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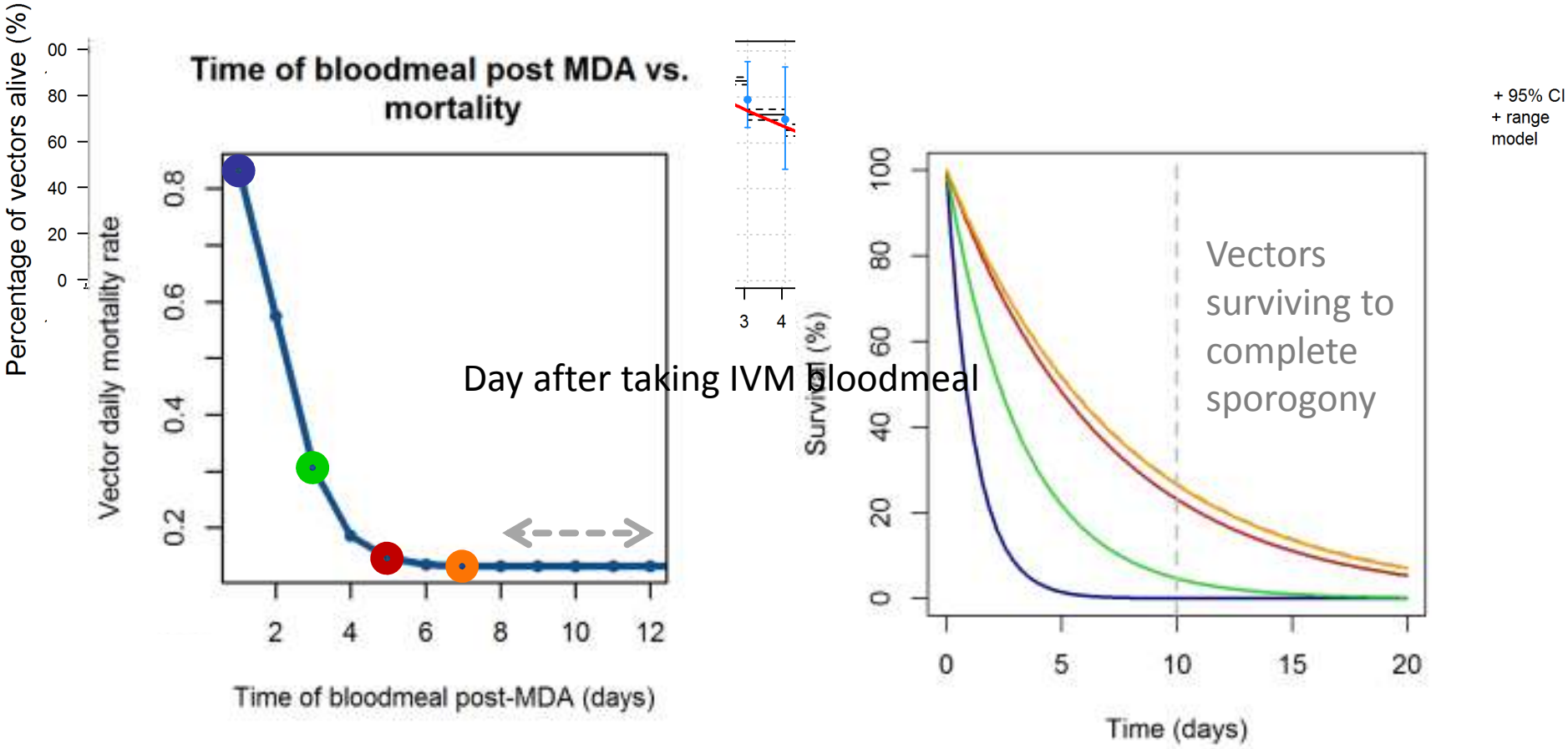
MRC Centre for Outbreak Analysis and Modelling

Modelling the impact of Ivermectin on the vector population and malaria transmission

Hannah Slater

Ivermectin model (1)

1) Cox proportional hazards survival model to determine the vector mortality based on the day post IVM ingestion that the bloodmeal was taken



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Ivermectin model (2)

