor of 100 (which is

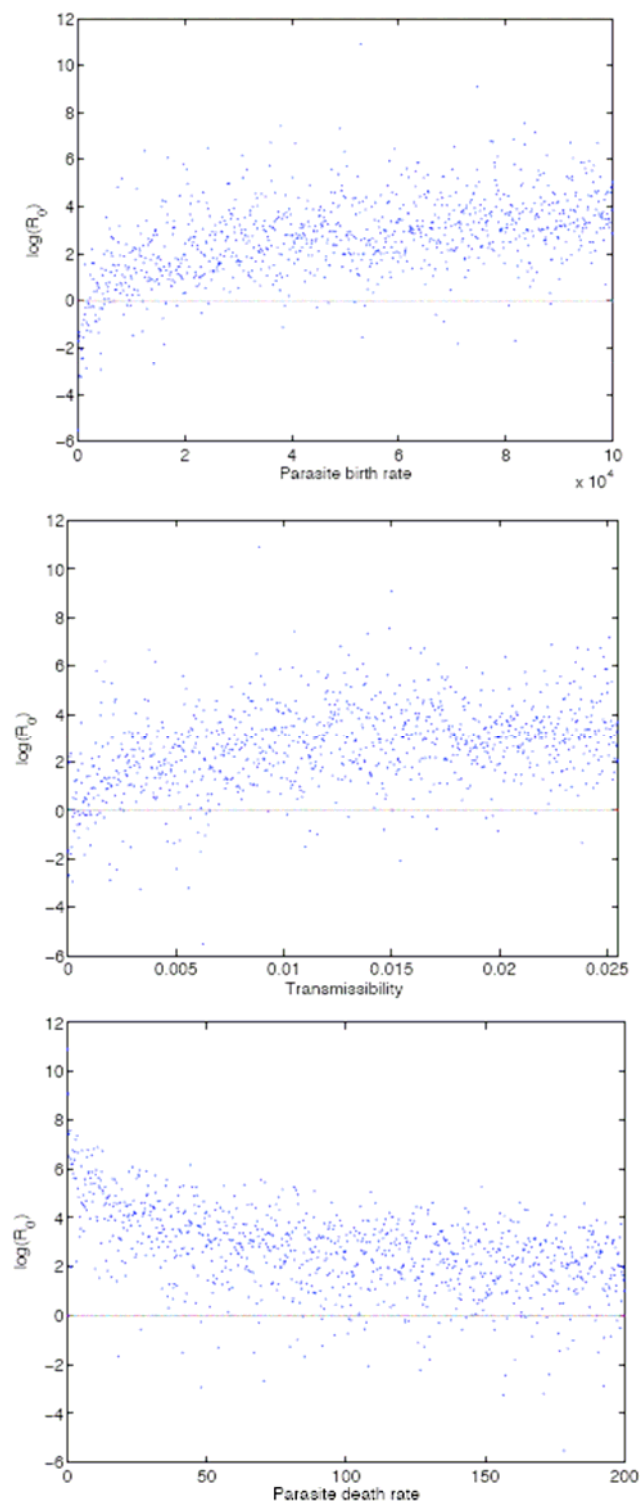


Figure 5. Sensitivity of the basic reproductive ratio R_0 to the three parameters we have the greatest control over: the parasite birth rate, the transmissibility and the parasite death rate. However, R_0 is only guaranteed to be less than 1 if the parasite birth rate or the transmissibility are sufficiently small. Even if the parasite death rate is extremely high, eradication is not guaranteed.

