A Mathematical Model of Onchocerciasis Resistance and Treatment

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Abstract

Onchocerciasis is a parasitic disease endemic in Sub-Saharan Africa and South America that spreads from black flies to humans. The disease causes skin nodules, itching, and in severe cases, permanent blindness, contributing to its nickname, River Blindness. The World Health Organization's current approach to Onchocerciasis is mass drug administration of Ivermectin. One issue with this approach is that prolonged use of Ivermectin may cause drug resistance. Another issue is that even without resistance, eradication does not seem to be occurring in places with high prevalence. The goal of this project is to model the spread of Onchocerciasis with resistance, analyze the impact of possible Ivermectin resistance, and figure out an alternative treatment plan with doxycycline that can eliminate the disease without causing widespread resistance. The model shows that the current approach for treatment while resistance is present does not allow for eradication within the timeframe of the WHO. Using treatment with both doxycycline and ivermectin, eradication is possible, though the timeline is still longer than desired.

1. Introduction

Neglected tropical diseases (NTDs) are so-called because they are underfunded and under-researched, often not posing an immediate threat to most countries. Consequently, they receive little attention, leaving afflicted regions to manage these diseases independently. Onchocerciasis, or river blindness, is one such NTD, primarily affecting tropical regions in Central and South America. It is caused by the parasitic nematode *Onchocerca volvulus*, transmitted by the black fly (*Simulium damnosum*) (Mullen, 2018). These flies require blood meals for reproduction but cannot pierce human skin, needing an open wound to transmit the parasite through their saliva. Infected humans can pass the parasite back to flies, perpetuating the cycle. The adult parasite can live for 9 to 14 years in the human body, with females producing up to 1,500 microfilariae daily. These microfilariae migrate to the skin and other organs, causing severe damage, including blindness, when they reach the eyes. Onchocerciasis is the second leading cause of infectious blindness, following trachoma. The disease also triggers inflammation, especially around lymphatic nodes, and skin lesions, worsening as microfilariae die and provoke immune responses (WHO, 1995).

In 1975, the World Health Organization (WHO) established the Onchocerciasis Control Program (OCP) to combat the disease in affected regions. Operating from 1975 to 2002 across 11 African countries, the OCP helped cure around 78 million people (Boatin, 2008). In 1987, the drug Ivermectin was approved for widespread use due to its safety, versatility, and low cost, making it the primary treatment for onchocerciasis. The plan involved treating over 81% of the population for 14 years, the parasite's lifespan, resulting in significant reductions in cases, such as a 67-91% decrease in Libya (WHO, 1995). Ivermectin works by gradually reducing microfilariae levels without triggering an inflammatory response, making it safer than other deworming drugs (Crump, 2011).

Despite its effectiveness, recent research questions the sufficiency of mass drug administration with Ivermectin for eliminating onchocerciasis. The ONCHOSIM model, developed using OCP data, showed promising results, but a 2018 study in Tanzania indicated that annual community-directed treatment with Ivermectin (CDTI) might not interrupt transmission in all high-prevalence areas (Hendy, 2018). Additionally, evidence suggests that the parasite can develop resistance to Ivermectin. Lustigman et al. found an increase in worms with the b-tubulin heterozygote genotypes after treatment, linked to resistance in other parasitic nematodes (Lustigman, 2007). This raises concerns about a potentially resistant strain of *Onchocerca volvulus* spreading in endemic regions.

Given the potential for Ivermectin resistance, alternative treatments are essential. Doxycycline, an antibiotic that targets the symbiotic bacteria *Wolbachia*, effectively starves the nematodes. Moxidectin, similar to Ivermectin but with a longer half-life, shows promise in reducing microfilariae levels. Researchers are also exploring combination therapies, including antibiotics and antifilarial drugs, to inhibit parasite development and reproduction. These alternatives aim to overcome the limitations of current treatments and enhance efforts to eradicate onchocerciasis.

In this research project, we developed a mathematical model to understand the dynamics of onchocerciasis transmission, the impact of Ivermectin resistance, and the effectiveness of alternative treatments. Our primary goal was to evaluate whether the current mass drug administration with Ivermectin could meet the WHO's eradication objectives. We addressed questions like, "Is the current treatment strategy sufficient for eradication?" and "What is the potential impact of Ivermectin resistance?" Additionally, we explored the feasibility of doxycycline as an alternative or supplementary treatment. We constructed differential equation models incorporating biological and epidemiological factors, conducted simulations, and analyzed the basic reproductive number (R_0) for different treatment scenarios.