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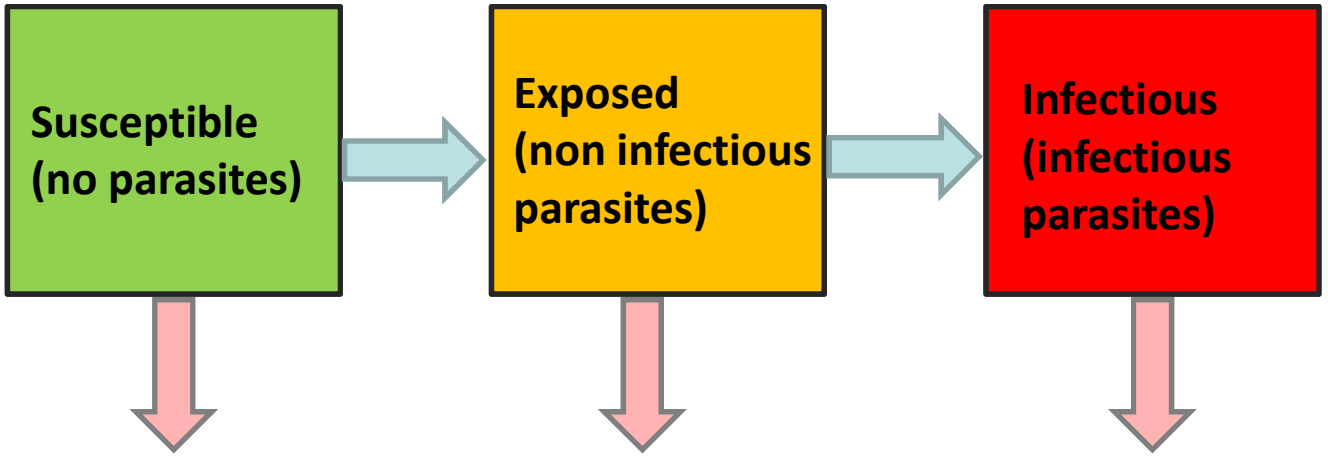
2) Vector population model to track the number of mosquitoes over time after IVM MDA

Track the day on which a IVM bloodmeal was taken

Assume vectors biting on a certain day post IVM will have a higher mortality rate for the rest of their lives



Track the proportion of mosquitoes that have oviposited (PARITY RATE)

Linked up to the Imperial College malaria transmission model to capture the human transmission dynamics

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Model output (1)

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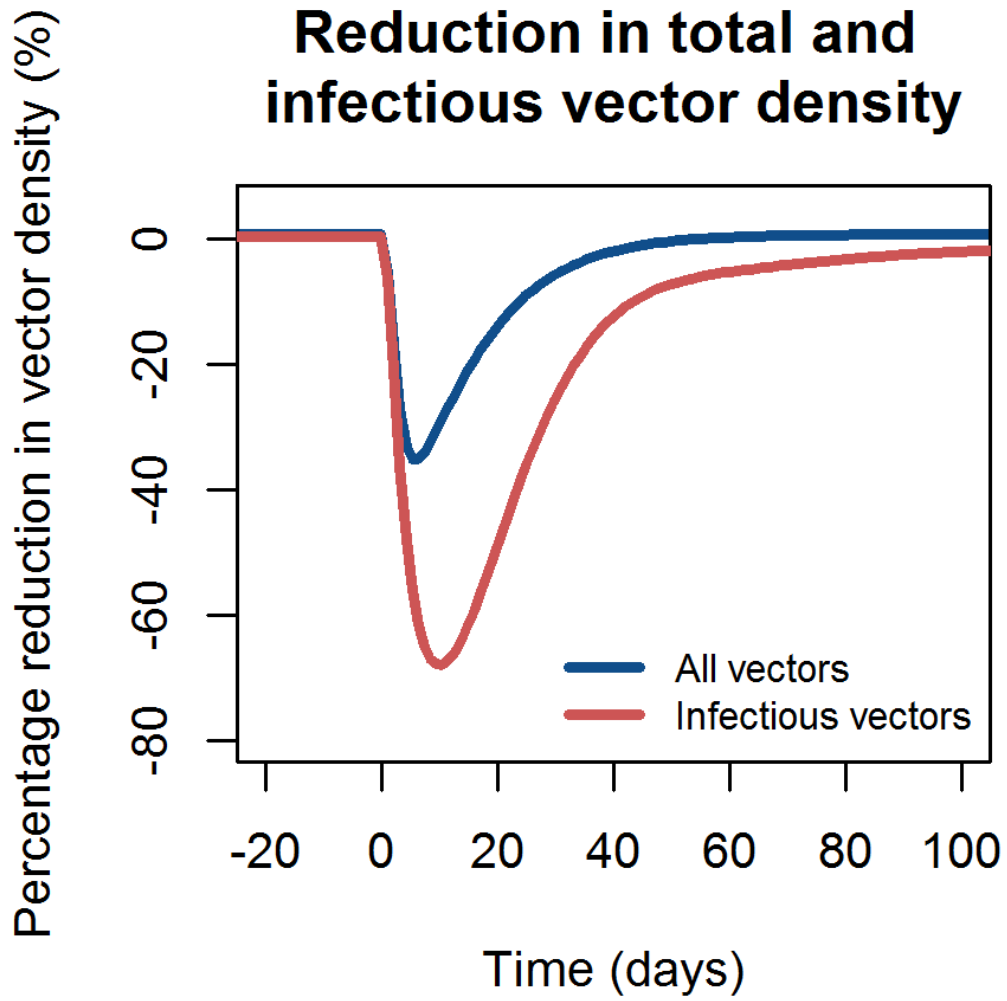