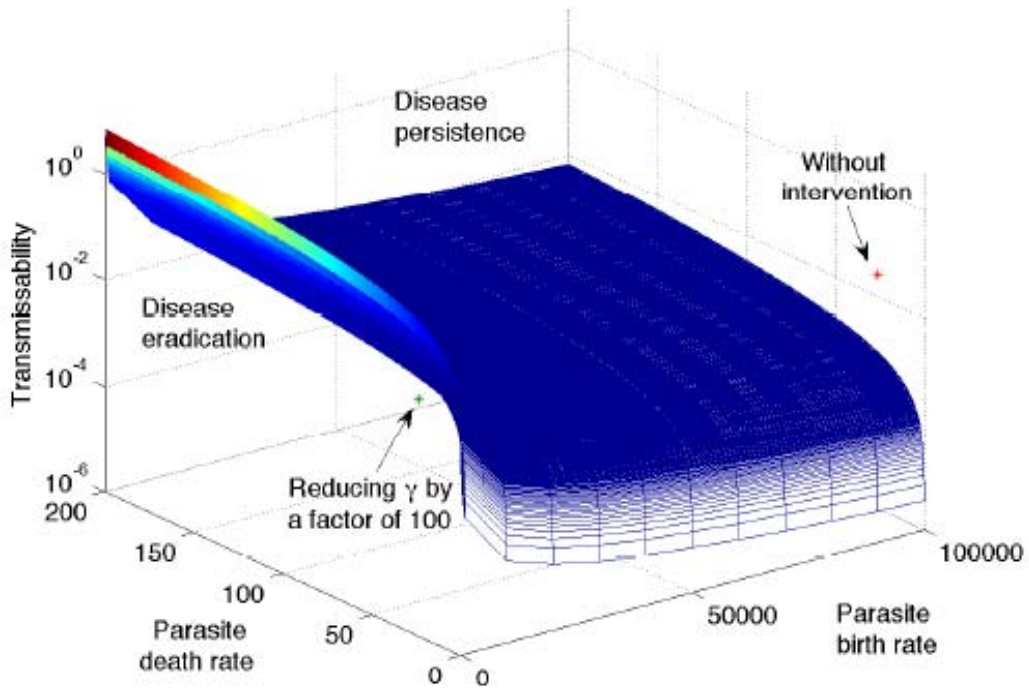


Figure 6. Eradication threshold for the three parameters with the greatest influence on R_0 . Eradication will occur if the infection rate is reduced to a tiny fraction of its current value (through filtration of drinking water) or the parasite death rate is increased more than tenfold (through chlorination) or if the parasite birth rate is reduced to approximately a 1% of its current size (through education).

Table 1. Parameter values. The average transmissibility β was derived from (7 drinks of water per day) \times (365 days)/(100,000 larvae)=0.02555. This represented the ratio of total yearly water ingested to number of parasites. The average lifespan $1/\mu$ was set to 70 years. The average infectious time $1/\kappa$ was set to be 1 hour (the length of time that an infected foot is actually submerged in the water), so that $\kappa = 24 \times 365 = 8760$ years⁻¹. The birth rates per 1000 people in the four endemic countries are 46.09 (Mali), 43.34 (Ethiopia), 33.25 (Sudan) and 28.09 (Ghana) [14], giving an average of 37. All parameters were distributed uniformly over their ranges.

Parameter	Definition	Range	Sample value	units	Reference
S	Susceptible individuals	(state variable)	$S(0) = \Pi/\mu$	people	-
E	Exposed individuals	(state variable)	$E(0) = 0$	people	-
I	Infectious individuals	(state variable)	$I(0) = 0$	people	-
W	Waterborne larvae	(state variable)	$W(0) = 200$	larvae	-
Π	birth rate	28 - 46	37	people years ⁻¹	[14]
β	transmissibility	0 - 0.03	0.0255	larvae ⁻¹ years ⁻¹	(calculated)
μ	death rate	0.01 - 0.02	0.0142	years ⁻¹	[14]
κ	recovery rate	4000 - 18000	8760	years ⁻¹	(calculated)
α	rate of worm emergence	0.8 - 1.5	1	years ⁻¹	[34]
γ	parasite birth rate	0 - 100,000	100,000	larvae people ⁻¹ years ⁻¹	[34]
μ_W	parasite death rate	0 - 200	26	years ⁻¹	[34]
τ	chlorine effectiveness	0 - 100%	90%	-	(assumed)

