

Is There a Worm on That Branch?

Predicting Extinction of Filarial Worm Infections

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Elimination of infectious diseases

The year 2019 marks a number of important anniversaries: 75 years since D-Day, 50 years since both the Stonewall riots and the first moon landing and 30 years since the fall of the Berlin Wall. It also marks 40 years since the global eradication of smallpox – the first infectious disease to be driven extinct by modern medicine. Prior to eradication, smallpox had existed for at least 3000 years and, with up to a 30% mortality rate, was considered one of the most feared human diseases in the world. Now, thanks to a global vaccination campaign, the virus is believed to exist only in two secure laboratories and there have been no reported cases since 1978.

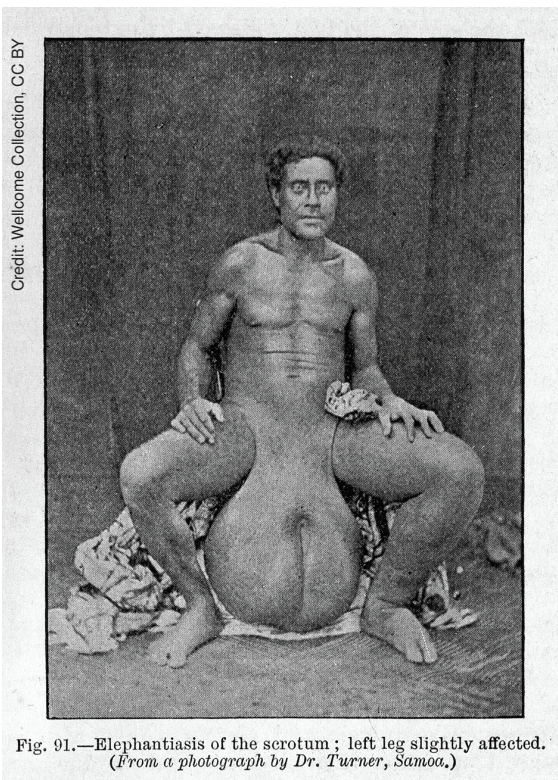


Figure 1: A depiction of scrotal enlargement caused by lymphatic filariasis in a patient in Samoa in the early 1900s.

The success of the smallpox programme led to an increase in discussions about the eradication of other diseases, such as polio, mumps and guinea worm. In 1993, The Carter Center, a not-for-profit organisation founded in 1982 by former US President Jimmy Carter, published a report declaring six diseases, including these three, as potentially eradicable with existing tools. Malaria eradication, previously abandoned after being unsuccessfully targeted in the 1950s and 1960s, also made a return to the global health agenda in 2008. Whilst the only other disease to join smallpox in the last 40 years has been rinderpest, a livestock disease eradicated in 1999, there has been some significant progress. Notably, global efforts have brought cases of guinea worm down from almost 100 000 in 1993 to only 30 in 2017.

Lymphatic filariasis was one of the diseases earmarked for eradication in 1993. Colloquially known as elephantiasis, lymphatic filariasis is a mosquito-transmitted worm infection that can cause lasting and debilitating disability if left untreated (Figure 1). Although reliable written records of the disease date back only to the 16th century, historians argue it has been around for a lot longer. Due to the distinctive nature of some disease symptoms, such as the severe swelling of limbs, there are ancient artefacts dating all the way back to Pharaoh Mentuhotep II's reign over Ancient Egypt around 2000 BCE that potentially provide evidence of filariasis in the ancient world (Figure 2).



Figure 2: Pharaoh Mentuhotep II. His swollen legs are characteristic of lymphatic filariasis.

Four thousand years later, in 2000 CE, infection was still widespread across tropical regions, with 120 million people estimated to be at risk. Due to over 7 billion treatments being delivered through mass drug administrations (MDA, where large proportions of the population are treated at the same time, usually yearly), the number of infected people is thought to have lowered substantially since the millennium, with 14 countries having been validated as reaching less than 1% prevalence across their endemic regions [1, 2].