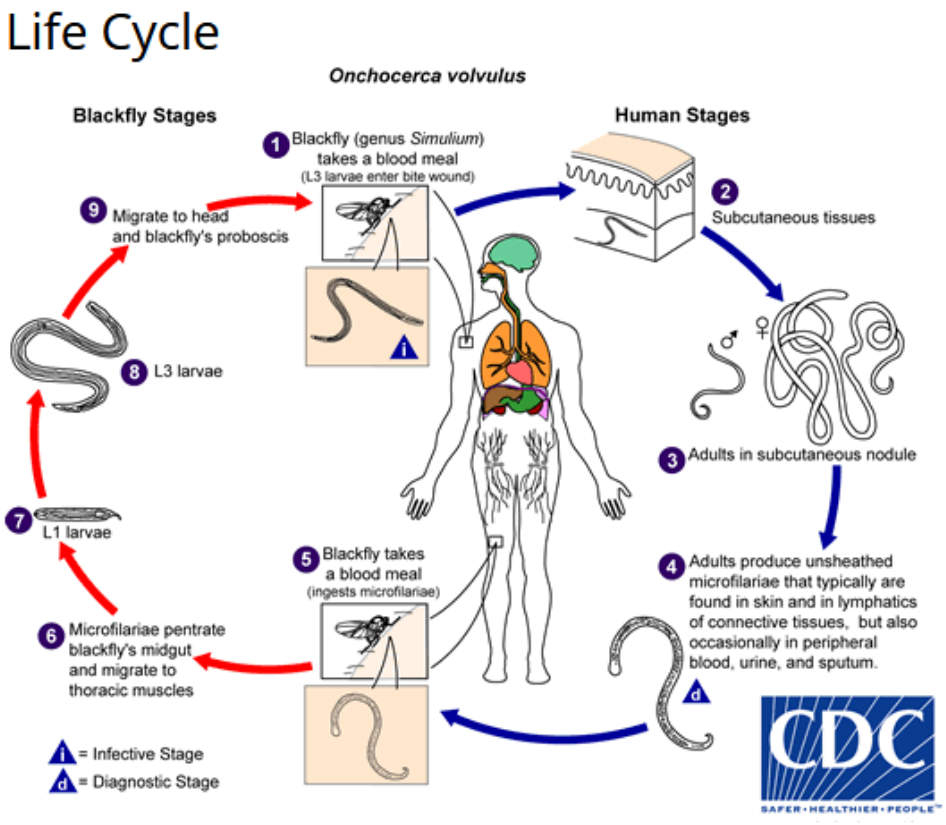


Fig 1. This describes the life cycle of the parasite (*Onchocerca volvulus*). *(CDC,2017)*

2. Model Development

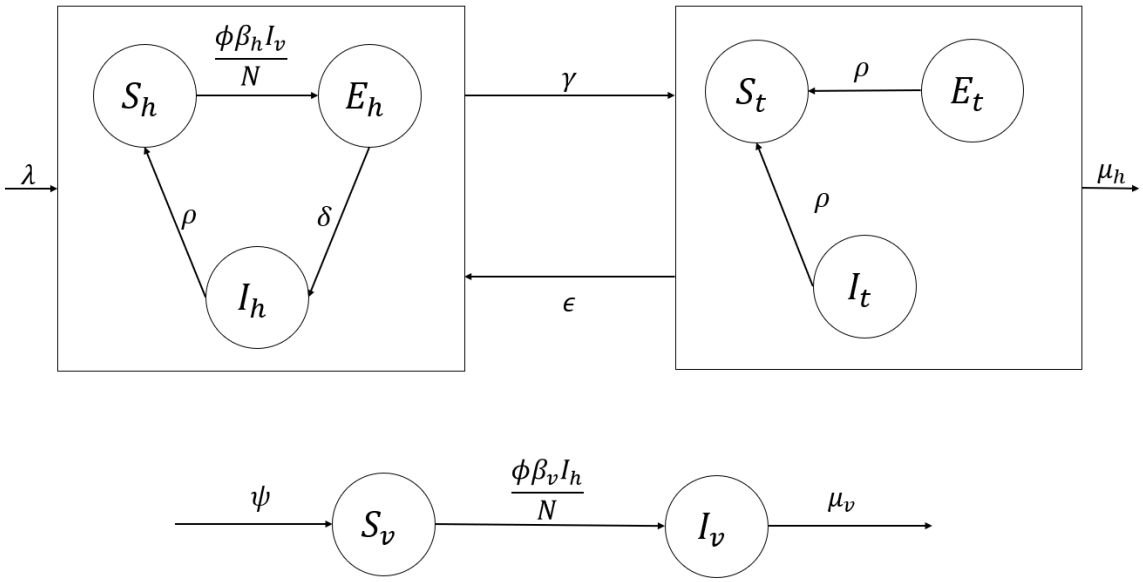


Fig 2. Flow diagram of the ODE model without resistance.

In developing of the model, it was crucial to consider the unique characteristics of the disease and its transmission dynamics. The disease does not spread through physical contact between individuals, but rather through transmission to flies by the infected host. Furthermore, recovery from the disease is only possible through proper treatment and there is no appropriate immunity given once off the treatment. With this information in mind, a Susceptible-Infected model that accurately captures the spread of the disease without the need for a recovered class explicitly. Therefore, a framework that is tailored to the specific dynamics of the disease is developed, ensuring that our model is both accurate and effective in informing future research and prevention efforts.

