Mathematical Models of Guinea Worm Disease Eradication: A Review

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Abstract

Guinea-worm disease (GWD) is a neglected tropical disease (NTD) caused by the parasitic worm *Dracunculus medinensis*. In 1988, the Carter Center launched the campaign to eradicate the disease. The global campaign has been very successful, bringing the world-wide number of GWD cases down from 3.5 million in 1986 to low double digits in 2015 and thereafter. However, GWD now shows a peculiar pattern and is resurfacing again: not in humans, but mostly in dogs and other animals. Moreover, despite the fact that mathematical modeling is a standard and indispensable tool for NTDs elimination efforts, there are fewer than ten models of GWD. In this paper, we review most of those models and illustrate their basic assumptions and modeling techniques. We demonstrate that as the understanding of the Guinea worm biology evolved, so did the mathematical models. We also point out to what is still missing in all of these GWD models and discuss potential future research directions.

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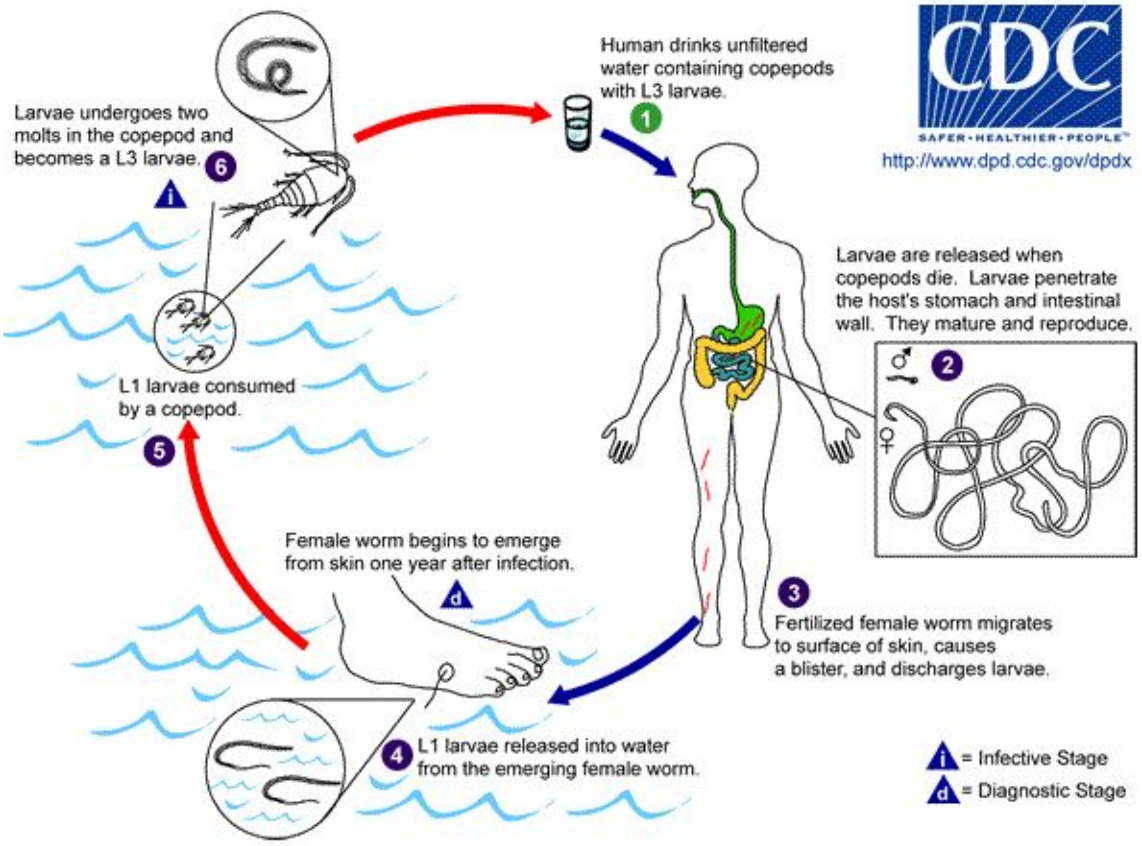

Figure 1. Guinea worm life cycle with humans as the only primary host for mature worms. Image courtesy of DPDx, Centers for Disease Control and Prevention (https://www.cdc.gov/dpdx)

Introduction

Guinea-worm disease (GWD) is caused by the parasitic worm *Dracunculus medinensis*. The disease used to affect primarily poor communities in remote rural areas without adequate access to safe water [Muller 1979]. It has been known and recognized since antiquity, mostly due to the impressive size of the parasite, up to 800 mm–1200 mm in length, and its unusual mode of life [Muller 1971].

The complex life cycle, as known by the early 2000s, is shown in **Figure 1**. In humans, the mature female worm migrates to the lower extremities and creates a painful blister. The pain causes the host to immerse the blister in the water, typically a source of drinking water for the whole community. Once in water, the worm releases millions of larvae into it. The free larvae are eaten by copepods (tiny crustaceans) or by water fleas. Inside the copepods, the larvae undergo two molt stages. If, at that point, the infected copepods are swallowed by humans, the larvae can then grow into maturity, mate, and the cycle continues.

