Modelling the control of artemisinin resistance

MORU Modelling Team:

Wirichada Pan-Ngum

Sompob Saralamba

Richard Maude

Lisa White

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy

WASHINGTON DC • NEW DELHI

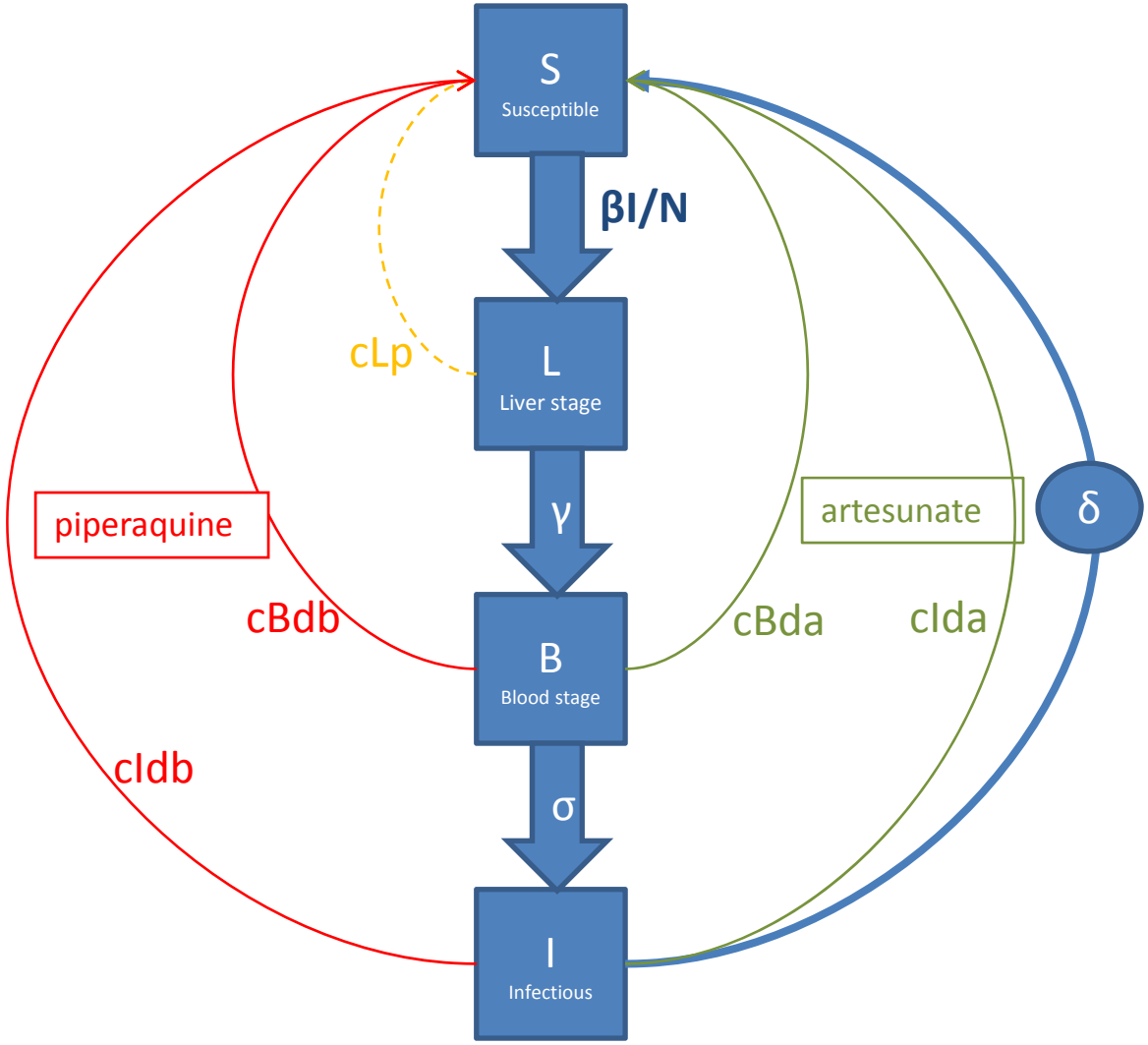
At least two levels of organisation

- **Individual level**
  - patient responses to artesunate treatment in Pailin, Cambodia.
- **Population level**
  - The spread of resistance in a population
  - Must model simultaneously
    - drug use and clearance at population level
    - transmission dynamics
- Combining individual and population levels
  - not easy!