equivalent to decreasing the parasite lifespan to 1%). Figure 7 illustrates the four scenarios for 1000 simulations each, with all other parameters kept at their sample values. Without intervention, R_0 remains firmly above 1. If the parasite death rate is increased by a factor of 100, then the average R_0 is lowered but still above 1. This suggested that eradication is unlikely. If the transmissibility is decreased to 1% of its sample value, then the average is below 1, but the upper quartile value is not. This suggests that eradication is possible, but may not always occur. If the parasite birth rate is decreased to 1% of its sample value, then both the average and the upper quartile value are below 1. This suggests that eradication is likely.

We also determined the approximate cutoff values for eradication for our three parameters of interest. (The values are approximate since the LHS method produces slightly different results with every simulation.) Our requirement for “likely eradication” was that the upper quartile value of R_0 be less than 1. When the parasite birth rate was in the range 0-1000, $R_0 = 0.3$ (interquartile range 0.1-0.8). This corresponds to a decrease in worm emergence by a factor of 100. When the transmissibility was in the range 0-0.00016, $R_0 = 0.35$ (IQR 0.1-0.95 This corresponded to a decrease in the number

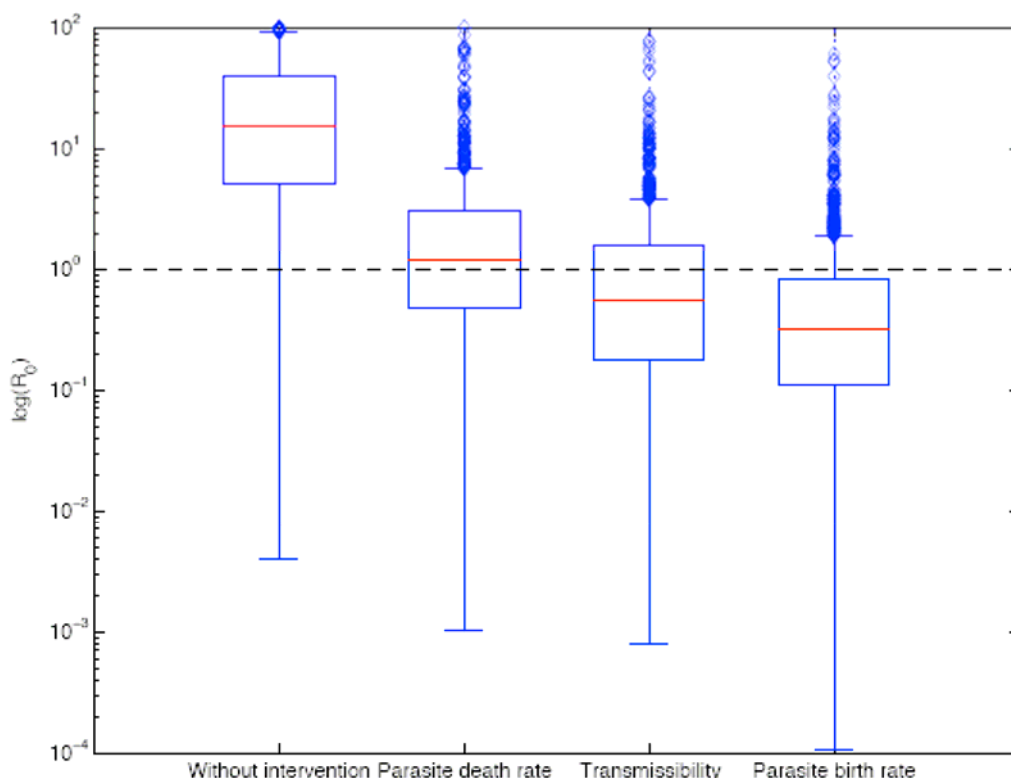


Figure 7. Boxplots illustrating the variation in R_0 without intervention, when the parasite death rate is increased by a factor of 100 or when the transmissibility or the parasite birth rates are reduced by a factor of 100.

of drinks per day by a factor of 159.6. When the parasite death rate was in the range 0-8500, $R_0 = 0.35$ (IQR 0.1-0.95). This corresponded to an increase of the parasite death rate by a factor of 327, or a lifespan of approximately 1 second. Thus, eradication through parasite control is extremely unlikely.