Through the global education campaign and drinking only filtered water, GWD was thought to be essentially eradicated in most countries by the early 2000s. However, in 2011, GWD resurfaced in Chad despite the re-

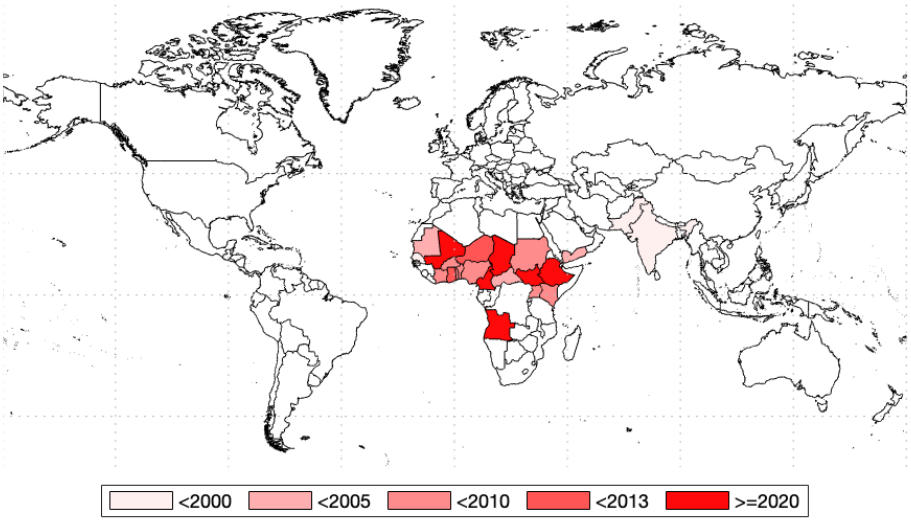

Figure 2. Geographical distribution of times of the last reported human GWD cases. Data collected from Our World in Data [2022] and map was made with the aid of borders.m file [Greene et al. 2019] in MATLAB.

ported absence of human cases for 10 years [The Lancet 2019]. Since 2015, there have been fewer than 55 human cases worldwide annually. Yet, in 2021, there were still cases in Chad, Ethiopia, South Sudan and Mali; see **Figure 2**. Chad, Ethiopia and Mali have also reported animal GWD cases [The Carter Center 2022].

Recently, GWD developed a peculiar pattern [Eberhard et al. 2014]. Domestic dogs, rather than humans, have been observed as the terminal hosts for the worm. The infections are concentrated along the entire Chari river and its tributaries [Cleveland et al. 2019; Hopkins et al. 2014, 2018]. The working hypothesis is that the Guinea worm life cycle involves fish, frogs, or other aquatic hosts that serve as intermediate hosts in which no development of the parasite occurs [Hopkins et al. 2018; Molyneux and Sankara 2017]. New infections are thought to occur when humans consume inadequately cooked paratenic hosts and when such hosts are consumed raw by dogs [Eberhard et al. 2014]. The up-to-date life cycle is illustrated in **Figure 3**.

There are very few mathematical models of GWD; we provide a basic overview of most of them. The purpose of most of the models is to investigate which steps should be taken to eradicate the disease. For each model, we briefly describe the background anf assumptions and display its diagram. We outline general ideas behind the model's analysis and discuss issues with model calibration and validation. We include a discussion about what constitutes a good model. We conclude by identifying several promising directions for future research in GWD modeling.

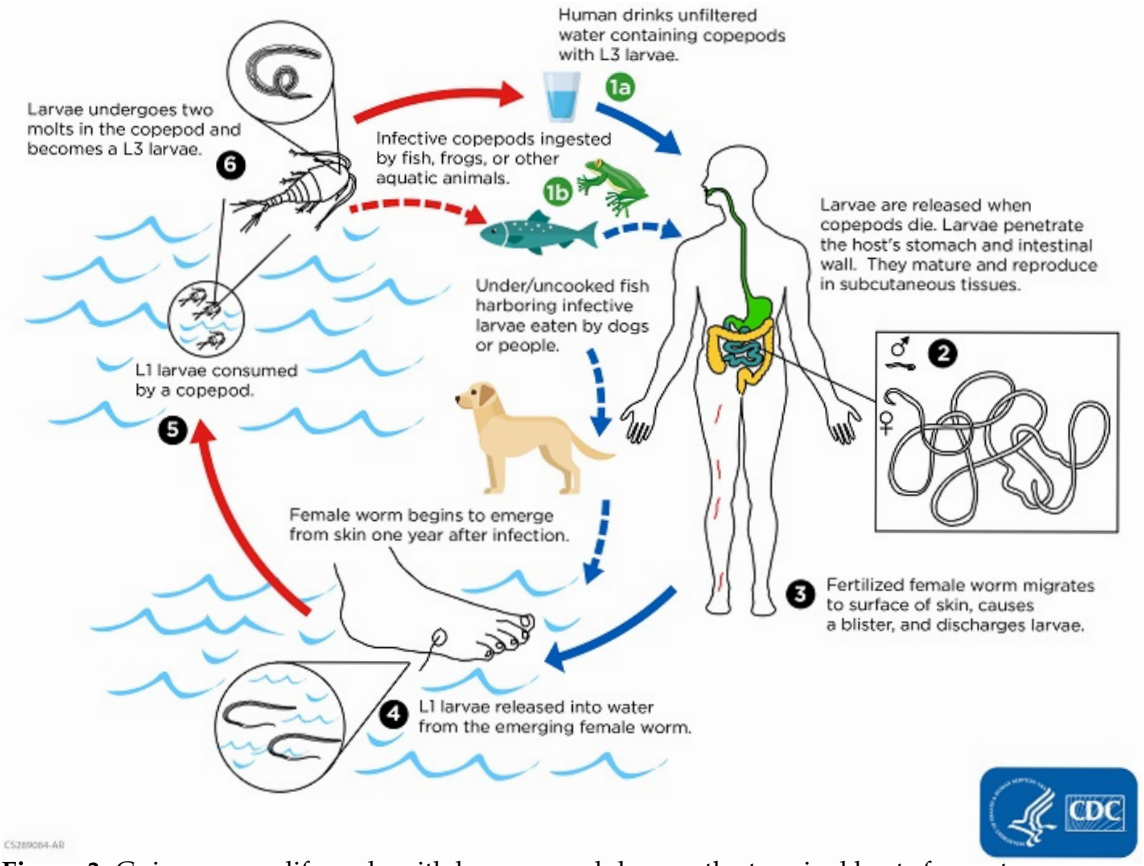

Figure 3. Guinea worm life cycle with humans and dogs as the terminal hosts for mature worms. Image courtesy of DPDx, Centers for Disease Control and Prevention (https://www.cdc.gov/dpdx).