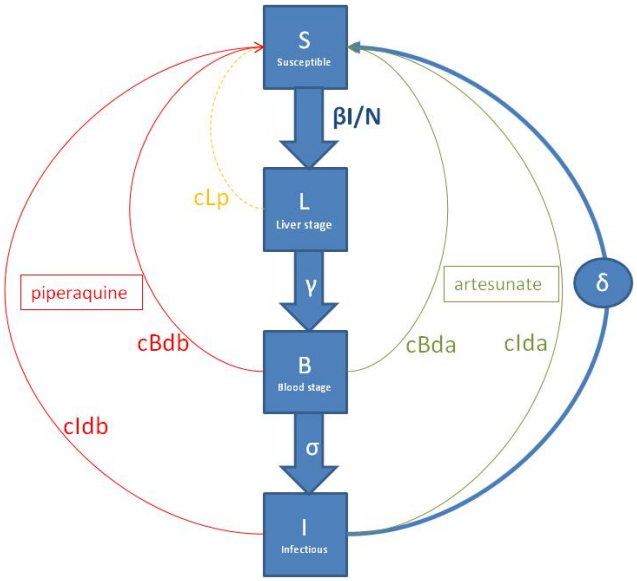
Modelling Process

- **Simple models** – starting point
  - Biologically parsimonious – do not require data
  - Flexible
  - Fast running
  - To be used for exploration of general behaviour and trends
- **Complex models** – end point
  - Biologically comprehensive – require data
  - Inflexible
  - Slow running
  - To be used for confirmation of simple model predictions and quantitative predictions

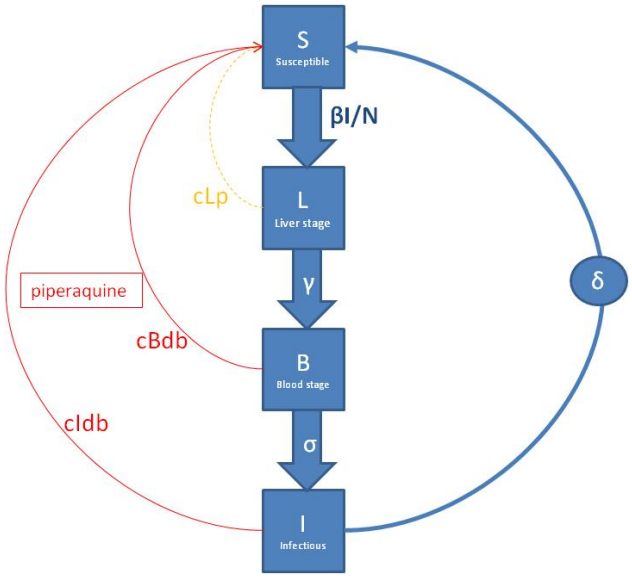
The Basic Transmission Dynamic Model



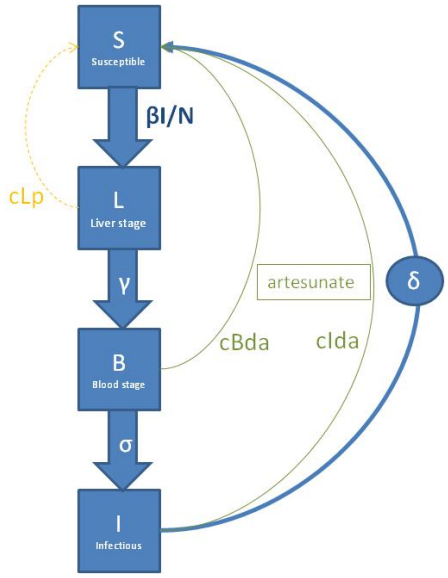
Transmission Population Dynamics



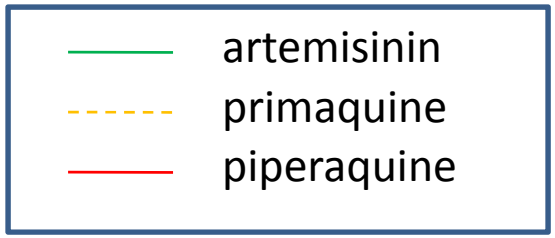
Resistant to none (ro)