Following that framework seen in Figure 2, there are three classes for the human population which would govern how the disease spreads. The first would be a susceptible host population (S_h), the population of people that aren't infected but are still able to get infected. This class would have a normal birthrate λ, a death rate μ_h, and an infection parameter. This infection parameter would include a biting rate ϕ, an infection rate for the host β_h, the total number of infected flies I_v, and is dependent on the total population.

When a person gets infected, they would move to an exposed class via the infection parameter. They would not move directly to an infected class because it takes approximately six months to show symptoms. Hosts can only pass the disease to flies when they exhibit symptoms. This waiting period is represented by the parameter δ and this class will have a natural death rate μ_h. After the parasites die the people in this class go back to susceptible which is represented by the parameter δ. Infected hosts also have a natural death rate μ_h.

The treated classes are similar to host classes however it is assumed you cannot get infected while receiving treatment. This also partly extends to progression of symptoms as well. Host classes gain treatment at a rate γ and go off treatment at a rate ϵ. Both the host and treated classes will also have a rate of recovery present within the exposed and infected classes. This is represented as the parameter ρ which mean E_t go back into the either the susceptible host or treated class. The susceptible treated class also does not have a birth rate because it is assumed they do not receive treatment when they are born.

The vectors (Black flies) are similar to the host but without the exposed class since the flies do not have to wait six months to pass the disease along. Susceptible vectors (S_v) are born at a rate ψ, are infected at a rate that depends on the biting, ϕ and the infection parameter β_v. Vectors may become infected from both I_h and E_t, but at a reduced rate ρ from the exposed treated hosts. Infected hosts on Ivermectin cannot spread the disease to vectors as the treatments kill off the microfilaria soon after treatment. The vectors have a natural death rate μ_v.

The equations are given by:

Phase with treatment

$$S_h' = \lambda - \frac{\phi\beta_h I_v}{N} S_h - (\gamma + \mu_h) S_h + \varepsilon S_t + \rho I_h$$

$$E_h' = \frac{\phi\beta_h I_v}{N} S_h - (\delta + \mu_h + \gamma) E_h + \varepsilon E_t$$

$$I_h' = \delta E_h - (\gamma + \mu_h + \rho) I_h + \varepsilon I_t$$

$$S_t' = \gamma S_h - (\varepsilon + \mu_h) S_t + \rho (E_t + I_t)$$

$$E_t' = \gamma E_h - (\varepsilon + \mu_h + \rho) E_t$$

$$I_t' = \gamma I_h - (\rho + \varepsilon + \mu_h) I_t$$

$$S_v{}' = \psi - \frac{\phi\beta_v I_h}{N} S_v - \mu_v S_v$$

$$I_v' = \frac{\phi\beta_v I_h}{N} S_v - \mu_v I_v$$

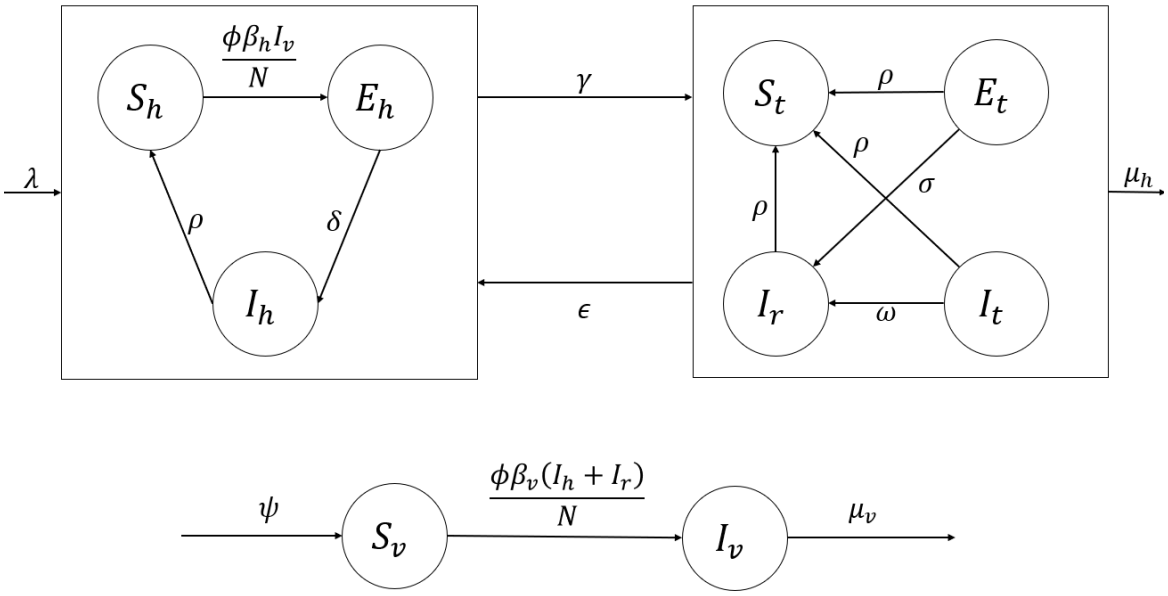


Fig 2. Flow diagram of the ODE model with resistance.

