Modelling alternative treatment strategies for onchocerciasis: moxidectin for control and elimination

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Introduction

Mathematical modelling has played an essential role in predicting the impact of onchocerciasis control strategies by mass drug administration (MDA). However, rarely is the inter-individual variability in responses to the anhelmintics taken into account. Phase II and III single-dose trials for moxidectin compared to ivermectin in ivermectin-naïve areas have revealed significant variation in responses to these anti-filarial drugs prior to widespread MDA. We assessed the potential impact that inter-individual variation to ivermectin or moxidectin may have on onchocerciasis elimination.

Methods

Using clinical trial data[1] and our individual-based, stochastic transmission model EPIONCHO-IBM, we capture skin microfilarial (mf) post-treatment dynamics based on previous parameterisations[2,3].

The variation in drug response is captured by fitting a log-normal distribution (mean = 1 and inverse variance = *k*) fitted to match:

1. **Point mf measures** = Median and arithmetic mean (at a given post-treatment time)
2. **Measures of variation from the mean** = IQR, Range, SD
3. **Complete mf clearance** = No. of patients with no detectable skin microfilariae

Results

Population Response

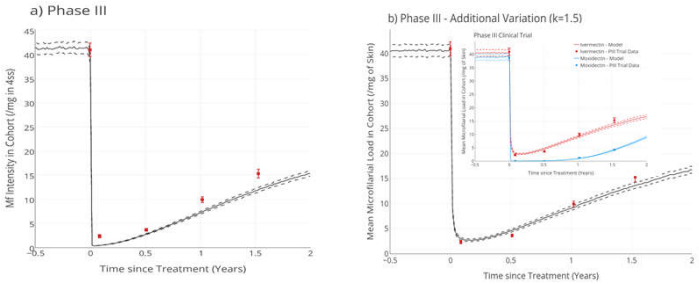
Fitting a statistical model to multiple post-treatment microfilarial measures provided estimates of variation in (phenotypic) response (as described by the overdispersion parameter *k* of a log-normal distribution):

Ivermectin (*IVM*)→ *k* = 1.5
Moxidectin (*MOX*)→ *k* = 4.0

The k parameter is inversely related to the strength of overdispersion. (Lower k = Higher variation)

The addition of variation in an individual host's response to either ivermectin or moxidectin showed:

- ***Much greater degree of variation in IVM than MOX***
- ***Reduced complete microfilarial clearance in IVM-treated individuals***
- ***Improved overall fit to mean microfilarial load at various times post-***



Model predictions of Phase III single-dose trial data for microfilarial dynamics post-ivermectin treatment assuming: (a) no inter-individual variation and (b) log-normally distributed variation in responses with overdispersion *k* = 1.5.

Impact of Variation on Elimination

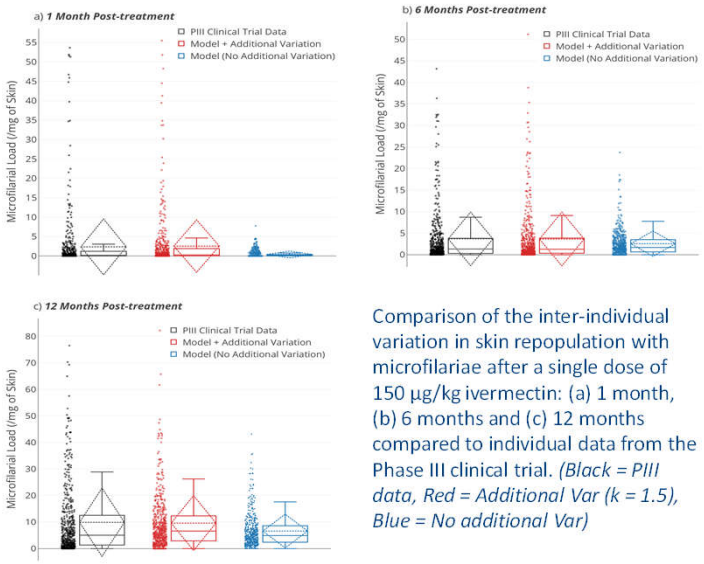
Phase II and III clinical trials for moxidectin (compared to ivermectin) were single-dose studies. We, therefore, modelled two possible ways variation (Var) can manifest over multiple MDA rounds:

a) Random Var – individuals' responses can vary from round to round
b) Systematic Var – poor responders remain poor responders across multiple treatment rounds (and vice versa).

Inclusion of drug response variation reduces the probability of elimination
(Lowest probability) **Systematic Var < Random Var < No Added Var** *(highest probability)*

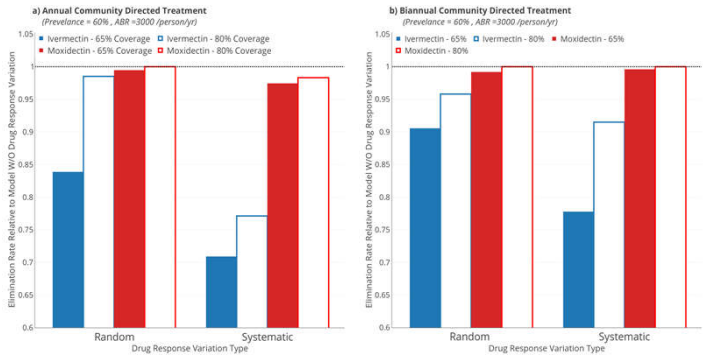
Factor	Magnitude of Relative Difference with Model w/o Added Var
↑ Transmission / Endemicity	↑
↑ MDA frequency	↓
↑ Coverage / Adherence	↓
Moxidectin (↓ Response Var)	↓

Individual Responses (e.g. to *IVM*)



Comparison of the inter-individual variation in skin repopulation with microfilariae after a single dose of 150 µg/kg ivermectin: (a) 1 month, (b) 6 months and (c) 12 months compared to individual data from the Phase III clinical trial. *(Black = PIII data, Red = Additional Var (k = 1.5), Blue = No additional Var)*

In the absence of additional variation, the model has on average only 12% of the standard error observed in the ivermectin arm of the Phase III moxidectin clinical trial. The addition of log-normally distributed **variation improves the ability of the model to capture the distribution of mf in individual trial participants** both for *IVM* (shown) and *MOX* (not shown). The amount of variation for *MOX* (*k* = 4) is markedly smaller than for *IVM* (*k* = 1.5).



Conclusions

- **Variation in drug responses that greatly departs from the average response can impede elimination and should be considered when modelling MDA interventions.**
- The causes and mechanisms of inter-individual host variation remain unclear. **More research is needed to understand why some individuals respond poorly (even before widespread use of MDA)[4]** and how that will influence the outcome of MDA-based programmes across multiple treatment rounds.
- **Drugs that exhibit minimal inter-individual variation, such as *moxidectin*, may have an increased benefit** beyond that of being a better microfilaricidal and embryostatic drug (as there is much less departure from the observed mean dynamics).

References

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