Overview of Compartmental Models

In this section, we provide a basic overview of the different compartmental models of GWD. We try to keep notation as uniform as possible, more or less following the conventions in Engelhard et al. [2021]. Thus, we often deviate from the notation used in the original papers.

- For the classical compartments of susceptible, exposed, and infectious individuals, we use capital letters S, E, and I. We also use R for recovered/removed and Q for quarantined population. If the model considers two populations of humans, we use superscripts (1) and (2).
- For transmission rates, we typically use lower-case Greek letters.
- We denote death rates by μ, contact rates by β, maturation rates by γ, larvae-shedding rates by σ, and recovery-from-infection rates by η.
- To distinguish among humans, dogs, copepods, and fish/frogs, we use subscripts H, D, C, and F; we also use T for tadpoles.
- Birth rates are denoted by Λ.

There are also some differences in modeling details; for example, some models consider logistic growth, use variations of the transmission rates, and/or explicitly account for copepod mortality from dogs or humans drinking copepods. In the interest of brevity, we use symbols such as $\widetilde{\Lambda}$, $\widetilde{\beta}$, or $\widetilde{\mu}$ and encourage interested readers to consult the original paper for detailed exposition.

Model of Smith? et al. (2012)

The first mathematical model of GWD was developed in Smith? et al. [2012]. The purpose of the model was to examine the theoretical likelihood of eradication of the disease using existing intervention techniques in resource-constrained settings. The possible interventions included water filtration, public education or chlorination of the water supply.

Smith? et al. [2012] consider a classic SEIS (Susceptible-Exposed-Infected-Susceptible) model with an additional compartment W_L for larvae present in the water. The model is illustrated in **Figure 4** and briefly described below.

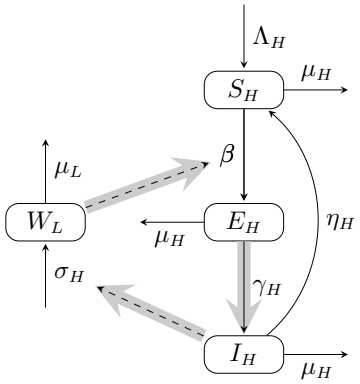

Figure 4. The schematic diagram of GWD transmission adapted from Smith? et al. [2012]. The solid arrows represent transition of individuals between compartments; the letters next to the arrows are (per capita) transition rates. The dashed arrows represent an influence of one compartment on a transition rate. The thick gray arrows represent the (simplified) life cycle of the parasite.

Individuals are born susceptible, S_H, at rate Λ_H. They become exposed, E_H, at rate βW_L, where β is the infection rate and W_L is the number of parasites in the water. Once inside the human body, the parasites mature at rate γ_H and the individual becomes infectious, I_H. Infectious individuals contribute to W_L at rate σ_H, and they recover and become susceptible again at rate η_H.

The graphical representation of the model in **Figure 4** yields the following system of differential equations:

$$\frac{dS_H}{dt} = \Lambda_H + \eta_H I_H - \mu_H S_H - \beta W_L S_H \tag{1}$$

$$\frac{dE_H}{dt} = \beta W_L S_H - \mu_H E_H - \gamma_H E_H \tag{2}$$

$$\frac{dI_H}{dt} = \gamma_H E_H - \mu_H I_H - \eta_H I_H \tag{3}$$

$$\frac{dW_L}{dt} = \sigma_H I_H - \mu_W W_L. \tag{4}$$

Each equation is based on a corresponding compartment of the model. For every solid arrow going into the compartment, one adds a product of the transition rate and the outgoing compartment. For every arrow going out, one subtracts a product of the transition rate and the compartment itself. The dashed arrows in the model diagram mean that the transition rate is multiplied by the outgoing compartment as well.

Smith? et al. [2012] also included impulse reduction of larvae in the water, W_L, by means of chlorination and showed that education was the most effective countermeasure.

Model of Link and Victor (2012)

Link and Victor [2012] extended the model from Smith? et al. [2012] by explicitly incorporating more details in the parasite life cycle; see **Figure 5**. The authors aimed to analyze key model parameters to determine effective combinations of intervention strategies.

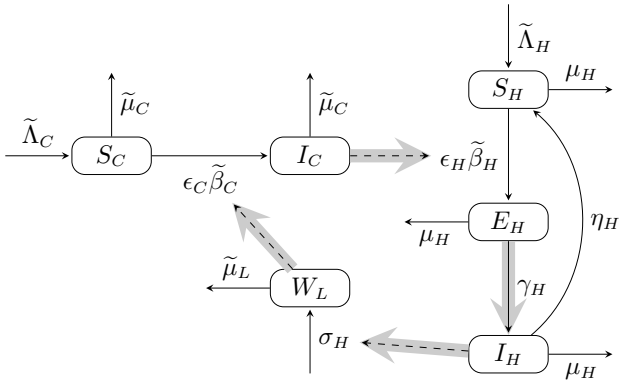

Figure 5. The schematic diagram of GWD transmission adapted from Link and Victor [2012]; the model created by Adewole and Onifade [2013] is very similar. For explanation, see the text and the caption to **Figure 4**. We note that Link and Victor [2012] assume that the adult mature female releases eggs that become larvae. Since this assumption is not supported by Guinea-worm biology, we omit this aspect in our description of their model.

The biological motivation behind a more detailed model is as follows. Once in contact with water, the mature adult female worms release Stage 1 larvae, W_L; see **Figures 1** and **3**. The larvae must first be eaten by copepods

to develop through further larval stages to be harmful to humans. The authors assume that copepods undergo classical SI (Susceptible-Infected) dynamics. The copepods are not infectious right away, because the larvae have to molt twice. However, the time needed for that is about two weeks and it is assumed negligible compared to other processes, such as 10–14 months the worms need to mature in humans [Muller 1985]. At the same time, the copepods do not live long enough to recover from the infection; in fact, the larvae damage copepods and cause their premature death [Bapna 1985], although this fact was not explicitly modeled.

