Modelling Macroparasitic Diseases

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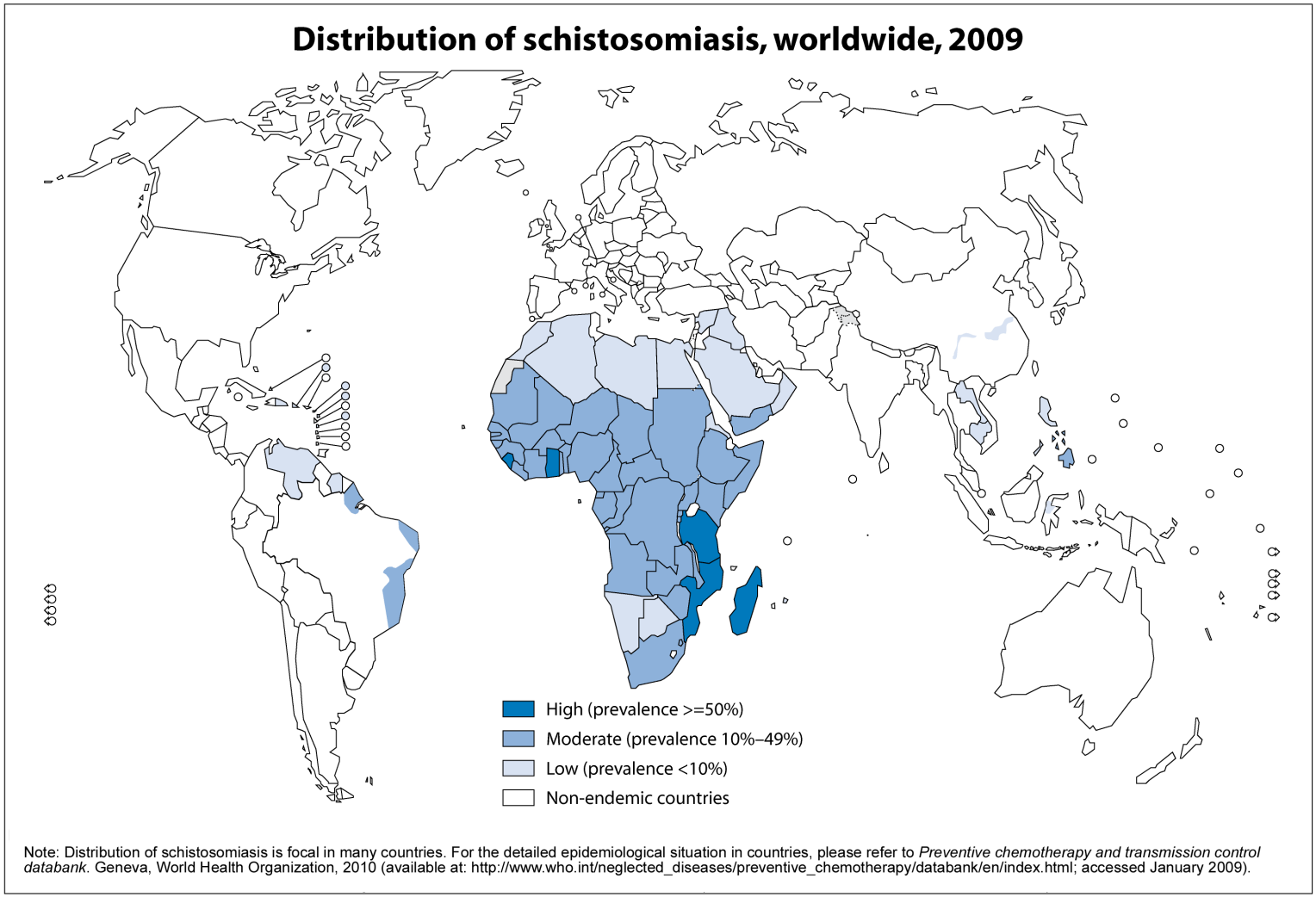
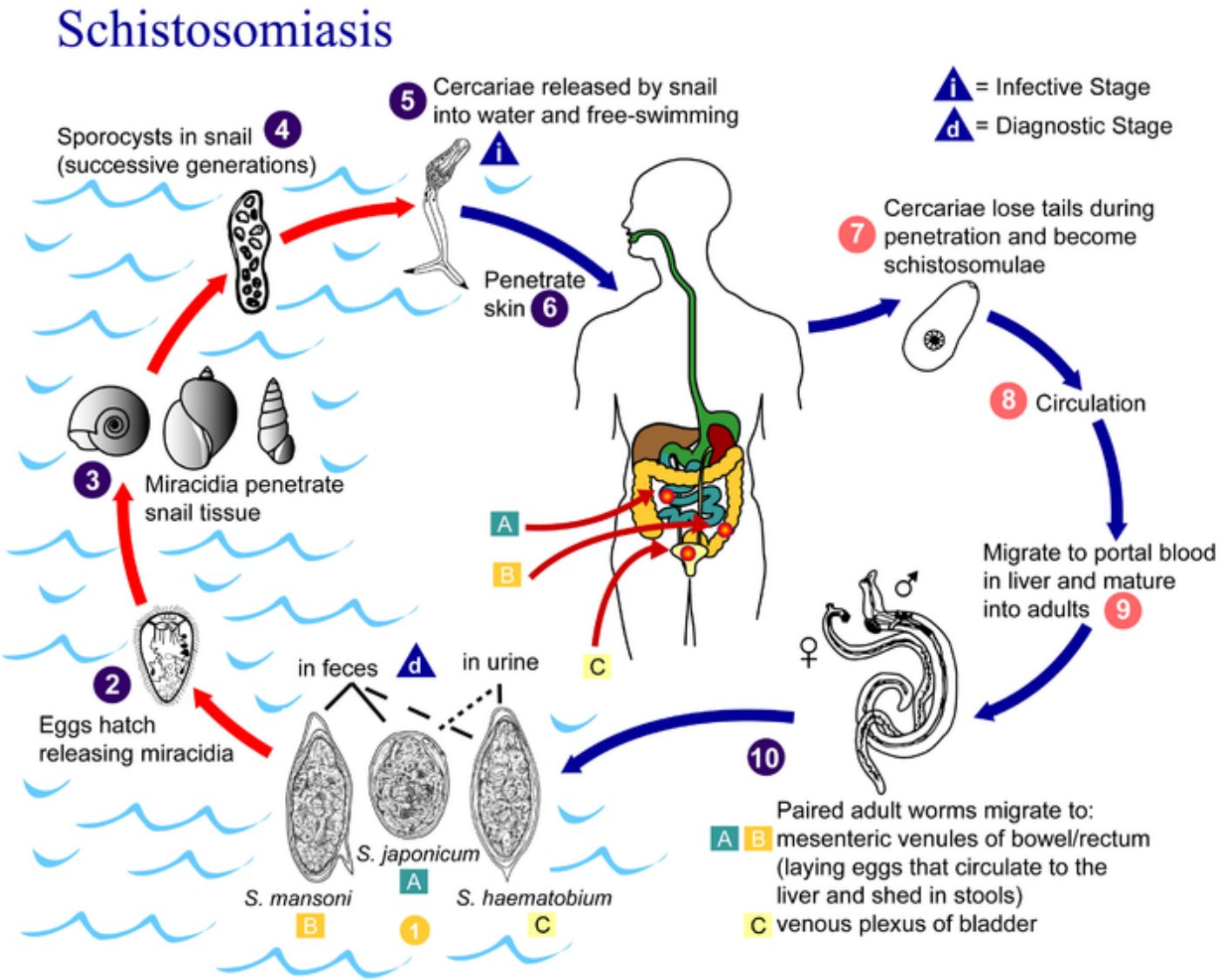
- We will focus on schistosomiasis, which effects around 300 million people worldwide, contributing to around 200,000 deaths per year.
- Symptoms include abdominal pain, blood in urine/stool, diarrohoea. Long term it causes damage to internal organs, anaemia, stunted growth, reduced cognitive ability.