Impact of three daily doses of $150\mu g/kg$ on vector density

Impact is greater on infectious vectors – and these are the important ones to target

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Model output (2)

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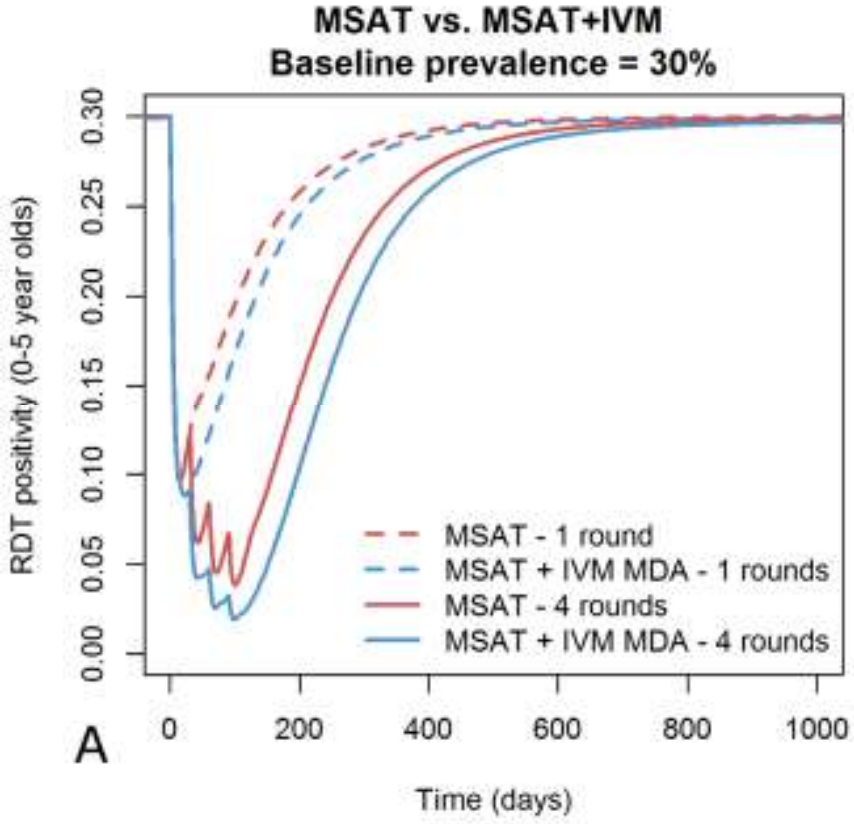
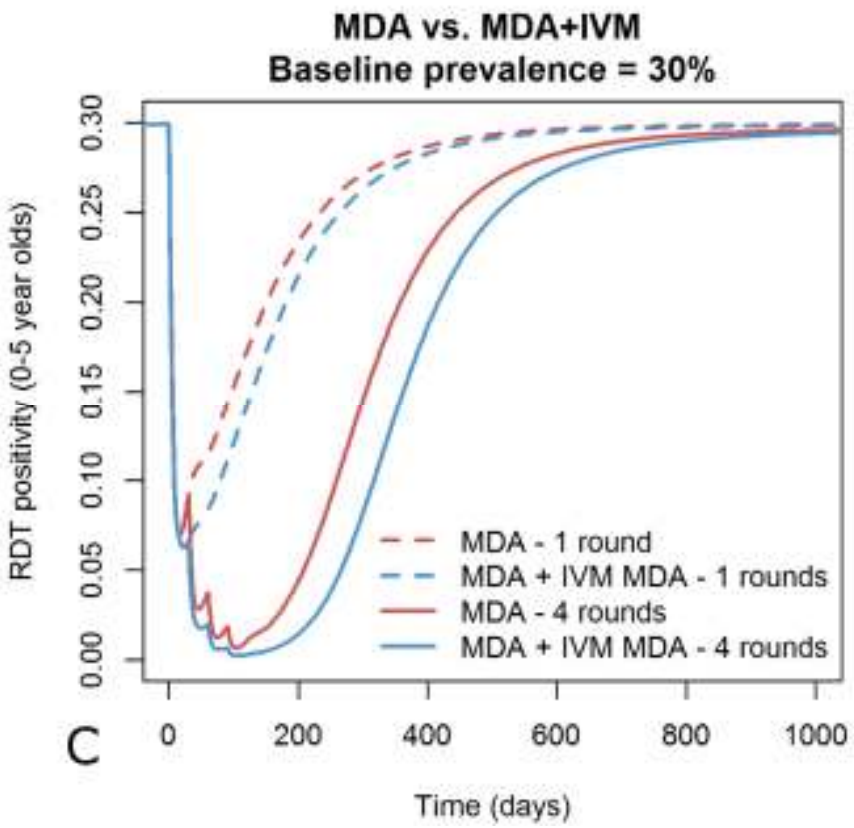
Alongside an ACT in a mass screen & treat or mass drug administration intervention