As an additional layer of realism, authors also assume logistic growth of humans and copepods; i.e., the death rates are given by

$$\mu = b\,\frac{N}{K}$$

with appropriate subscripts, where b is the birth rate, K is carrying capacity, and N the total population size.

Also, on top of natural deaths, the authors assume that larvae are eaten by copepods at the per-capita rate $\widetilde{\beta}_C N_C$, where

$$\widetilde{\beta}_C = \frac{\beta_C}{W_L + K'_L},$$

K'_L is a saturation parameter, and β_C is the contact rate. Similarly, they assume that copepods are eaten by humans at rate $\widetilde{\beta}_H S_H$, where

$$\widetilde{\beta}_H = \frac{\beta_H}{N_C + K'_C}.$$

Perhaps a bit more precise would be to consider this rate to be $\widetilde{\beta}_H N_H$ or $\widetilde{\beta}_H(S_H + E_H)$, since there is no reason to believe that exposed individuals in E_H would modify their behavior and consume fewer copepods.

Finally, the authors assume that not every larva or copepod eaten results in an infection, and thus the transmission rates are given by

$$\epsilon_H \beta_H \frac{N_N}{N_C + K'_C} \qquad \text{and} \qquad \epsilon_C \beta_C \frac{N_C}{L + K'_L}.$$

The advantage of creating a more realistic model is that it allows for a better and more accurate parameter estimation. The model predictions will also be more quantitatively precise.

Model of Losio and Mushayabasa (2018)

Losio and Mushayabasa [2018] extended the model of Smith? et al. [2012] in yet another way. Most importantly, they consider two communities sharing the same source of water. Consequently, instead of one human

population undergoing an SEIS cycle, they have two human populations (with subscripts (i) for $i = 1, 2$) do so. Furthermore, they add a parameter p to account for the fact that individuals can learn from the unpleasant experience and modify their behavior. For example, after individuals recover from the infection, they may opt to drink only filtered water from then on. Such individuals become effectively removed (R) from the SEIS cycle, as they do not contribute to the parasite life-cycle any longer. The model is shown in **Figure 6**.

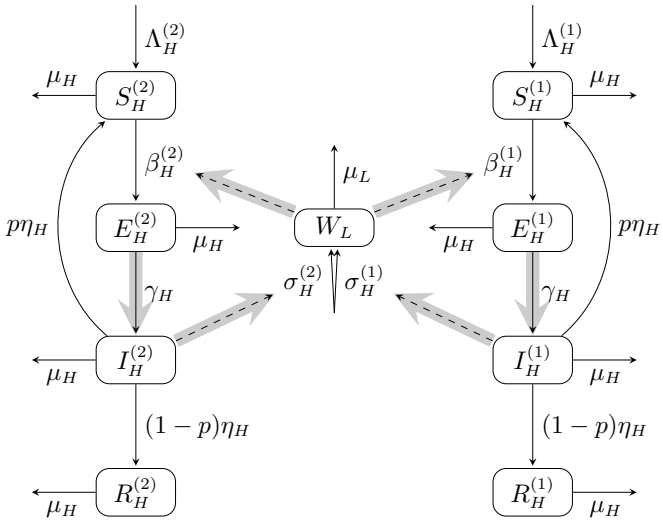

Figure 6. The schematic diagram of GWD transmission adapted from Losio and Mushayabasa [2018]. See caption to **Figure 4** and the text for explanation. We note that the original model of Losio and Mushayabasa [2018] did not formally separate compartments $E_H^{(i)}$, $I_H^{(i)}$, and $R_H^{(i)}$.

As another modification, the authors introduce seasonal variation into the parameter values; i.e., instead of considering the parameters β_H, γ_H, σ_H, and μ_W to be constant in time, they assume that the parameters are periodic functions with given means and periods. The model is set up in such a way that the amplitudes of the variations are the same for all parameters.

The aim of the model was to understand the effects of spatial heterogeneity and seasonality on GWD transmission. Furthermore, Mushayabasa et al. [2020] consider the optimal control of GWD using this model.

Model of Ghosh et al. (2018)

Ghosh et al. [2018] created a model that effectively combines the models of Link and Victor [2012] and Losio and Mushayabasa [2018]. This model includes a realistic description of larvae being eaten by copepods (which are assumed to follow an SI dynamics). The model also considers two sets of individuals, depending on their awareness of the disease. Aware individuals intentionally prevent the emerging mature females from con-

taminating sources of potable water; i.e., these individuals do not spread the infection further. Also, at the time when this model was created, dogs were already known to act as terminal hosts, so dogs are incorporated into the model. The Guinea worm develops in dogs almost in the same way as in humans [Cairncross et al. 2002; Guagliardo et al. 2020], and thus the dogs are assumed to undergo SEIS dynamics similar to that of the human population. Furthermore, the authors incorporate dog quarantine into the model. The model is illustrated in **Figure 7**.