Schistosomiasis distribution



Schistosomiasis life-cycle



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- Worm *burden* as well as infection needs to be considered. How do we do this?
- Lets start off by considering a population of human hosts of constant size N.
- Let $p_i(t)$ denote the probability that a human host is carrying i adult worms at time t
- The mean adult worm burden is just $M(t) = \sum ip_i(t)$

Modelling - Initial considerations

- Humans are infected by juvenile worms. Supposing there are $L(t)$ of them, the rate of contact/infection per person is β, and they take a time τ_1 to become adults during which they die at rate d_1, then

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- Lets assume that humans die with a rate μ (killing worms inside), and that worms die within humans with rate μ_1

$$\frac{dM}{dt} = \beta L(t - \tau_1) d_1 - \mu \sum i p_i(t) - \sum \mu_1(i) i p_i(t)$$

Modelling - Initial considerations

- Now lets consider L. If ϕ is the probability that a female worm is mated, s is the proportion of female worms in the population, $\lambda(i)$ is the per capita egg production rate of female worms, and τ_2 is the time taken for eggs to reach juvenile age during which they die at rate d_2, then we get

$$\frac{dL}{dt} = s\phi N d_2 \sum \lambda(i) i p_i(t - \tau_2)$$

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$$\frac{dL}{dt} = s\phi N d_2 \sum \lambda(i) i p_i (t - \tau_2)$$

- If infective juvenile worms die at rate μ_2, and infect humans with rate βN then

$$\frac{dL}{dt} = s\phi N d_2 \sum \lambda(i) i p_i (t - \tau_2) - \mu_2 L - \beta N L$$

Basic model

- This gives us the basic model

$$\frac{dM}{dt} = \beta L(t-\tau_1)d_1 - \mu \sum ip_i(t) - \sum \mu(i) ip_i(t)$$
$$\frac{dL}{dt} = s\phi N d_2 \sum \lambda(i) ip_i(t-\tau_2) - \mu_2 L - \beta NL$$

Empirical distribution of parasites among hosts

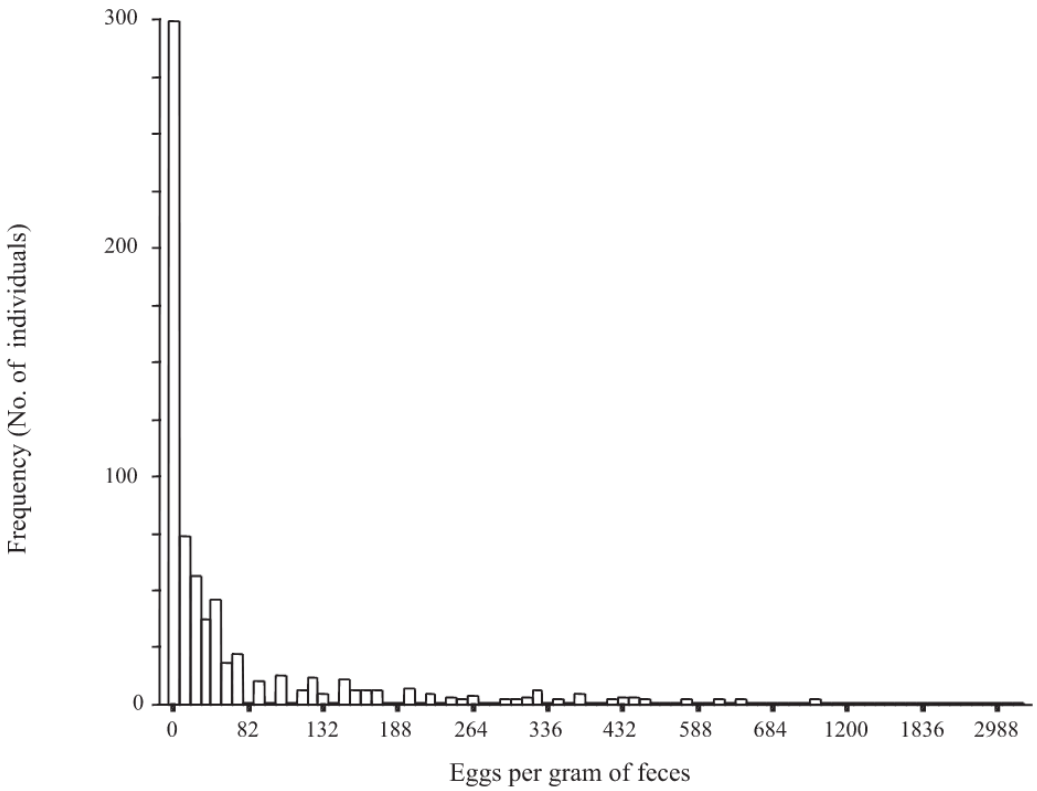


Figure 1 Distribution of *S. mansoni* eggs in the study sample expressed in eggs per gram of faeces (n = 597).