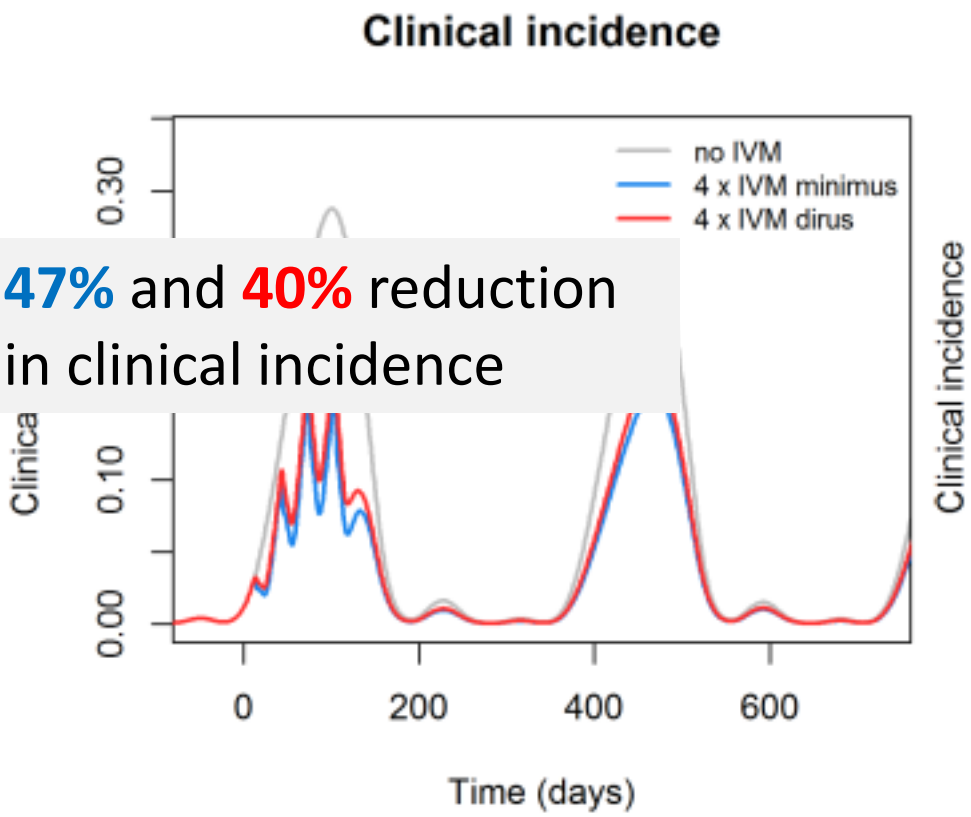




Model output (3)