The question which now faces the Global Programme to Eliminate Lymphatic Filariasis (GPELF) is whether and where lymphatic filariasis is likely to be eliminated once this low level of infection is achieved. The mathematical literature on infectious diseases has been crucial in informing the discussion on eliminating infections, and a number of challenges remain [3]. Here we address the particular challenges of modelling the elimination of a sexually reproducing parasite which is transmitted by a mosquito.

Lymphatic filariasis elimination

Evidence from an elimination campaign in China suggested that once the prevalence of lymphatic filariasis fell below 1%, infection did not re-emerge [4]. Whilst it was acknowledged that this was data from only one location, it was a key piece of evidence in support of the global programme's choice to set their long-term goal of elimination. The empirical data has shifted again recently, with evidence of ongoing transmission in Sri Lanka and Samoa,

even once this prevalence has been reached and maintained for several years [5].

Lymphatic filariasis is a worm infection, in which both male and female worms must infect the same host to reproduce and cause onward transmission. As with all parasites of this type, there is a classically skewed distribution of the number of worms across hosts, with some people hosting many more worms than average. In the 1980s, as summarised in their well-known book, Anderson and May formulated a classic deterministic model and illustrated a key feature of this system – the elimination breakpoint [6]. As transmission increases (e.g. the number of mosquito bites increases) the system develops a stable equilibrium mean worm burden, which increases with the transmission rate. However, the system also has an unstable equilibrium for low worm burdens at the same transmission rate (Figure 3). This unstable equilibrium acts as a breakpoint, where transmission cannot be maintained if disease levels fall below this point.

According to this theory, the lymphatic filariasis breakpoint could lie at prevalence levels of much less than 1 in 1000 or 1 in 10 000 infected individuals [7]. Such low prevalence is extremely hard to measure and requires practically implausible sample sizes for a large-scale programme. Therefore there has, for a long time, been a disconnect between the mathematical and empirical data on this process.

Once infection levels are low, we know that stochastic processes become important, and it is likely that the transmission process may fade out to extinction from levels much above those of the breakpoint. Here we outline how a branching process approach, which takes account of key parts of the life cycle, can help us estimate whether and when lymphatic filariasis is likely to be eliminated once prevalence drops below 1%. This approach is informed by work on related worm infections by Cornell et al. [8].

Branching process extinction

The most common branching process formulation is the Galton–Watson process, which we outline here before adapting it for lymphatic filariasis (Figure 3, right).

Let X_n denote the number of infectious individuals in generation n and for each infectious individual, i , let $Z_{n,i}$ be the number of new infectious cases directly caused by that individual. $Z_{n,i}$ are independent and identically distributed random variables over $n \in 0, 1, 2, \dots$ and $i \in 1, \dots, X_n$.

Assuming we start a chain of infection with one infectious individual, $X_0 = 1$, we then have the recurrence equation,

$$X_{n+1} = \sum_{i=1}^{X_n} Z_{n,i}. \quad (1)$$

The extinction probability of one chain of infection is the probability that $X_n = 0$ for some $n > 0$, or that $\lim_{n \rightarrow \infty} P[X_n = 0]$.

Define p_m ($m = 0, 1, 2, \dots$) as the probability of an individual producing m offspring and d_m as the probability of extinction by the m th generation; $d_0 = 0$ as we start with one individual in generation 0. Hence d_m is an increasing, bounded sequence ($0 = d_m \leq d_1 \leq d_2 \leq \dots \leq 1$) and therefore converges to some limit, d , where $0 \leq d \leq 1$ is the ultimate extinction probability.

$$d_1 = p_0 \quad (2)$$

$$d_2 = p_0 + \sum_{j=1} p_j (d_1)^j \quad (3)$$

...

$$d_m = p_0 + \sum_{j=1} p_j (d_{m-1})^j. \quad (4)$$

We can write this as

$$d_m = f(d_{m-1}) \quad (5)$$

where f is the ordinary generating function:

$$f(d) = p_0 + \sum_{j=1} p_j d^j. \quad (6)$$

Since $d_m \rightarrow d$, we can find the probability of ultimate extinction by solving $d = f(d)$.