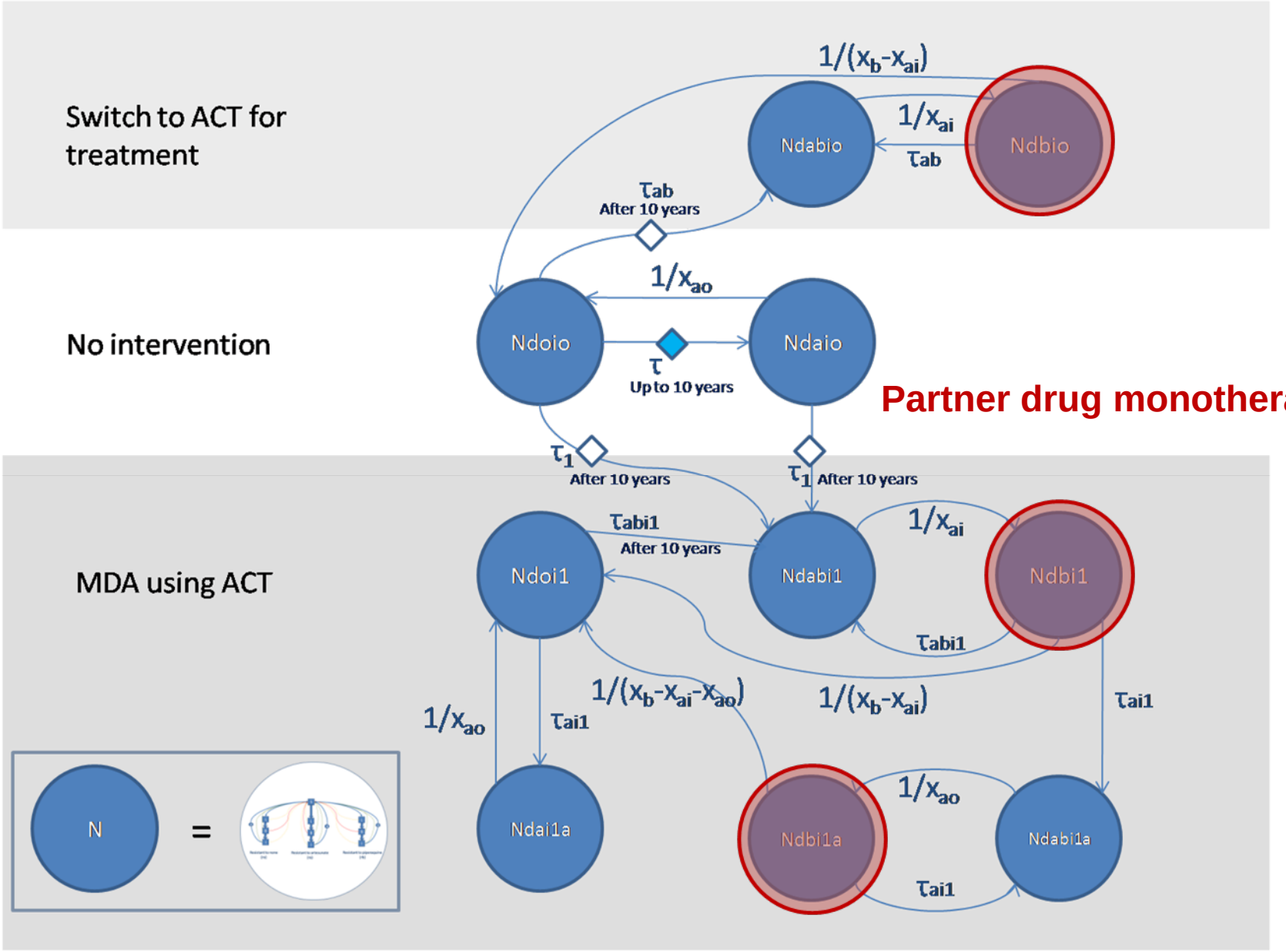
Resistant to artemisinin (ra)



Resistant to piperaquine (rb)