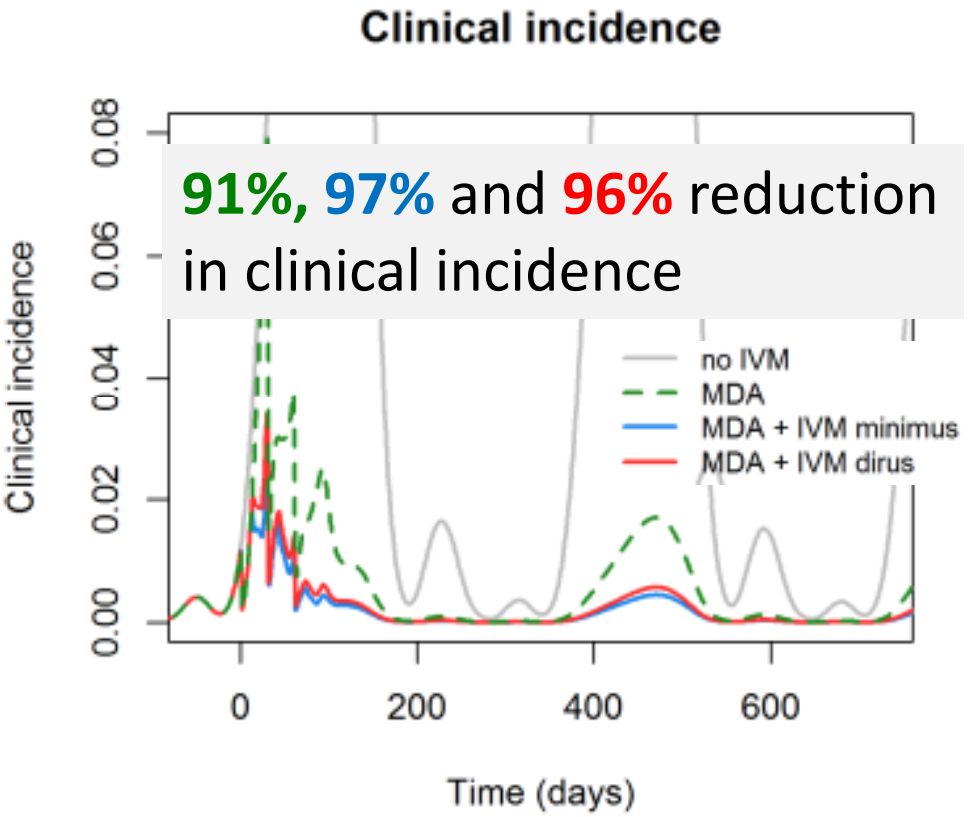
To slow the spread of artemisinin resistant infection in SE Asia

4 rounds of IVM MDA at the start of the rainy season



47% and **40%** reduction in clinical incidence

3 rounds of MDA with IVM + DHA-P at the start of the rainy season



91%, 97% and **96%** reduction in clinical incidence

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Model output (4)