We want to show that d is the smallest non-negative root of this equation. Take $b > 0$ also a root with $b \neq d$ and $b = f(b)$, then we have that $d_1 = f(0) \leq f(b) = b$, hence $d_1 \leq b$. Assume $d_k \leq b$ for some k , then

$$d_{k+1} = f(d_k) \leq f(b) = b, \quad (7)$$

since f is an increasing function. Hence, by induction d is the smallest non-negative root. The function, f , is also convex and

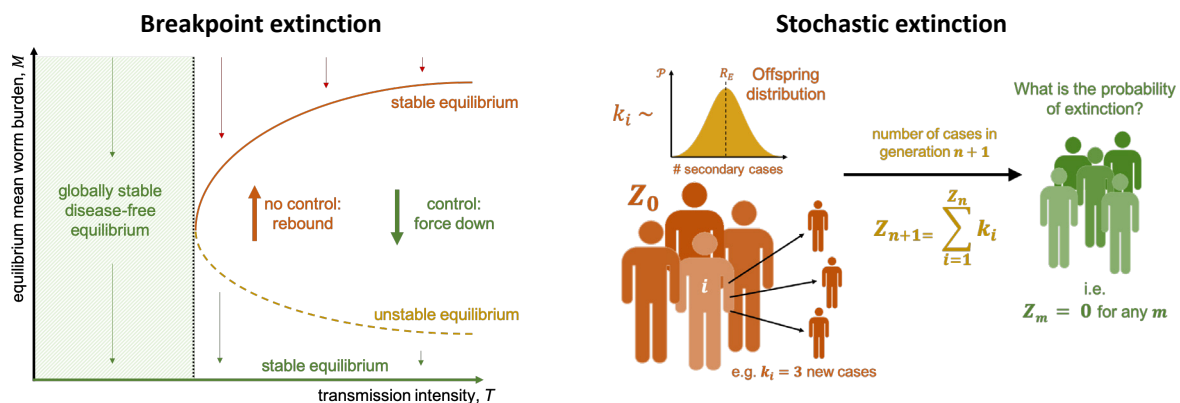


Figure 3: Theory behind elimination of a macro-parasite infection. In the deterministic system (left), if transmission is high enough then there is an endemic equilibrium and an unstable equilibrium, or breakpoint – a mean worm burden that cannot sustain transmission. In the branching process representation of the system (right), each infectious individual has a probability of infecting a certain number of others and this is used to give a probability that the infection will fade out.

hence has at most two real roots. Since one is always a root, $f(1) = \sum_{j=0} p_j = 1$, then the probability of ultimate extinction is only less than one if the second root both exists and lies between zero and one.

By considering the gradient of f at one, $f'(1) = \sum_{j=1} j p_j$, we can determine the location of the other root – namely there is only a second root in $[0, 1]$ if $f'(1) > 1$. Notably this gradient, $f'(1)$, is equal to the average number of secondary cases caused by a single infectious individual, often called the basic reproduction number to describe early outbreak dynamics. Since we are considering a situation where there is a background population prevalence that has been artificially lowered to 1%, we call this the effective reproduction number, R_e .

In our model (further details below), we want to take account of the heterogeneous worm distribution across hosts, as it is a key feature of the system. Therefore, it is not possible to directly calculate either the effective reproduction number or the probability of extinction, but both can be calculated numerically by considering the outcome distributions of stochastic simulations. In particular, by calculating the proportion of simulated individual infections that result in each number of onward infections, we can generate a discrete numerical approximation of our secondary case offspring probability distribution.

From this, we can iterate through each generation to find the probability that extinction has occurred. This probability converges over time and, if sufficient generations are considered, can be used to approximate the ultimate extinction probability, d .