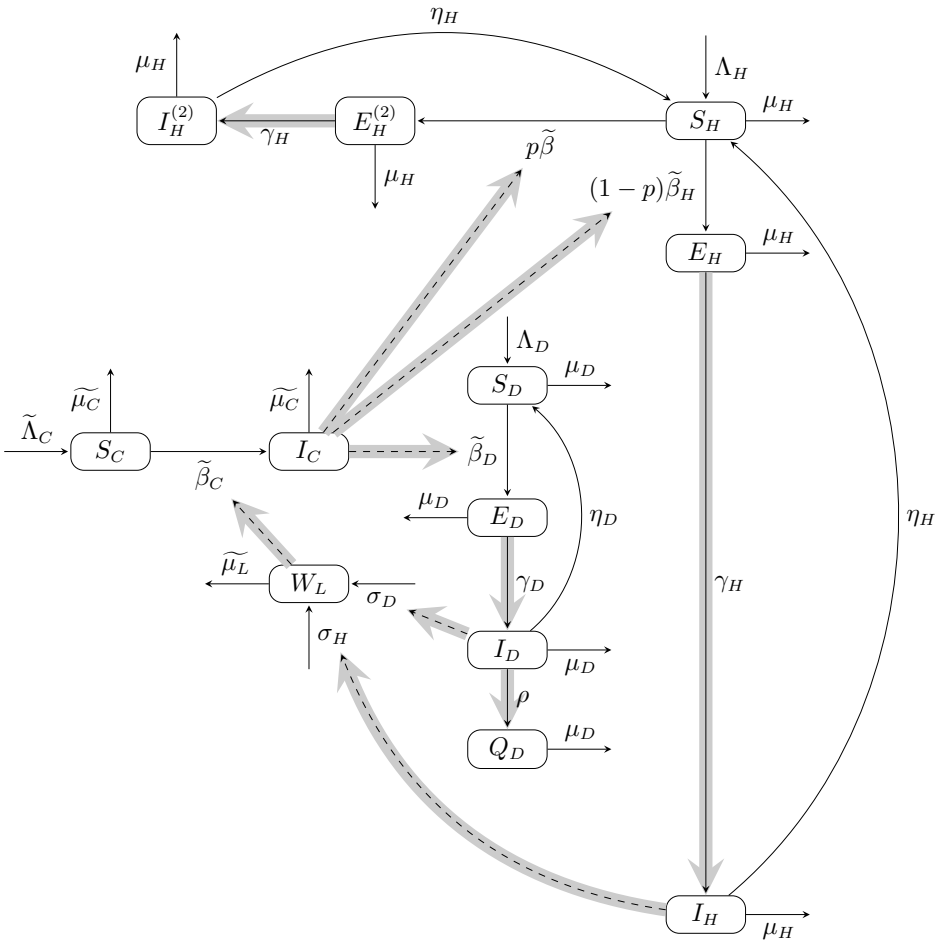

Figure 7. The schematic diagram of GWD transmission adapted from Ghosh et al. [2018]. See caption to **Figure 4** and the text for explanation. The aware individuals in $I_H^{(2)}$ do not contaminate water sources, and the same holds for quarantined and tethered dogs. For simplicity, we keep the notation $\widetilde{\Lambda_C}$ for the birth rate of copepods, but we note that the original model considered logistic growth. We also use $\widetilde{\mu_L}$ and$\widetilde{\mu_C}$ for the death rate of larvae and copepods, which stand for natural death, removal by being eaten (by copepods, dogs, or humans) and by reduction via intervention. Quarantined dogs were not in the original diagram in Ghosh et al. [2018]; but based on that article's equations and Table 1, quarantined dogs belong in the diagram.

Similarly to previous models, the main goal was to investigate the impact of three control interventions: awareness of humans, isolation of infected dogs, and copepod clearance from contaminated water sources. The authors also addressed the impact of combination interventions.

Model of Engelhard et al. (2021)

The purpose of the model in Engelhard et al. [2021] was to validate theoretically the hypothesis that the current spread of GWD along the Chari river region in Chad can be explained by fish and frogs being eaten by dogs (and humans). The authors adapted the model from Ghosh et al. [2018] and added fish/frogs into the model, as illustrated in **Figure 8**.

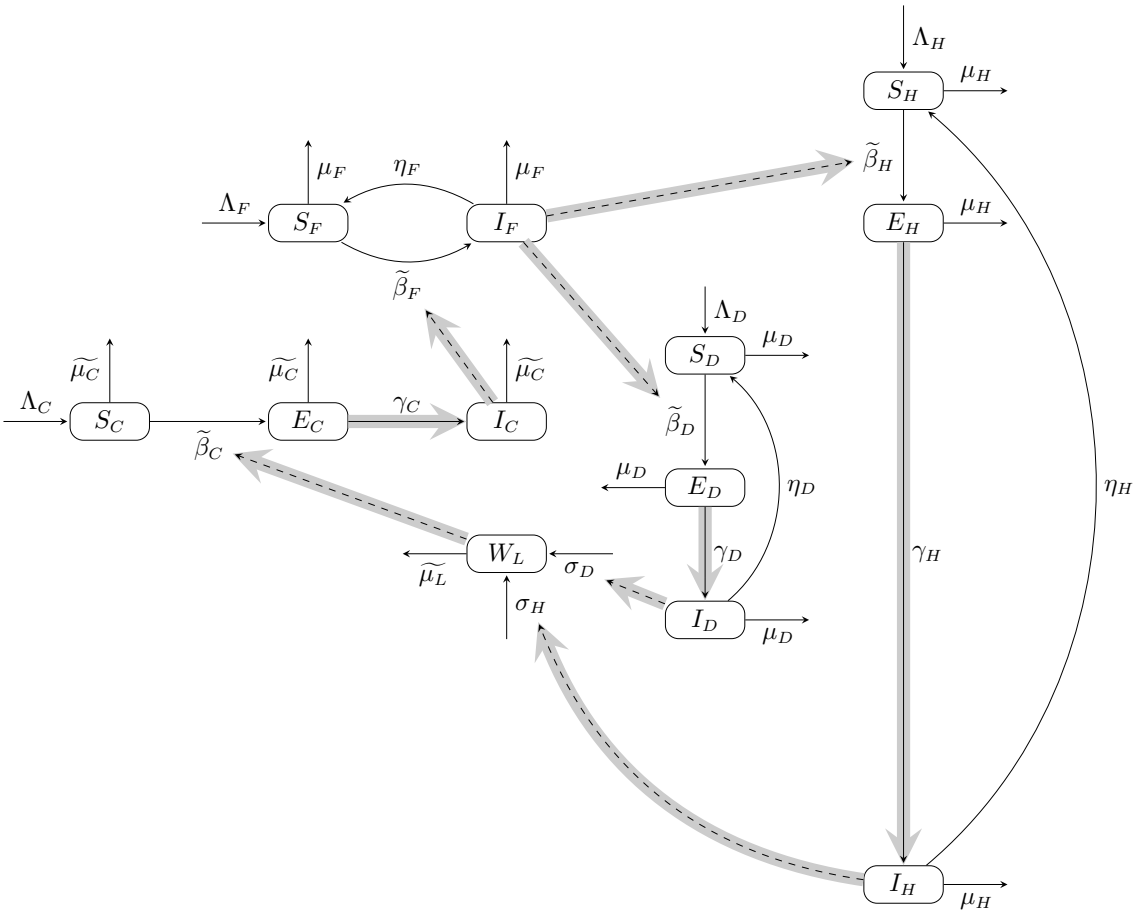

Figure 8. The schematic diagram of GWD transmission adapted from Engelhard et al. [2021]. See caption to **Figure 4** and the text for explanation.