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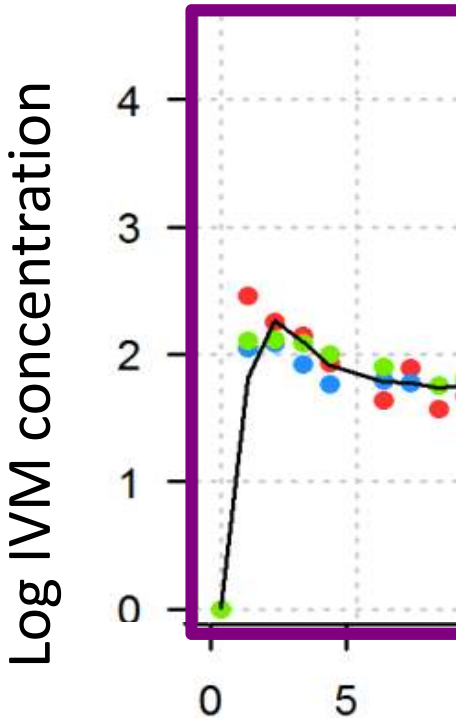
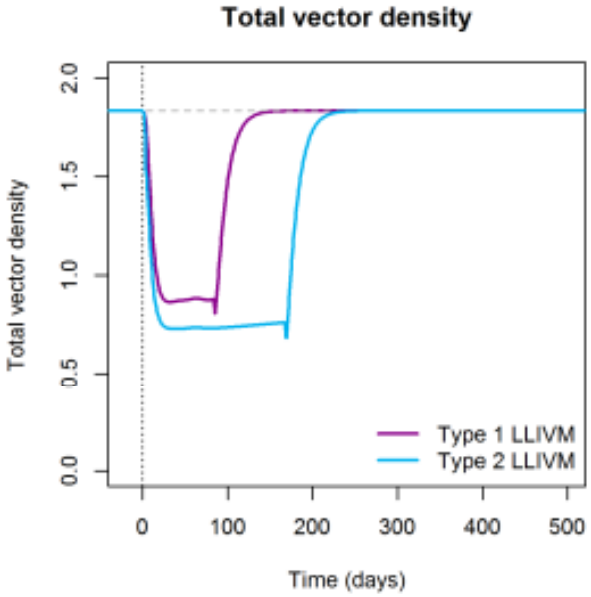
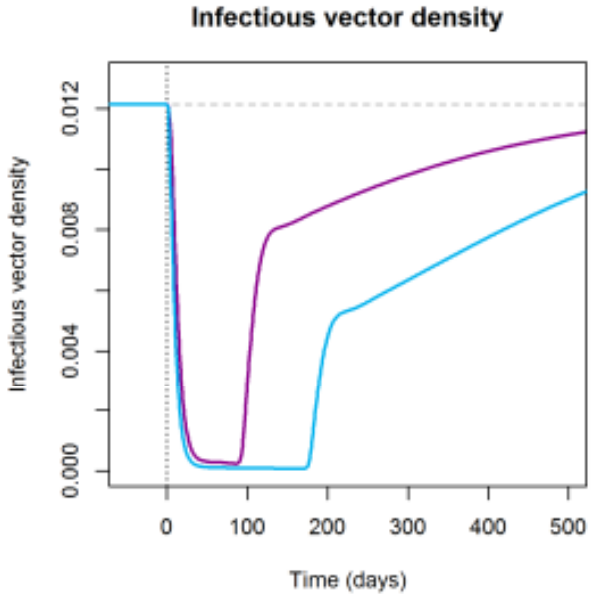
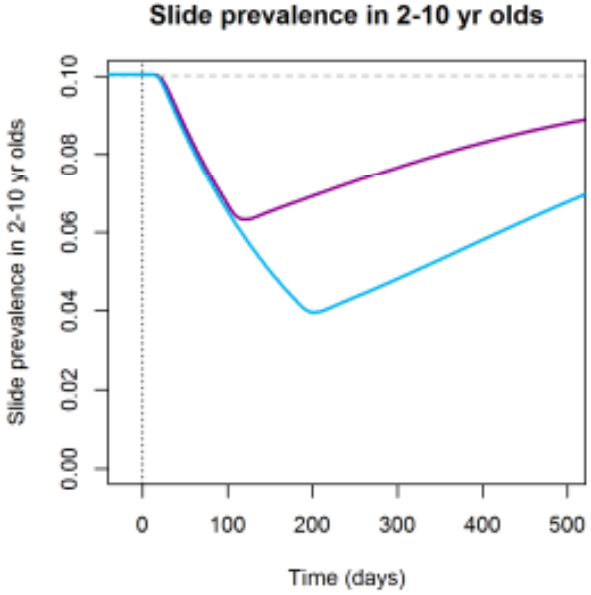
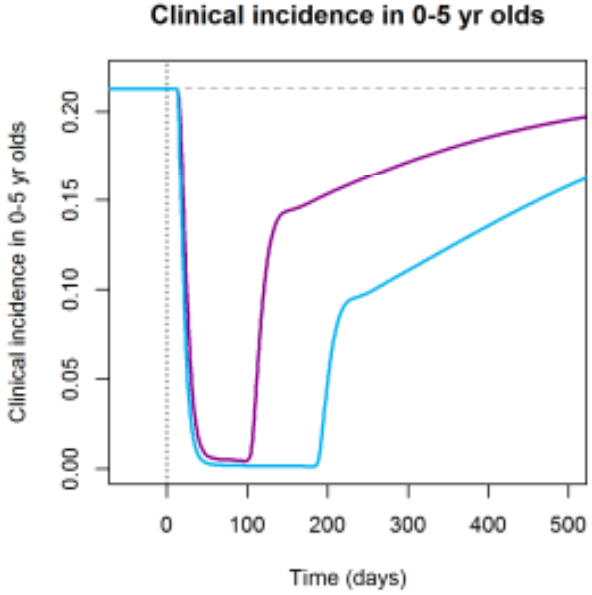
To model the p