The effect of annual chlorination is illustrated in Figure 8A. In this case, despite significant reductions in the larval population immediately after chlorination, the population returns to high levels quite quickly. The number of

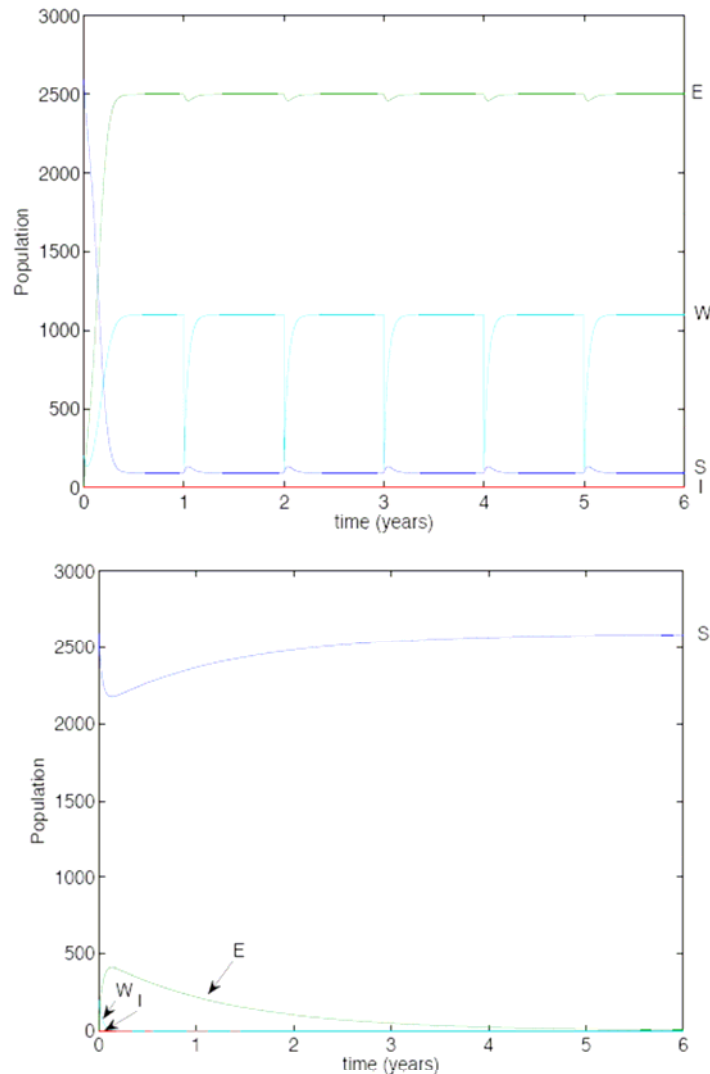


Figure 8. The long-term effects of interventions. A. Persistence of the disease under annual chlorination. Chlorination was assumed 90% successful and applied annually. All parameters were their sample value in the table. Note that infection levels are low, since individuals are infectious for only a brief time (the amount of time they physically submerge their foot in water). However, the burden of the disease is expressed through the exposed class, where individuals are infected with Guinea worms for months at a time. B. Eradication of the disease when the parasite birth rate is decreased. Parameters used were the same as the previous scenario, except that $\gamma = 1000$ (see Figure 6).

susceptibles remains low, while almost all individuals remain infected.

The effect of reducing the parasite birth rate by 99% is illustrated in Figure 8B. In this case, the number of exposed and infectious individuals approaches zero and the entire population becomes uninfected.