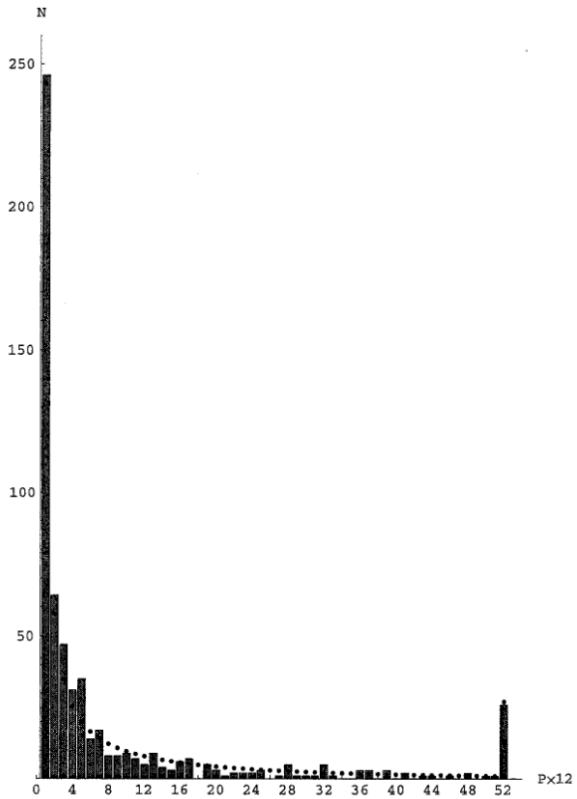
- Distribution of *Schistosoma Mansoni* burden (measured as eggs per gram of faeces) among individuals from a village in Brazil (*Bethony et al., 2001*)

Empirical distribution of parasites among hosts

- Fit of data with negative-binomial distribution (Feng et al 2004)
- Negative binomial is a discrete probability distribution, parameterised by mean m and aggregation parameter k, defined by

$$p(i) = \frac{(k+i-1)!}{i!(k-1)!}(1+m/k)^{-k-i}(m/k)^i$$

For this data $\bar{x} = 9.5 \times 12$, $k = 0.24$.



Back to our model

- First, lets over-simplify our model by neglecting the density dependent effects of worm death and egg production i.e. $\mu_1(i) = \mu_1$, $\lambda(i) = \lambda$, and setting the probability of worm mating $\phi = 1$. Then we get

$$\frac{dM}{dt} = \beta L(t - \tau_1)d_1 - (\mu + \mu_1)M(t)$$
$$\frac{dL}{dt} = sNd_2\lambda M(t - \tau_2) - (\mu_2 + \beta N)L(t)$$

Basic reproduction rate, R_0

- It can be shown that this pair of equations leads to ever increasing M and L under the condition

$$R_0 := \frac{s\lambda\beta N d_1 d_2}{(\mu + \mu_2)(\mu_2 + \beta N)} > 1$$

- If $R_0 < 1$ then the worm population will die out.
- Alternatively, we can reformulate this as a threshold population size for humans above which the number of hosts is able to support a worm population

$$N_T = \frac{\mu_2(\mu + \mu_1)/\beta}{s\lambda d_1 d_2 - (\mu + \mu_1)}$$

Density dependent fecundity

- Without any density dependent effects the basic model does not produce a stable non-zero equilibrium.
- Empirical evidence suggests that there is a decline in per capita fecundity of female worms, and it can be modelled approximately by the relationship

$$\lambda(i) = \lambda_0 \exp\left(-\gamma(i-1)\right)$$

- Assuming a negative binomial distribution, and subbing this into $\sum \lambda(i) i p_i$ means that λ is replaced in the simplified model with

$$\lambda \to \lambda_0 \left(1 + M(1-z)/k\right)^{-(k+1)}$$

where $z = e^{-\gamma}$

Some more simplifying

- The maturation times are short compared to the life of a worm, so lets set $\tau_1 = \tau_2 = 0$.
- It is reasonable to assume that the dynamics of the juvenile worms occur on much shorter time-scales than the dynamics of mature adults, so L will be very close to its equilibrium value obtained by setting $dL/dt = 0$:

$$L(t) = sd_2\lambda NM(t)/(\mu_2 + \beta N)$$

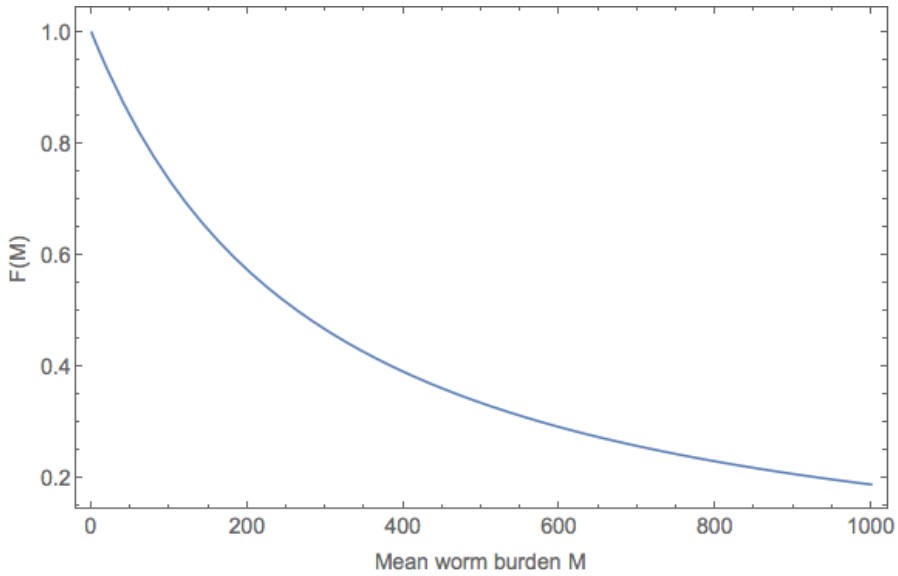
- Which results in a single ODE for M(t)

$$\frac{dM}{dt} = (\mu + \mu_1)(R_0 f(M) - 1)M(t)$$

- where $f(M) = (1 + M(1 - z)/k)^{-(k+1)}$

Equilibrium M^*

This is what f looks like with parameters $k = 0.25$, $\gamma = 0.0003$.



- The non-zero equilibrium mean worm burden for this model is given by $R_0 f(M^*) = 1$:

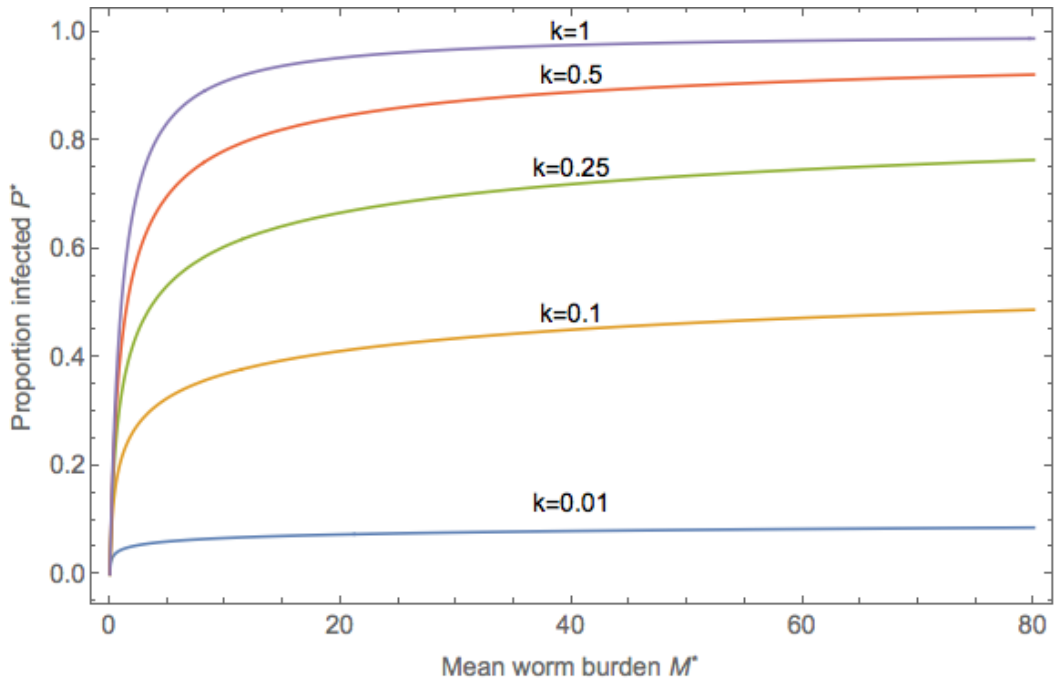
$$M^* = k(R_0^{1/(k+1)} - 1)/(1 - z)$$

which is stable iff $R_0 > 1$

Proportion of people infected

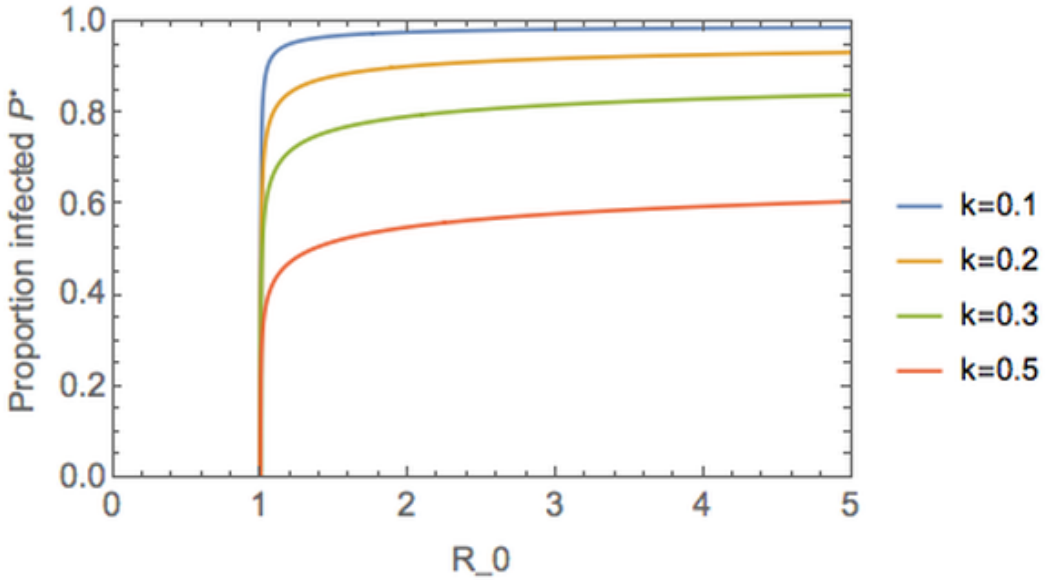
- Recalling that we are assuming a negative-binomial distribution of worms across the host population, the proportion of people infected (the prevelance) is just

$$P = 1 - (1 + M/k)^{-k}$$



Proportion of people infected

- We can also see the effect that R_0 has on the equilibrium prevalence.



Control strategies

In order to eradicate or control the disease, there are a few options we could look at:

- Change behaviour (hard)
- Kill snails (hard)
- Mass drug administration programs
- Vaccinate (no vaccine available yet)

The effect of chemotherapy

- There is a safe an effective drug, Praziquantel, that is able to reduce worm burden by 90%.
- The pharma company Merck is currently donating 250 million doses per year to the WHO
- Lets suppose we have a drug which we are able to administer randomly to a proportion g of the population per unit time, with efficacy h (the proportion of worm burden killed by a single dose). Then the death rate will increase by

$$c = -\ln(1 - gh)$$

The effect of chemotherapy

- With this additional death rate

$$\frac{dM}{dt} = (\mu + \mu_1)(R_0 f(M) - 1 - c/(\mu + \mu_1))M(t)$$

  which changes the equilibrium to

$$M^* = k\left(\left(\frac{R_0}{A\ln(1-gh)}\right)^{1/(k+1)} - 1\right)/(1-z)$$

- $A = 1/(\mu + \mu_1)$ is the life expectancy of the adult worm (without drug treatment)