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Validating the model

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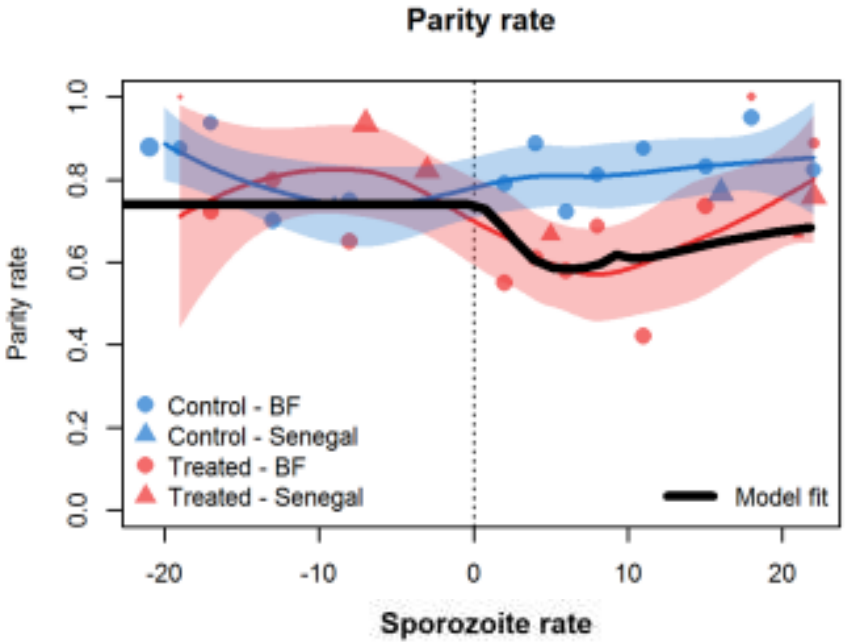

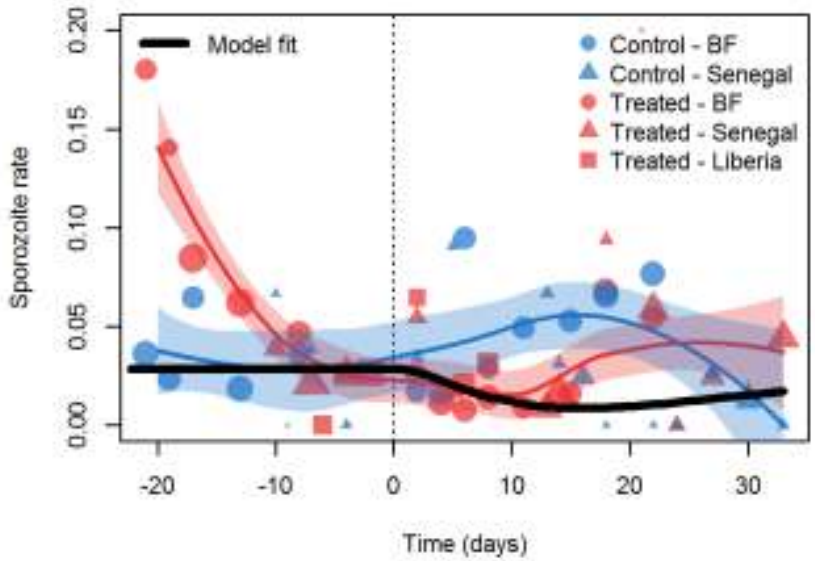

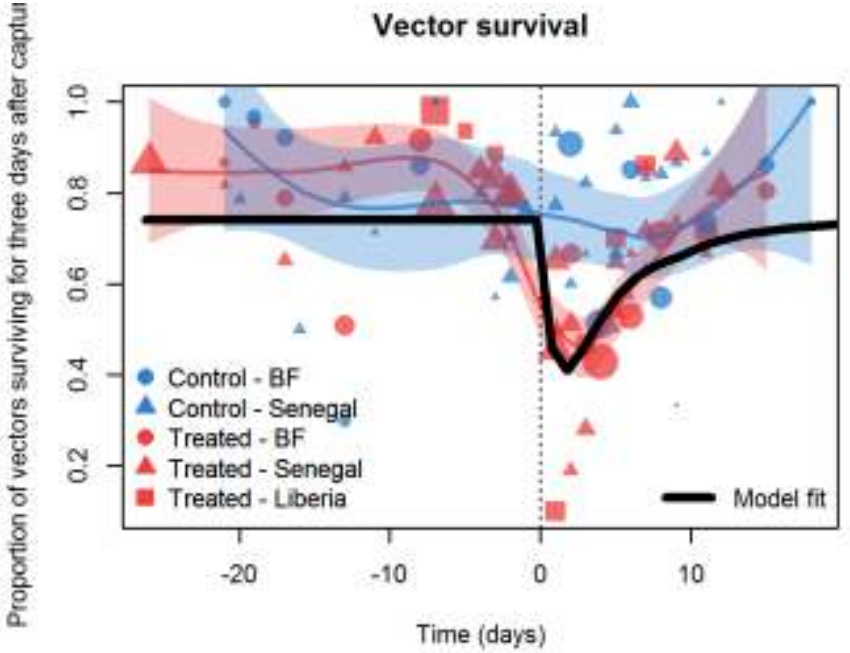

Assuming two bites to become parous - previously assumed 1 bite, so impact of IVM may be greater than previously predicted