They consider Susceptible-Infectious-Susceptible (SIS) dynamics for fish, since the fish seem to be only short-term transport hosts of the parasite [Cleveland et al. 2017; Eberhard et al. 2016]. They also make several simplifying changes. They remove the distinctions between the aware and unaware populations, consider regular growth rate Λ_C, and remove the compartment for dog quarantine. Dog quarantine is incorporated into the model by appropriate modification of the dogs' larvae-shedding rate σ_D. Similarly, human awareness is studied by modification of the larvae-shedding rate σ_H. Furthermore, the authors do not consider direct transmission from infected copepods to dogs or humans. Available data did not indicate repeated regular infections in the same location/village, sug-

gesting that direct transmission through local potable water sources is not happening. Removing all unnecessary transitions between compartments simplifies the model and the subsequent analysis [Bailey 1982]. At the same time, the authors use SEIS dynamics for copepods to properly account for the molting period that the larvae need to undergo inside the copepods; the two-weeks-long molting period is on par with the time the larvae spend in fish.

Model of Vinson et al. (2021)

Vinson et al. [2021] created the most recent model using the most recent biological knowledge. Their model considers only dogs as the terminal host (since the number of human GWD cases is indeed negligible). They use SEI dynamics for the copepods. In their model, the infected copepod is consumed by a tadpole. The tadpoles mature into frogs and the infected frogs cause infections in dogs. The model diagram is shown in **Figure 9**.

The goal of the model was again to study the most effective intervention strategies.

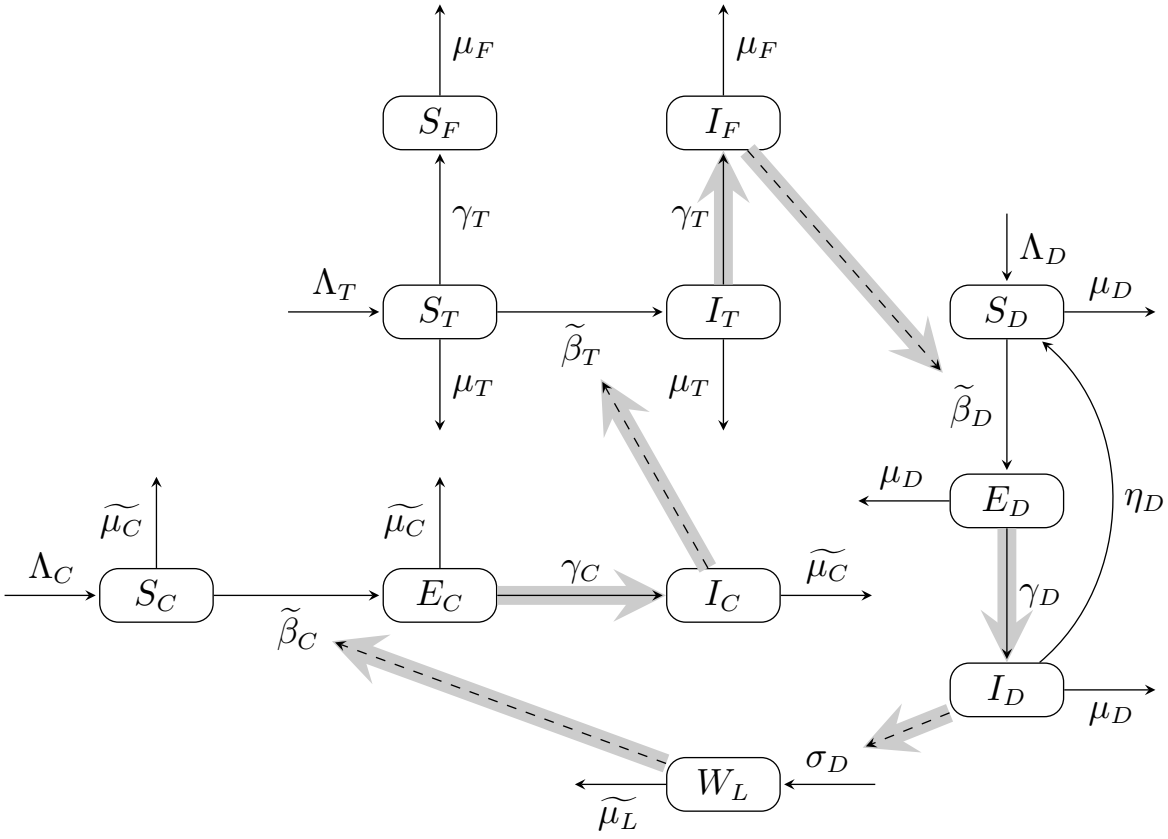

Figure 9. The schematic diagram of GWD transmission adapted from Vinson et al. [2021]. See caption to **Figure 4** and the text for explanation.

Analysis

While the details of the analysis of individual models differ based on the model purpose and setup, the analysis generally follows the same pattern.