Lymphatic filariasis model

To estimate the extinction probability for lymphatic filariasis, we simulate a population of 1000 individuals, with variable infection risk, of whom 1% are productively infected (producing transmissible offspring, microfilaraemia, mf), a proportion are unproductively infected and the remainder are uninfected (Figure 4).



Figure 4: The population of infected and uninfected individuals, with their variable risk of infection shown by shading.

We then calculate, for a randomly infected individual, the number of onward productive infections they produce according to a model of the life cycle (Figure 5). An infection lasts for a randomly selected period of time (exponential, mean $1/r$, the estimated fecund lifespan, 6 years), and has a lifespan equal to the mean human life expectancy. This individual has a risk of being

bitten relative to the rest of the population (gamma, mean = 1), which, depending on the annual bite rate (ABR), the expected number of bites per human per year, generates the expected number of bites received during their infectious period. For each bite, there is a probability, c , that the mosquito becomes infected.

Each mosquito then has an exponentially distributed life expectancy (mean $1/g$, 6.9 days) and has to survive an incubation period (also exponential, mean = ν , 8.5 days). From this we can derive the probability a mosquito survives to infectiousness and, using a binomial distribution, calculate the total number of infected mosquitoes, V , which survive the incubation period. The number of infectious bites caused by these mosquitoes is then Poisson distributed at a daily rate, $f = 0.335$, per mosquito, and of these bites only a small proportion, $b \ll 1$, will successfully lead to a productive infection. The efficacy of transmission from mosquito to host is so low due to the route the larvae must take to establish; rather than being injected into the bloodstream during the bite, the larvae must instead independently fall onto the skin and find the hole left by the mosquito after feeding.

This describes the number of new adult worms Y , that are established in humans resulting from the entire duration of this one individual's infection (one distinct outcome per iteration, creating a distribution). From the total number of new adult worms, Y , we can derive the effect on prevalence by sampling Y individuals, with replacement, according to bite risk. Each time an individual is sampled they gain 1 adult worm. We then compare new worm burdens with previous worm burdens – how many new infectious (≥ 2 worms) cases are there that were previously not infectious (≤ 1 worm)? This gives our number of secondary infections, Z .

Then the mean number of new infectious cases is R_e . If $R_e < 1$ then eventual extinction will occur – implying that prevalence is below the theoretical system breakpoint. However, if $R_e > 1$ then extinction is not guaranteed but may still occur. We need to consider the offspring distribution of the branching process, p_j being the probability of having j secondary cases, which we approximate by the scaled frequency of secondary infectious case counts, in order to calculate the probability of extinction.

Extinction probability

Using these simulations, we can characterise the probability of extinction from a starting condition of 1% prevalence (Figure 6, orange). When the ABR is low, then infection is highly likely to fade out, but this probability declines as the biting rate increases. This emphasises the importance of local context in determining the extinction probability from this endpoint. We additionally simulated the curve for a halving of the endpoint – a prevalence of 0.5%. This, of course, increases the probability of extinction, but would require much larger sample sizes to evaluate.

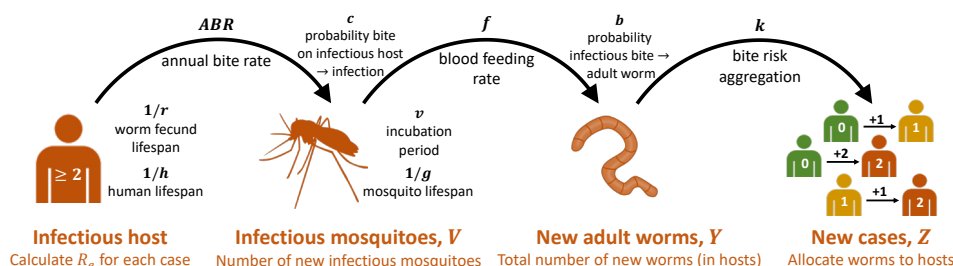


Figure 5: Model of the transmission cycle of lymphatic filariasis.