6. Discussion

We stand at the brink of eradicating one of humanity's oldest scourges [22]. There are three criteria for the eradication of an infectious disease: 1. Biological and technical feasibility; 2. Costs and benefits; and 3. Societal and political considerations [2]. GWD satisfies all three. While eradication efforts have been immensely successful thus far, the final phase of eradication will occur in resource-poor and underfunded areas of the world. Knowing which strategies may be optimal will be of enormous benefit.

Smallpox remains the only disease we have completely eradicated, despite eradication hopes for malaria, yaws and yellow fever in the twentieth century [2], and current eradication programs, such as polio [41] and leprosy [25]. Measles, rubella, and hepatitis A and B are biologically and technically feasible candidates for eradication [28]. Mathematical models have also examined the potential for eradication of other diseases, including trachoma [32], sleeping sickness [13] and HIV/AIDS [30, 36, 40].

A critical tool for smallpox eradication, in addition to an extremely effective vaccine, was photographic disease-recognition cards [17], demonstrating that non-biomedical interventions were also important. Barriers to smallpox eradication included cultural traditions, a lack of societal support and religious beliefs. Despite strong biological, technical and cost-benefit arguments for eradication of many infectious diseases, securing societal and political commitment has been recognised as a substantial challenge [2].

The most effective way to eradicate GWD is to reduce the parasite birth rate. This can be achieved via education; specifically, teaching people not to put infected limbs into the drinking water. Although behaviour changes are, in general, notoriously difficult, GWD eradication programs have had significant success in altering people's behaviour. If 99% of people can be persuaded not to put their infected feet in the drinking water, then eradication is assured. While chlorination can theoretically control the disease and we have provided estimates for the necessary frequency and strength of chlorination, numerical simulations demonstrate that education is far more effective. Thus, our results here are not advocating for something untested, but rather point to the importance that one of the three existing intervention methods - namely, persuading people not to put infected limbs in the drinking water - will have in the final push towards complete eradication.

Mathematical models of large parasites, such as Guinea worms, are often referred to as models of macroparasites, with the biological distinction referring to the fact that these worms cannot complete their life cycle within the individual host. A central factor in such models is that large worms do not usually confer immunity and that the removal of one worm does not imply that the host is free of infection [3]. Here, we simplify this notion, in order to understand the transmission dynamics of GWD with a simpler model, taking the presence of the parasite in the environment as a single homogeneous compartment. This formulation allows us to analyse an impulsive system that overestimates the environmental parasite load, giving us insight that more complex models may struggle to achieve. Examples of similar formulations for non-impulsive systems include cholera [15], schistosomiasis [16] and baculovirus [4].

There is a complex interplay between education and eradication; more educational tools may become available in future years which may affect the speed of eradication. However, we note that the simple education strategy we have considered here – convincing people not to put their inected feet in the water – has a significant payoff: 100,000 parasites are immediately prevented from entering the water system. Conversely, chlorination is unlikely to be as efficient and has other issues, such as toxicity.

The model has a number of limitations, which should be acknowledged. Chlorination does not occur instantaneously, but rather takes some time. However, impulsive differential equations have been shown to be robust, even for quite large delays [37]. Chlorination may not reach every drinking source, depending on the difficulty of reaching certain areas. Education and filtering may not be applied uniformly, depending on access to information of particular communities, as well as their ability to absorb it. We have also restricted our simulations to small communities rather than large urban centres. As a result, we have used mass-action transmission and constant birth rates, rather than recruitment rates. Future work will include the effects of secondary infection, as well as more detailed stages of the life cycle of the disease.

While we used sample parameters to illustrate the potential for eradication, Latin Hypercube Sampling allows us to explore sensitivity of the results to variations in those parameters. This allows us to capture the inherent variation present in the real world, such as non-uniform education, filtering or chlorination effects.

The final steps towards eradication of GWD should take place within the next few years. Our modelling shows that education is the most effective intervention method, but a combination of education, chlorination

and filtration will likely be required to achieve the final steps in the long journey to eradication. By mustering both scientific and cultural resources, we can successfully defeat one of the oldest diseases in human history.

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