In the next phase, resistance is introduced into the treatment model. It is assumed that resistance only arises while a host is being treated. Resistance only affects the individuals if they are infected and currently on treatment. This ultimately means only the I_t and E_t classes will be affected with this change. The E_t class does not have any physical changes but when its population progresses and leaves the class those people will be split into those that develop resistances and those that do not, represented by the parameter σ.The I_t class will also have its own parameter which is the rate of resistance developing ω. The E_t and I_t classes are separated as the chance for developing resistance should be significantly higher in the I_t class compared the E_t ($\sigma < \omega$) class because I_t should have significantly more parasites that can develop resistance.

$$Resistance\ Phase$$

$$S_h' = \lambda - \frac{\phi\beta_h I_v}{N} S_h - (\gamma + \mu_h) S_h + \varepsilon S_t + \rho I_h$$

$$E_h' = \frac{\phi\beta_h I_v}{N} S_h - (\delta + \mu_h + \gamma) E_h + \varepsilon E_t$$

$$I_h' = \delta E_h - (\gamma + \mu_h + \rho) I_h + \varepsilon I_t$$

$$S_t' = \gamma S_h - (\varepsilon + \mu_h) S_t + \rho(E_t + I_t + I_r)$$

$$E_t' = \gamma E_h - (\varepsilon + \mu_h + \rho + \sigma) E_t$$

$$I_t' = \gamma I_h - (\rho + \varepsilon + \mu_h + \omega) I_t$$

$$I_r' = \sigma E_t + \omega I_t - (\mu_h + \rho) I_r$$

$$S_v' = \psi - \frac{\phi\beta_v (I_h + I_r)}{N} S_v - \mu_v S_v$$

$$I_v' = \frac{\phi\beta_v (I_h + I_r)}{N} S_v - \mu_v I_v$$

All parameters values and their descriptions are given in Table 1.

Table 1:

List of parameters for the Onchocerciasis model.

Parameter	Description	Value	Units	Reference
μ_h	Death rate of hosts	0.022	$year^{-1}$	[17]
μ_v	Death rate of vectors	0.8	$year^{-1}$	[1]
ɣ	Gain of treatment	0.5	$year^{-1}$	[2]
ϵ	Loss of treatment	Varies	$year^{-1}$	
δ	Progression of symptoms for exposed class	2	$year^{-1}$	[4]
Φ	Biting rate of vectors	1.10	$\frac{bites}{flies}$	[3]
ρ	Rate of recovery of treated infectious host	0.0833	$year^{-1}$	[4]
λ	Birth rate of host	403,358	$\frac{People}{year}$	[4]
ψ	Birth rate of vectors	1,393,228,383	$\frac{flies}{year}$	[1]
βh	Infection rate for hosts	0.2	$year^{-1}bites^{-1}$	[18]
βv	Infection rate for vectors	0.097	$year^{-1}bites^{-1}$	[18]
N	Total number of people	Dependent on country	$people$	[19]
ω	Chance of moving from infected treated to infected resistant	0.025	$year^{-1}$	Data fitted
σ	Chance of moving from exposed treated to infected resistant	0.025	$year^{-1}$	Data fitted.
S_h	Susceptible non-treated host population		$people$	
S_t	Susceptible treated host population		$people$	
S_v	Susceptible treated vector population		$flies$	
E_h	Exposed non-treated host population		$people$	
Et	Exposed treated host population		$people$	
I_h	Infected host population		$people$	
I_t	Infected treated host population		$people$	
I_v	Infected vector population		$flies$	
I_r	Infected resistant host population		$people$	

3. Model Results

Using the equations of the model above the basic reproductive number (R_0) is derived using the next-generation methods (Van den Driesche & Watmough 2002, Diekman Hiesterbeek & Metz,1990) The basic reproductive number is defined as the number of new infections that are spawned from one infected individual in a fully susceptible population in the time they are infected. If $R_0 < 1$ then the disease-free equilibirum is stable and if $R_0 > 1$ then it is unstable. The disease free equilibrium of the treatment model and the resistance model were found using Mathematica.

In order to see verify the model, Maximum a Posteriori Estimates (MAP) data-fitting was done on the country of Cameroon using data from the WHO. Cameroon has a basic reproductive number of 7.7.

The left side of Fig 3. shows the model with treatment of 50% of the population. With an $R_0 = 1.13$ the disease will not die out and the infection persists within the population. If the treatment is increased to 100% of the population (right side of Fig 3.) then $R_0 < 1$ and the infection will eventually die out, though it would take 140 years in order to see this eradication.