$$R_e = \Sigma(\text{new})$$

Effective reproductive ratio
The average number of secondary infectious cases caused by one infectious individual

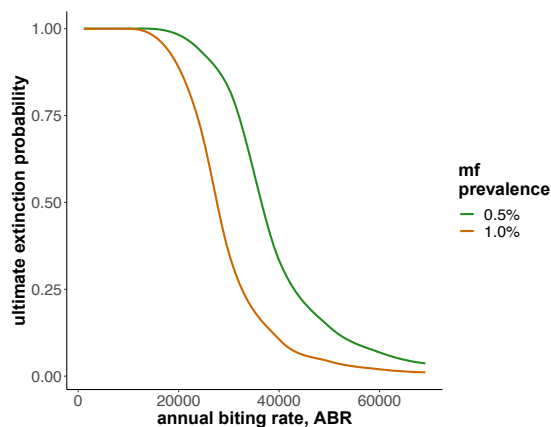


Figure 6: The probability that transmission will become extinct for different ABRs and different starting prevalences.

So, what are realistic biting rates in endemic areas? There are remarkably few estimates of biting rates in lymphatic filariasis endemic areas, with the majority coming from malaria endemic areas (some of the same mosquitoes transmit malaria). However, it is likely that while the majority of places may have less than 10% baseline prevalence, which is related to moderate biting rates, some have very high prevalence, equating to ABRs in the 10 000 range upwards [7, 9].

In addition to the ABR, we know that locations vary in terms of the characteristics of the mosquitoes and also in how skew the distribution of worms is between people. Again, we have remarkably few measurements from which to evaluate these parameters, suggesting that there is much uncertainty in these estimates.

Implications

These analyses lead to a number of policy-relevant implications:

- *Adjusting the endpoint to local conditions:* The GPELF currently has one surveillance strategy for locations with the same mosquito and worm species. Fully tailoring strategies to local epidemiology would improve utility, but the cost of evaluating the local epidemiology is likely to far exceed that of the existing surveys, prompting the need for adaptive survey designs.
- *Adjusting the endpoint to capture variability:* Recent empirical evidence suggests the current survey does not capture ongoing transmission. By altering the survey design, through different diagnostics, measuring mosquitoes or more detailed spatial sampling, it will be possible to pick up areas of high transmission earlier.
- *Timelines:* The theory of branching processes also allows us to consider likely timelines to extinction. As we know from the deterministic model, the epidemic growth rate for a worm with a lifespan of the order of a decade is extremely slow [6]. Therefore infection can oscillate at low levels for many years before either re-emerging or fading out – a challenge that will need investment in long-term surveillance.
- *Improving biological knowledge:* Although we have not presented the details here, these methods have been used to demonstrate that variability in parameter estimates for this poorly studied disease can change extinction probabilities dramatically. This highlights the need for both refinement of the experimental evidence base and for careful selection of parameters from the literature when building models.

Concluding remarks

The elimination of an infectious disease requires a number of pieces of the puzzle to work together. Biological plausibility, usually due to the availability of a particular tool, such as a vaccine, or drugs donated for MDA, together with political will and funding at all levels, are essential parts of the puzzle. Mathematical modelling can inform our understanding of the biological plausibility, identifying important drivers of success and informing the design of not only interventions, but how targets are set, measured and evaluated.

In the case of lymphatic filariasis, hopes for elimination in the coming decades are high. The slow epidemic growth rate, the lack of amplification in the mosquito (a mosquito can only transmit as many worms as they ingest, usually fewer), the low probability of infection of a host and the hope that global development will improve the living conditions of those exposed to these diseases mean that there are many reasons to expect that elimination is possible. The branching process presented here, whilst mathematically relatively straightforward, provides a practical basis for informing policy discussions. In particular, it shows that there are likely to be many areas where additional interventions and surveys may be needed. In these areas mathematical and statistical modelling in its many forms will continue to be central to discussions on how to identify, manage and control infection.

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