The effect of chemotherapy

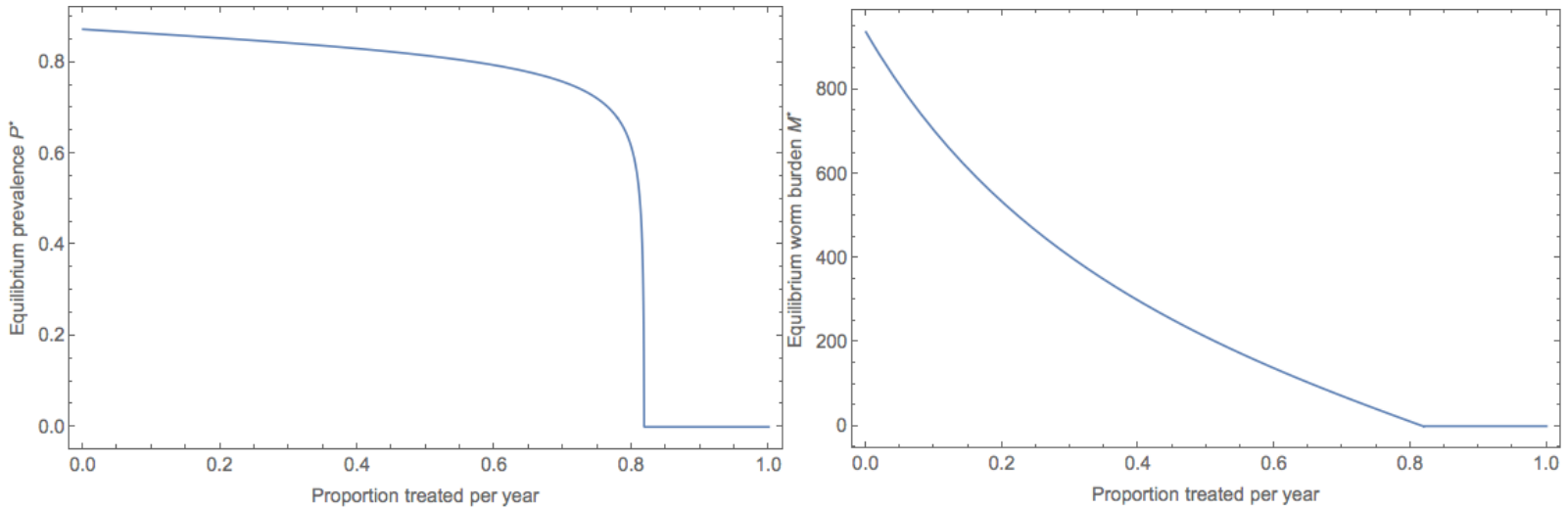
- This has effectively modified the basic reproductive rate R_0. For the drug treatment program to eradicate the disease we need this rate to be less than one.
- Expressed in terms of a threshold proportion of the population per unit time needed to treat, this is:

$$g_c = \left(1 - e^{(1-R_0)/A}\right)/h$$

- For an area badly effected area by schistosomiasis, we might expect $R_0 = 5$, adult worm life-span $A = 3$ years, and praziquantel has an efficacy of $h = 0.9$ so we would need to treat 82% of the population.

The effect of chemotherapy

- Here we have the equilibrium prevalence and mean burden as a function of proportion treated ($R_0 = 5$, $z = 0.99$, $A = 3$, $k = 0.25$, $h = 0.9$).



Some extra stuff

- We've been assuming that the probability of a female worm being mated $\phi = 1$.
- In reality, the chance of a randomly selected female being mated will be dependent on the density of worms in the population, and also the aggregation k.
- Can you think of a reasonable functional form for ϕ? How will this affect the long term behaviour?

Reading list

- Anderson, Roy M., Robert M. May, and B. Anderson. Infectious diseases of humans: dynamics and control. Vol. 28. Oxford: Oxford university press, 1992.
- Hollingsworth, T. Dirdre, et al. "Quantitative analyses and modelling to support achievement of the 2020 goals for nine neglected tropical diseases." Parasites & vectors 8.1 (2015): 630.
- Anderson, R. M., et al. "What is required in terms of mass drug administration to interrupt the transmission of schistosome parasites in regions of endemic infection?." Parasites & vectors 8.1 (2015): 553.
- Stylianou, Andria, et al. "Developing a mathematical model for the evaluation of the potential impact of a partially efficacious vaccine on the transmission dynamics of Schistosoma mansoni in human communities." Parasites & Vectors 10.1 (2017): 294.

some more

- Truscott, J. E., et al. "A comparison of two mathematical models of the impact of mass drug administration on the transmission and control of schistosomiasis." Epidemics 18 (2017): 29-37.
- Gurarie, David, and Charles H. King. "Population biology of Schistosoma mating, aggregation, and transmission breakpoints: more reliable model analysis for the end-game in communities at risk." PLoS One 9.12 (2014): e115875.