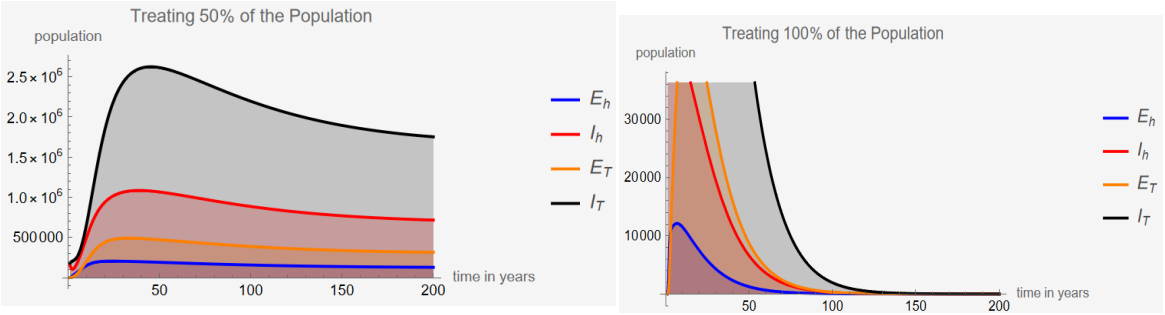


Fig 3. Left side shows simulation results for treating 50% of the population with $R_0 = 1.13$. The infection does not die out and the disease-free equilibrium is unstable. The right side shows the results if 100% of the population is treated with an $R_0 = 0.614$ and the disease dies out in 140 years. All parameters are taken from Table 1.

When resistance is added, the resistance class overtakes all other populations and $R_0 = 1.4$. So treatment with just ivermectin will not eliminate the disease according to the simulations and this model also produces a R_0 that is significantly closer to Cameroon's actual R_0 value.

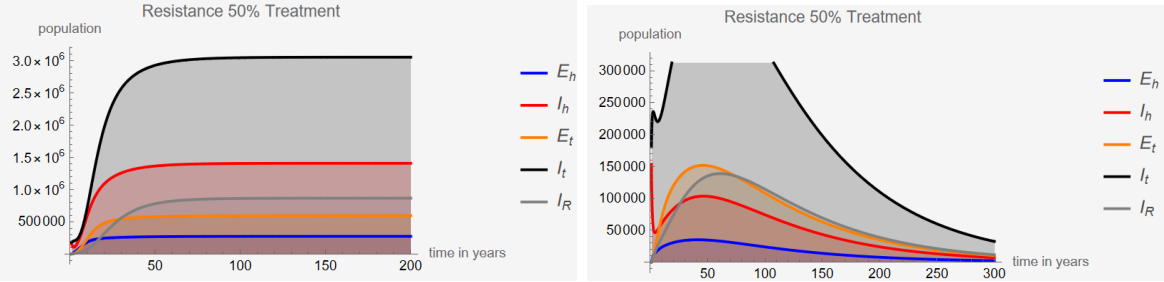
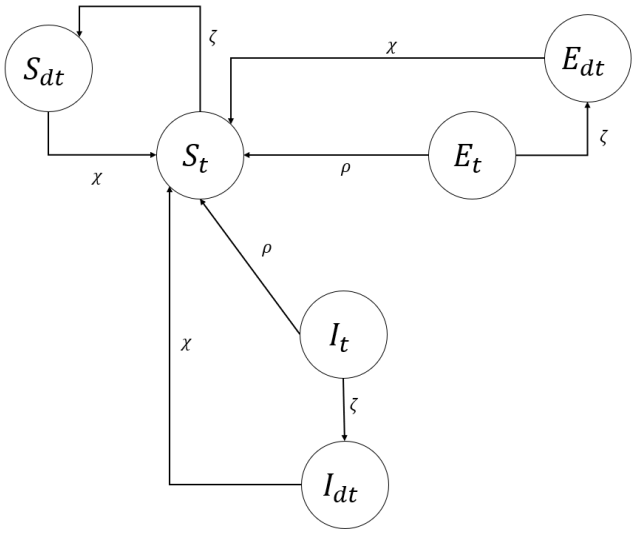


Fig 4. Left side shows simulation results for treating 50% of the population with $R_0 = 1.4$. The infection does not die out and the disease-free equilibrium is unstable. The right side shows the results if 100% of the population is treated with an $R_0 = 0.91$ and the disease dies out in 300 years. All parameters are taken from Table 1.

Alternative Treatment

The next phase of the project looked at alternative methods of treatment. The most popular alternative treatment is an antibiotic called Doxycycline. This drug kills off the bacteria Wolbachia which is a major food source of the parasite. This will starve the parasite killing them much faster than ivermectin can. The main drawbacks are the fact that this drug is an antibiotic which has its own issues with resistance and individuals must take a regimen of one dose every day for six weeks.