Model accurately matches changes in parity rate and vector survival

Changes in sporozoite rate are much harder to detect

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What we don't know…

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- The impact on the number of infectious vectors in the field

- Most the data on IVM-induced vector mortality is from membrane feeding studies. To accurately capture IVM impact in the field we need a better understanding of:

  1. How IVM concentration in the peripheral blood (i.e. what is taken up by the mosquito) relates to IVM concentration in the venous blood (i.e. what is measured in IVM pharmacokinetic studies)

  2. How mortality due to IVM in the laboratory corresponds to mortality due to IVM in the field

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BILL & MELINDA GATES foundation

Discussion

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Ivermectin model (1)

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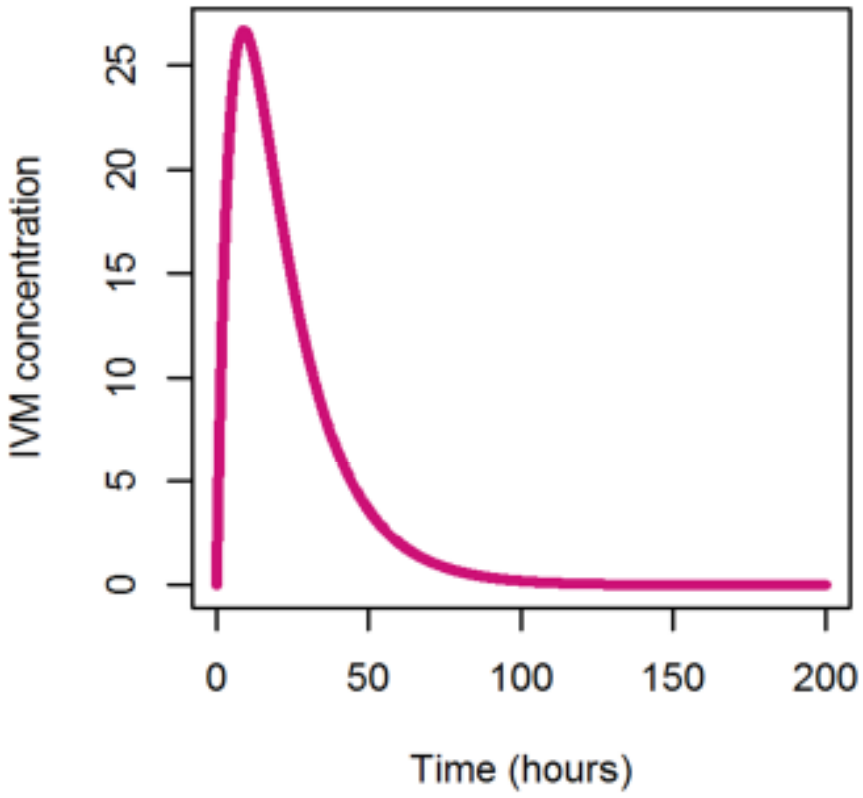
1) <u>Pharmacokinetic model</u> of ivermectin concentration in the host



Based on data from 7 studies consisting of PK time series data for 149 patients.

Currently updating this model with Joel Tarning to include new data, to produce uncertainty estimates and to analyse covariates such as 'fasting' and gender

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What we don't know…

MRC Centre for Outbreak Analysis and Modelling

The impact on the number of infectious vectors in the field – this is the most important parameter for determining the impact on malaria transmission –and is really hard to accurately measure in the field as mosquito catches are massively variable, affected by changes in climate, and require huge amounts of effort. Also, the number of infectious vectors, as a proportion of the total number of vectors is generally small (<5%,); detecting significant changes in small proportion values requires enormous sample sizes.

Most the data on IVM-induced vector mortality is from membrane feeding studies. To accurately capture IVM impact in the field we need a better understanding of:

1) How IVM concentration in the peripheral blood (i.e. what is taken up by the mosquito) relates to IVM concentration in the venous blood (i.e. what is measured in IVM pharmacokinetic studies)
2) How mortality due to IVM in the laboratory corresponds to mortality due to IVM in the field (currently assumed the additional hazard of mortality compared to baseline mortality is the same in the field as the lab, but with different baselines)