- First, authors check whether the model and resulting system of equations (like the one shown in **(1)**–**(4)**) is epidemiologically and mathematically well-posed [Hethcote 2000]. Doing so amounts to checking that, given biologically reasonable initial conditions, the solutions of the system will always be biologically reasonable (i.e., positive and finite).
- Next, authors solve for equilibria, the steady states of the dynamics. This is done by setting the left-hand side of the equations to 0 and solving the system of algebraic equations. There are typically two kinds of solutions: disease-free equilibrium (DFE) and endemic equilibrium (EE). The DFE, as the name suggests, is an equilibrium in which there is no stage of parasite in the system. For the system **(1)**–**(4)**, it means $W_L = 0$, $I_H = 0$, and $E_H = 0$. The EE is an equilibrium at which GWD is constantly maintained at a baseline level, i.e., W_L, I_H, and E_H are all positive constants.
- Once the equilibria are identified, their stability is examined; that is, whether, given biologically reasonable initial conditions, the solutions of the system converge to the equilibrium. We distinguish between
  - local stability, for which we consider initial conditions to be already near the equilibrium; and
  - global stability, for which we consider any biologically reasonable initial conditions.

  The local stability of the DFE is determined with the help of $\mathcal{R}_0$, the *effective reproduction number*. The value of $\mathcal{R}_0$ can be understood as the number of secondary infections caused by a single infectious individual in an otherwise healthy (parasite-free) population. The DFE is stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$ [van den Driessche and Watmough 2002]. For simple systems such as the one in **Figure 4**, one can often determine $\mathcal{R}_0$ by going through the disease cycle; but it is preferred to use the next-generation matrix method developed in van den Driessche and Watmough [2002]. The method can be adapted even for models with non-constant transmission rates as done in Losio and Mushayabasa [2018]. The local stability of EE is determined by finding the Jacobian matrix of the system at the EE, finding the characteristic polynomial, and studying its roots.

  The global stabilities of the DFE and the EE are typically harder to analyze, but it is possible to use general methods developed, for example, in Castillo-Chavez et al. [2002] and La Salle [1976].

Model Parameters: Calibration, Sensitivity and Uncertainty Analysis, Validation

Even the simplest model of GWD transmission has a lot of parameters. Model calibration is a fancy term for assigning numerical values to the model parameters. Ideally, all values should come directly from demographic, epidemiological, and biological observations and measurements. For example, birth and mortality rates are often known and recorded for various countries and even regions of the countries [CIA 2019; World Bank 2019].

The parasite needs 10–14 months to develop from L3 larva to a mature worm. This means that it takes about 12 months for an individual to move from the exposed compartment E_H to the infectious compartment I_H, so we set $\gamma_H = \frac{1}{12}$ months^{-1}. Similarly, an individual stays infectious for about a week, so we set $\eta = \frac{1}{0.25}$ months^{-1}. And one can estimate how many larvae that an infectious individual sheds, giving a good estimate of σ_H. Also, the mortality μ_L of larvae and the birth and death rates of copepods can be measured experimentally [Muller 1979; Tayeh et al. 2017].

On the other hand, estimating or measuring the contact or transmission rate β is very hard. Most mathematical models in general thus contain at least one parameter whose value is not based on direct observations.

Even when a parameter value can be measured or observed, it is rarely as a single number but rather as a range. For example, we know that the worm needs 10–14 months to mature, not just a simple 12 months. There is evidence that GWD occurs in annual cycles; i.e., we can justify using 12 months in the model. However, it is always good practice to perform sensitivity and uncertainty analysis. As the name suggests, by doing sensitivity analysis, we study how an outcome of the model is sensitive to a change of a parameter. For example, we may want to study $\partial \mathcal{R}_0 / \partial \mu_C$ to understand how the change of mortality of copepods influences the stability of the DFE and the EE. A general method for sensitivity analysis is described by Arriola and Hyman [2009]. The sensitivity analysis also yields important answers related to the purpose of the model, since it quantifies what happens when a given parameter is changed.

The uncertainty analysis quantifies or illustrates how outcomes change if we change all the parameters within their given range. This is often done by the method of Latin hypercube sampling with partial rank correlation coefficient (LHS-PRCC) scheme [Blower and Dowlatabadi 1994; Saltelli et al. 2004]. The scheme is described in detail by Marino et al. [2008] and the MATLAB and R implementations can be found in Kirschner [2020].

Finally, a crucial part of every model is the validation: making sure that the model agrees with reality. This is often done by comparing model outcome(s) with known data. For example, Losio and Mushayabasa [2018] were able to fit their model to GWD-observed cases in South Sudan, while

Engelhard et al. [2021] were able to match reasonably the annual number of dog GWD cases in Chad.

Conclusions and Discussion

Why So Many Models of GWD?

- Compared to other diseases, there are practically no models of GWD. Indeed, just two years after the emergence of COVID-19, there are thousands of models of its transmission, prevention, and elimination; see, for example, Agusto et al. [2022]. However, the very first model of GWD appeared in 2012, thousands of years after the disease began to plague humanity and a century after the first models of malaria [Ross 1905; Smith et al. 2012]. This circumstance only confirms that GWD is a *neglected* tropical disease (NTD). Many other NTDs, such as yaws [Kimball et al. 2022] or visceral leishmaniasis [Fortunato et al. 2021], have a comparably small number of mathematical models [Kealey et al. 2010].
- The models evolve as our understanding of GWD changes. The model of Link and Victor [2012] is a reasonably accurate approximation of the GWD life cycle as known at that time. Once it became evident that dogs are part of the cycle, Ghosh et al. [2018] incorporated dogs into their model. Similarly, Engelhard et al. [2021] incorporated fish and frogs as intermediary hosts. Finally, Vinson et al. [2021] incorporated even more-accurate biology related to tadpoles and frogs as intermediary hosts.
- Different models are useful for different purposes. On the one hand, one may consider the model of Link and Victor [2012] to be superior to the model of Smith? et al. [2012] simply because the first model mimics reality better. However, the relative simplicity and elegance of the latter model is used to study deeper problems related to GWD eradication by impulsive water chlorination. Carrying such an analysis within more complicated models would be an unnecessarily hard task. The model of Smith? et al. [2012] contains all important parts needed to carry out its purpose, compared, for example, to Bailey [1982].