As Ivermectin and Doxycycline are targeting different aspects of the parasite life cycles, it might be useful to determine their effectiveness when used as a treatment together. It should be stated that it is not currently known what the side effects of taking both drugs at the same time will be. They are still being tested. To implement this treatment model, the original treatment model is used but with the addition of three new classes. These classes will be treatment with both Ivermectin and doxycycline labeled with the subscript dt for double treatment. Only the treated classes can get into the double treated class by the

parameter ζ. It is assumed that individuals must be on a treatment regimen of ivermectin first before taking doxycycline. These new classes also recovery at the doxycycline rate which will be represented by the parameter χ. The flow diagram is given above.

Below is the full double treatment model.

$$S_h' = \lambda - \frac{\phi\beta_h I_v}{N} S_h - (\gamma + \mu_h) S_h + \epsilon S_t + \rho I_h$$

$$E_h' = \frac{\phi\beta_h I_v}{N} S_h - (\delta + \mu_h + \gamma) E_h + \epsilon E_t$$

$$I_h' = \delta E_h - (\mu_h + \gamma) I_h + \epsilon I_t - \rho I_h$$

$$S_t = \gamma S_h - (\epsilon + \mu_h + \zeta) S_t + \rho(I_t + E_t) + \chi(S_{dt} + E_{dt} + I_{dt})$$

$$E_t = \gamma E_h - (\epsilon + \mu_h + \rho + \zeta) E_t$$

$$I_t = \gamma I_h - (\rho + \epsilon + \mu_h + \zeta) I_t$$

$$S_v' = \Psi - \frac{\phi\beta_v(I_h + \rho E_t)}{N} S_v - \mu_v S_v$$

$$I_v' = \frac{\phi\beta_v(I_h + \rho E_t)}{N} S_v - \mu_v I_v$$

$$S_{dt} = \zeta S_t - (\chi + \mu_h) S_{dt}$$

$$E_{dt} = \zeta E_t - (\chi + \mu_h) E_{dt}$$

$$I_{dt} = \zeta I_t - (\chi + \mu_h) I_{dt}$$

The simulations show that the disease will eventually die out after 4000 weeks, or 65 years, which is significantly faster than the ivermectin alone model. The $R_0 = 0.27$ showing the disease-free equilibrium is stable.

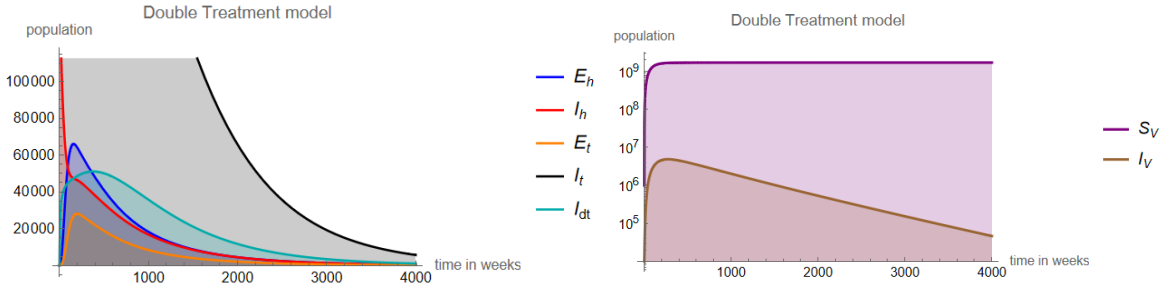


Fig 5. Simulation of the double-treatment model with parameters values from Table 2. $R_0 = 0.27$.

5. Discussion

Upon analyzing the World Health Organization's approach to combating and eliminating the spread of Onchocerciasis, it has become apparent that their current strategy is unlikely to achieve their intended goals. The analysis of the current model suggests that the best possible outcome of their current approach is merely a level of outbreak control with elimination remaining elusive. The worst-case scenario is that the WHO's efforts may inadvertently facilitate the growth of a new class of nematodes that are resistant to Ivermectin, which could quickly overtake all other classes within a few decades, as our resistance model demonstrates. Even if the WHO were able to treat a greater number of people, as demonstrated in our model, treating 100% of the population, eradication is on too long of a timeline to be feasible. The solution to this problem isn't as simple as "treat more people" because that also contains a range of issues. It will cost a significant amount of resources to buy all the medicine required to treat everyone and fund many people to go into these villages to distribute the treatment. That also does not mention a method of ensuring that everyone in the village takes the medicine once it is distributed. The gravity of the situation increases further when we consider that the analysis indicates that the resistance model most closely aligns with the current situation in Cameroon.

To try and remedy the situation, new methods of treatment were used. Doxycycline, an antibiotic drug, is showing a lot of promise in eliminating the parasite. The main appeal is that it kills the parasite in six weeks as opposed to Ivermectin's twelve to fourteen years. That being said, it is not without its major drawbacks. The model where doxycycline alone is used did not see elimination; its R_0 value was 1.18. The main factor for this was that there was a large class of untreated individuals that arose because of the frequency at which individuals had to take the drug as compared to ivermectin. Doxycycline must be taken every day for six weeks to see elimination as compared to ivermectin, which only needs to be taken twice a year. This drawback is what inspired the last model simulation, which was using both ivermectin and doxycycline together to achieve elimination. This simulation did show possible results with elimination in four thousand weeks or sixty-five years and produced the lowest R_0 value of 0.67; but it should be stated that the main drawbacks from the other simulation become even worse here. Since doxycycline is an antibiotic, resistance will arise faster in it than in Ivermectin. Theoretically, a resistance simulation of this model should produce a worse result than our normal resistance model.

This model is not without limitations. One of the primary limitations is the oversimplification of treatment dynamics. In reality, the administration of treatments such as Ivermectin and doxycycline involves complex interactions between the drug, the parasite, and the host's immune system, which are not fully captured in our model. The model assumes uniform drug efficacy and compliance across the population, while in practice, variations in drug absorption, individual health conditions, and adherence to treatment regimens can significantly influence outcomes. Additionally, the model does not account for potential side effects or the impact of co-infections, which can alter the effectiveness of the treatments. The resistance dynamics are also simplified, assuming a uniform rate of resistance development, whereas in reality, genetic variations in the parasite

population and environmental factors can cause heterogeneous resistance patterns. These simplifications may lead to an over- or underestimation of the treatment's impact and the time required for disease eradication, highlighting the need for more comprehensive models that incorporate these complexities.

Of course, this model is not without its limitations. The first and biggest problem is the aspect of resistance. Resistance is one of the biggest factors this paper has estimated to be the reason why elimination is currently not possible. Not only did this model not consider resistance in this model, but resistance should occur faster in this model than in the Ivermectin models because resistance to antibiotics occurs faster than resistance to antiparasitic because bacteria reproduce a lot faster than nematodes. The side effects of taking the two drugs together were not considered in this model. The treatment dynamics were oversimplified in this model as well since it was assumed that treatment would work similarly to how treatment occurs with Ivermectin when in reality the level of loss of treatment should be the same as the doxycycline model.

6. Conclusion and Future Work

In this research project, we set out to investigate the neglected tropical disease onchocerciasis and identify the main factors preventing its elimination. Our findings suggest that resistance to Ivermectin is a significant barrier to achieving eradication, even with mass drug administration efforts in the afflicted regions. The mathematical models we developed indicate that while Ivermectin is effective in reducing the prevalence of onchocerciasis, it may not be sufficient to eliminate the disease entirely, especially in areas with high transmission rates and potential drug resistance.

Furthermore, our exploration of alternative treatments, such as doxycycline, showed promise in addressing some of the limitations of Ivermectin. By targeting the symbiotic bacteria *Wolbachia*, doxycycline can effectively reduce the nematode population more rapidly. However, this approach also has drawbacks, including the need for a prolonged treatment regimen and the potential for developing antibiotic resistance.

Our research also highlighted the potential benefits of combination therapies, utilizing both Ivermectin and doxycycline to achieve a more effective and faster reduction in the parasite population. The double-treatment model demonstrated that combining these drugs could significantly reduce the basic reproductive number (R_0) and hasten the eradication process.

Despite these promising results, our model has limitations that must be addressed in future work. The oversimplification of treatment dynamics, uniform drug efficacy assumptions, and lack of consideration for co-infections and individual health variations indicate the need for more comprehensive models. Future research should focus on refining these

models to incorporate the complexities of drug interactions, resistance mechanisms, and population heterogeneity.

Additionally, future work should involve data fitting our parameters to current and more comprehensive datasets from the World Health Organization and other health agencies. This will help validate our models and ensure they accurately reflect real-world scenarios. Further investigations should also explore the socio-economic factors influencing treatment adherence and the feasibility of large-scale implementation of alternative and combination therapies.

In conclusion, while our research provides valuable insights into the challenges of eradicating onchocerciasis and the potential of alternative treatments, continued efforts are necessary to refine our models and develop more effective strategies. By addressing the limitations of current approaches and exploring innovative solutions, we can make significant strides towards the ultimate goal of eliminating onchocerciasis as a public health threat.

REFERENCES

1. Mullen, Gary R., and Lance A. Durden. *Medical and Veterinary Entomology*. 3rd edition, Charlotte Cockle, 2018, pp. 237–256.

2. "Onchocerciasis." *WHO | World Health Organization*, 11 2022, https://www.who.int/news-room/fact-sheets/detail/onchocerciasis#:~:text=The%20African%20Programme%20for%20Onchocerciasis,the%20transition%20to%20onchocerciasis%20elimination.