  Similarly, the model of Link and Victor [2012] might have realistically described the GWD life cycle, but it did not accurately mimic what was happening in the human populations. Often, there are multiple communities using the same water source, and the model of Losio and Mushayabasa [2018] was able to address exactly that.

Statistical vs. Mathematical Models

We need to stress a difference between mathematical and statistical models. A statistical model can

- take a data set, such as the number of annual GWD cases in a given country;
- run a time series analysis, a regression, or other statistical methodology; and
- predict the number of cases for several years into the future.

Such models are useful and valuable for their projections. However, their power comes in part from their major weakness: Unlike mathematical models, they do not consider the source of the data, and the statistical model is completely detached from the reality of the disease. This feature is important, because most diseases are never properly understood and yet countries need to be ready to treat cases year after year.

On the other hand, the mathematical models presented in this paper are internally consistent, to various degrees, with the actual disease; and thus one can make a lot of "what if" predictions. What will happen if we try to remove more copepods from the water? Is chlorination of water once a year enough to break the cycle, or do we need to do it more frequently?

Attributes of a Good Mathematical Model

A lot can be written about what constitutes a good mathematical model. We refer the reader to an excellent book [Kokko 2007] for a general overview and Bailey [1982] for specific compartmental models. Here we focus on recommendations for modeling NTDs as described in Behrend et al. [2020], where the authors suggest to adhere to the following five principles.

1. Don't do it alone. Engage stakeholders throughout, from the formulation of questions to the discussions on the implications of the findings.
2. Prepare and make available (preferably as open-source material) complete documentation of all the code, calculations, and assumptions and their justification. This allows others to reproduce the model.
3. All data used for model quantification, calibration, goodness of fit, or validation should be described in sufficient detail to allow the reader to assess the type and quality of these analyses. When referencing data, apply Principle 2.
4. Perform a sensitivity analysis of all key parameters, and for each paper reporting model predictions, include an uncertainty assessment of those model outputs within the paper.
5. Articulate model outcomes in the form of testable hypotheses. This allows comparison with other models and future events as part of the ongoing cycle of model improvement.

The first principle is crucial—yet often neglected—in undergraduate projects. Ideally, one should indeed collaborate with biologists, local medical professionals, and eradication experts from WHO and/or CDC—on all stages of the project, starting from the model development. Practically, time and other constraints makes this collaboration close to impossible for a project in a 6–10-weeks-long summer Research Experience for Undergraduates (REU) or even in a semester-long course. Yet one can still engage the stakeholders by sending the preprints or final published papers out to WHO or CDC experts and by presenting the research at conferences.

Principles 2–5 are items that should be achievable even for undergraduate projects, and one should adopt good modeling practice by following those principles.

How to Create a Good Mathematical Model

Start with a good purpose. Ideally, as mentioned above, the stakeholders should already be involved at this stage. What do you want to accomplish with your model? While this question seems obvious, in reality one often creates a nice model using the latest and nicest technique that one just learned; and only after that, one searches for the purpose and/or application of the model. This latter approach is not entirely bad, but a true modeler should start with a question or a goal. For example, as in Smith? et al. [2012]: How can one best eradicate GWD using known interventions?

Next, look at available data. A lot of data is available, for example, at Our World in Data [2022]; WHO [2020] or The Carter Center [2022]. Also, review the literature or work with biologists, epidemiologists and other stakeholders to collect all necessary information about the disease itself. Decide on the desired granularity, both spatial/geographical as well as temporal. For example, will you consider data from the whole country or region or are you interested in modeling incidences of GWD cases in villages along the Chari river? Will you consider month-to-month data as in Losio and Mushayabasa [2018], or will you mostly ignore the seasonality and consider aggregated annual data only?

Then, decide on the mathematical modeling technique(s) to use; the selection of the appropriate techniques comes only now, not earlier. Will you use compartmental ordinary differential equations (ODEs), as did the models described in this review? Or will you use stochastic simulations or agent-based modeling to study individual behavior in more detail? Perhaps partial differential equations (PDEs) to study the spatio-temporal patterns? The technique should be selected based on the model purpose and available data and knowledge, not the other way around.

Potential Extensions and Future Modeling Opportunities

There are several potential improvements and modifications that could be incorporated into existing models.

- As the number of human GWD cases dwindles, the underlying assumption of large and effectively infinite populations behind ODE compartmental models may start to be violated. It is still not an issue for models such as the one in Engelhard et al. [2021], which effectively focused on stability or instability of disease-free equilibria when the number of cases start low and eventually grow. Probabilistic models and stochastic simulations—as done, for example, in yaws modeling [Dyson et al. 2017, 2019; Holmes et al. 2020; Marks et al. 2017; Mooring et al. 2019]—are more appropriate approaches for modeling eradication endgames. This is also a reason why the latest GWD model [Vinson et al. 2021] considers only dogs and not the human GWD cases. So far, the only stochastic model of GWD was done by Perini et al. [2020].
- All of the GWD models presented in this review ignored the important fact that Guinea worm is a macro-parasite. Among other things, for its life-cycle to continue, the terminal host has to carry both a male and a female worm. A modeling methodology that is typical for modeling macro-parasites such as lymphatic filiarisis is the next step in modeling efforts; see Anderson and May [1992] for a general overview of macro-parasitic models and Stolk et al. [2008], Chan et al. [1998], Norman et al. [2000], and Irvine et al. [2015] for specific lymphatic filiarisis models that take into account parasite distribution in the host population.
- Finally, to see whether the fish, the frogs, or the tadpoles play the crucial role in the current outbreak along the Chari river in Chad, it would be beneficial to create an explicit spatial model incorporating fish and/or frogs/tadpoles movement and to match it with the spatio-temporal distribution of GWD cases.

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- E.P.: investigation, and writing of original draft
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