3. B. Boatin (2008) The Onchocerciasis Control Programme in West Africa (OCP), Annals of Tropical Medicine & Parasitology, 102:sup1, 13-17, DOI: 10.1179/136485908X337427

4. WHO Expert Committee on Onchocerciasis Control (1993: Geneva, Switzerland) & World Health Organization. (1995). Onchocerciasis and its control: report of a WHO Expert Committee on Onchocerciasis Control. World Health Organization

5. A. SÉKÉTÉLI, G. ADEOYE, A. EYAMBA, E. NNORUKA, P. DRAMEH, U. V. AMAZIGO, M. NOMA, F. AGBOTON, Y. AHOLOU, O. O. KALE & K. Y. DADZIE (2002) The achievements and challenges of the African Programme for Onchocerciasis Control (APOC), Annals of Tropical Medicine & Parasitology, 96:sup1, S15-S28, DOI: 10.1179/000349802125000628

6. Plaisier, A. P. (1996). *Modelling Onchocerciasis Transmission and Control*. Rotterdam: Erasmus Universiteit, Instituut Maatschappelijke Gezondheidszorg, 1996.

7. Plaisier, A. P., et al. "ONCHOSIM: A Model and Computer Simulation Program for the Transmission and Control of Onchocerciasis." *Computer Methods and Programs in Biomedicine*, no. 1, Elsevier BV, Jan. 1990, pp. 43–56. *Crossref*, doi:10.1016/0169-2607(90)90030-d.

8. Oguoma, I. C., & Acho, T. M. (2014). Mathematical modelling of the spread and control of onchocerciasis in tropical countries: Case study in Nigeria. *Abstract and Applied Analysis*, *2014*, 1–12. https://doi.org/10.1155/2014/631658

9. Turner, H. C., Walker, M., Churcher, T. S., & Basáñez, M.-G. (2014). Modelling the impact of ivermectin on river blindness and its burden of morbidity and mortality in African Savannah: Epioncho projections. *Parasites & Vectors*, *7*(1), 241. https://doi.org/10.1186/1756-3305-7-241

10. Crump, Andy & Ōmura, Satoshi. (2011). Ivermectin, 'Wonder drug' from Japan: The human use perspective. Proceedings of the Japan Academy. Series B, Physical and biological sciences. 87. 13-28. 10.2183/pjab.87.13.
11. Omade, Shaib Ismail, et al. "Mathematical Modeling of River Blindness Disease with ..." Mathematical Modeling of River Blindness Disease with Demography Using Euler Method, 2015, www.iiste.org/Journals/index.php/MTM/article/download/22427/22740

12. Filipe, J. A. N., Boussinesq, M., Renz, A., Collins, R. C., Vivas-Martinez, S., Grillet, M.-E., Little, M. P., & Basanez, M.-G. . (2005). Human infection patterns and heterogeneous exposure in river blindness. *Proceedings of the National Academy of Sciences*, *102*(42), 15265–15270. https://doi.org/10.1073/pnas.0502659102

13. Basa¨·ez, M.-G., & Boussinesq, M. (1999). *Population biology of human onchocerciasis*. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1692549/pdf/10365406.pdf

14. Hendy, A., Krüger, A., Pfarr, K., De Witte, J., Kibweja, A., Mwingira, U., Dujardin, J.-C., Post, R., Colebunders, R., O'Neill, S., & Kalinga, A. (2018). The blackfly vectors and transmission of Onchocerca volvulus in Mahenge, southeastern Tanzania. *Acta Tropica*, *181*(181), 50–59. https://doi.org/10.1016/j.actatropica.2018.01.009

15. Taylor, M. J., Hoerauf, A., Townson, S., Slatko, B. E., & Ward, S. A. (2014). Anti-Wolbachia drug discovery and development: safe macrofilaricides for onchocerciasis and lymphatic filariasis. *Parasitology*, *141*(1), 119–127. https://doi.org/10.1017/S0031182013001108

16. Lustigman, S., & McCarter, J. P. (2007). Ivermectin resistance in Onchocerca volvulus: Toward a genetic basis. *PLoS Neglected Tropical Diseases*, *1*(1). https://doi.org/10.1371/journal.pntd.0000076

17. *Cameroon Death rate, 1950-2021 - knoema.com*. (2021, June). Knoema. https://knoema.com/atlas/Cameroon/Death-rate#:~:text=Cameroon%20%2D%20Crude%20death%20rate&text=In%202020%2C%20death%20rate%20for,per%201%2C000%20people%20in%202020.

18. Hassan, A., & Shaban, N. (2020). Onchocerciasis dynamics: Modelling the effects of treatment, education, and Vector Control. *Journal of Biological Dynamics*, *14*(1), 245–268. https://doi.org/10.1080/17513758.2020.1745306

19. World Health Organization. (n.d.). *Preventive chemotherapy*. World Health Organization. Retrieved July 2021, from https://www.who.int/data/preventive-chemotherapy

20. Center For Disease Control. (2017, December 14). *CDC - DPDx - Onchocerciasis*. Centers for Disease Control and Prevention. https://www.cdc.gov/dpdx/onchocerciasis/index.html

21. *Climate change and infectious diseases | What We Do | NCEZID | CDC*. (n.d.). Centers for Disease Control and Prevention. Retrieved February 25, 2023, from https://www.cdc.gov/ncezid/what-we-do/climate-change-and-infectious-diseases/index.html