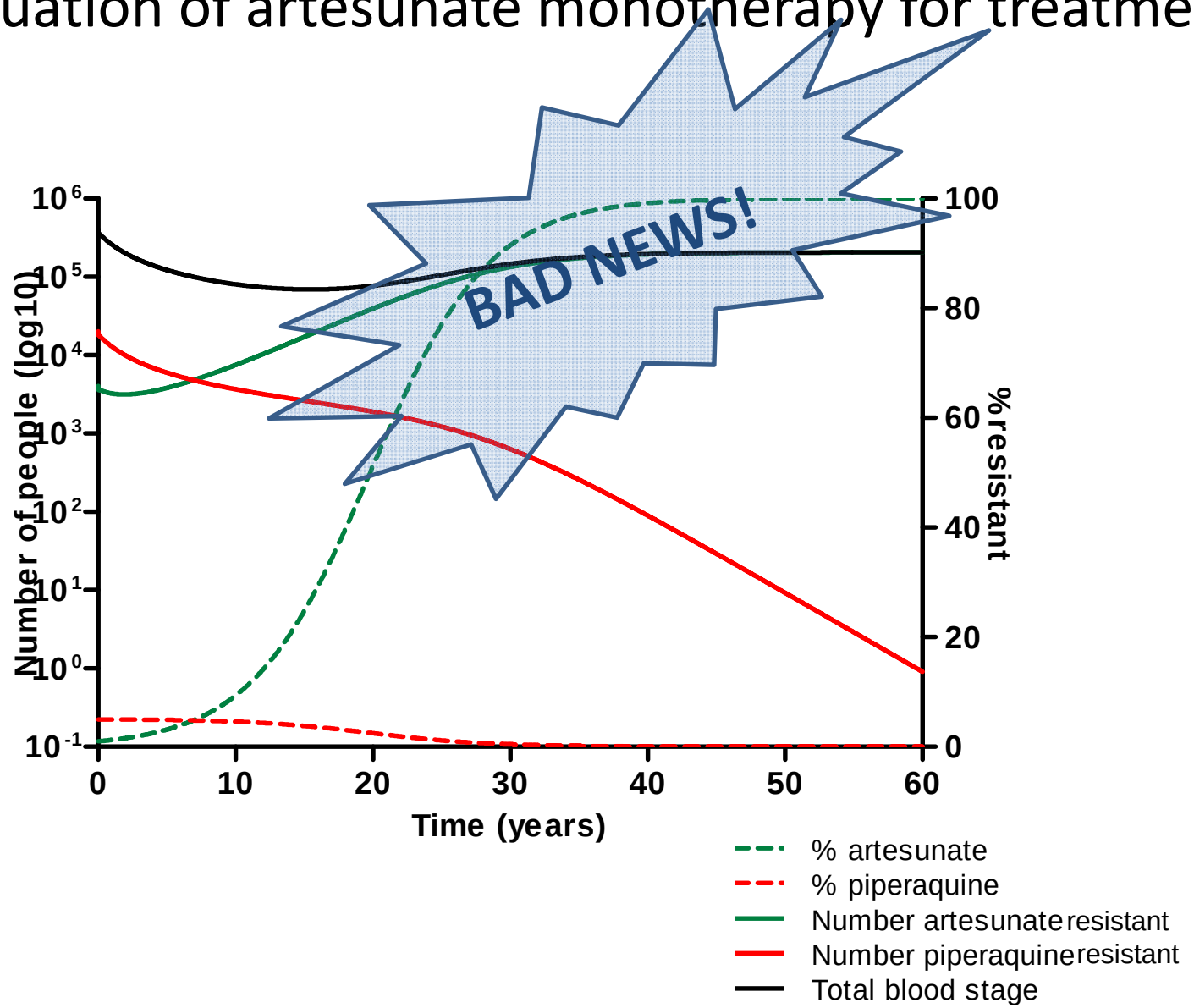
The Drug Population Dynamics



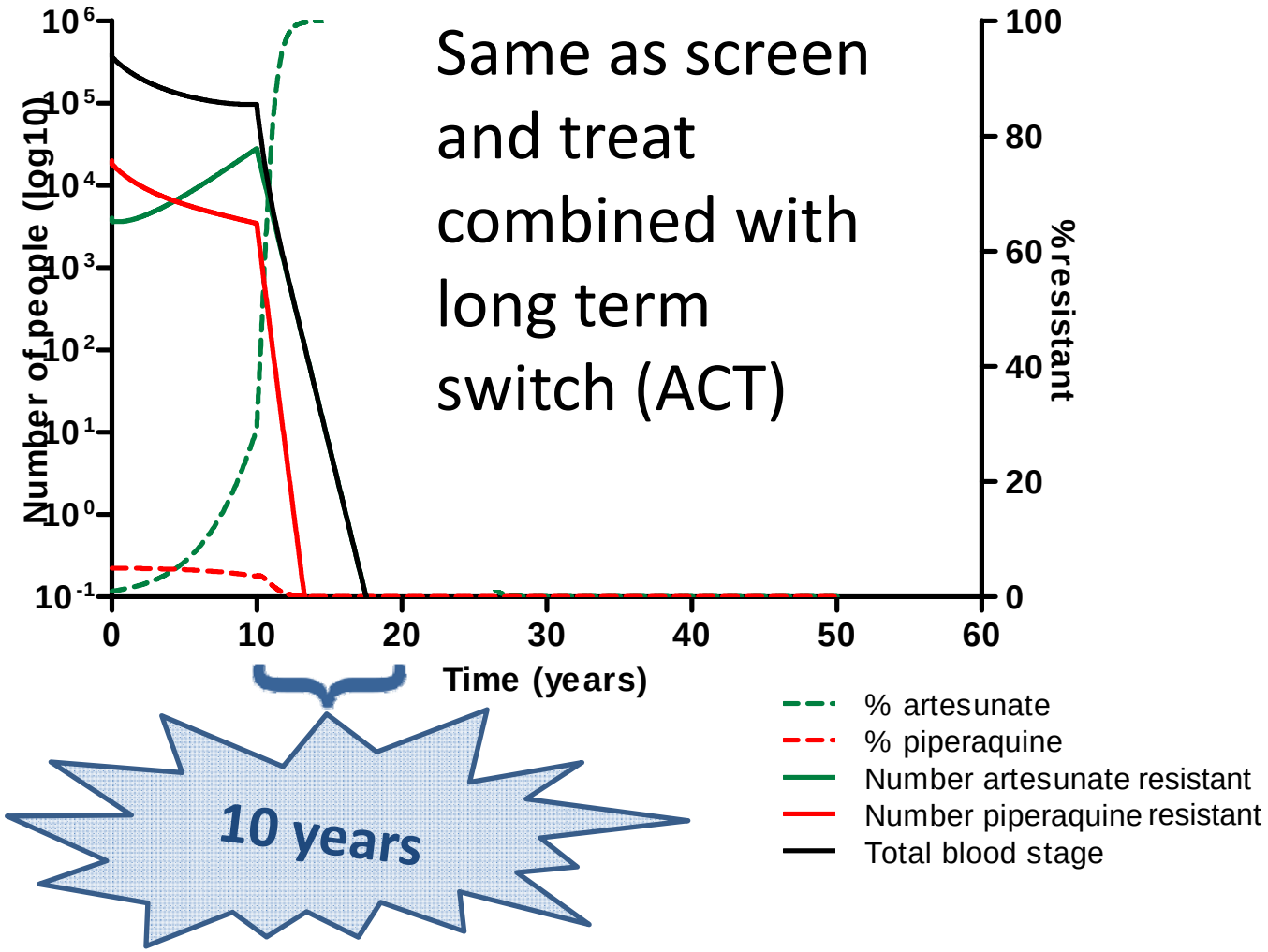
Strategies considered

- Continuation of artesunate monotherapy for treatment
- Switching from artesunate monotherapy to ACT for treatment of infected patients
  - treatment is sought within 14 days of inoculation (1-2 days fever)
  - 50% receive treatment
- A screen and treat strategy involving screening the general population regardless of symptoms and treating those with a positive malaria smear with ACT
  - positive smears are detected and treatment started within 14 days of inoculation
  - 50% receive treatment
- Three months of mass drug administration (MDA) with dihydroartemisinin/piperaquine to the general population regardless of whether they have detectable malaria

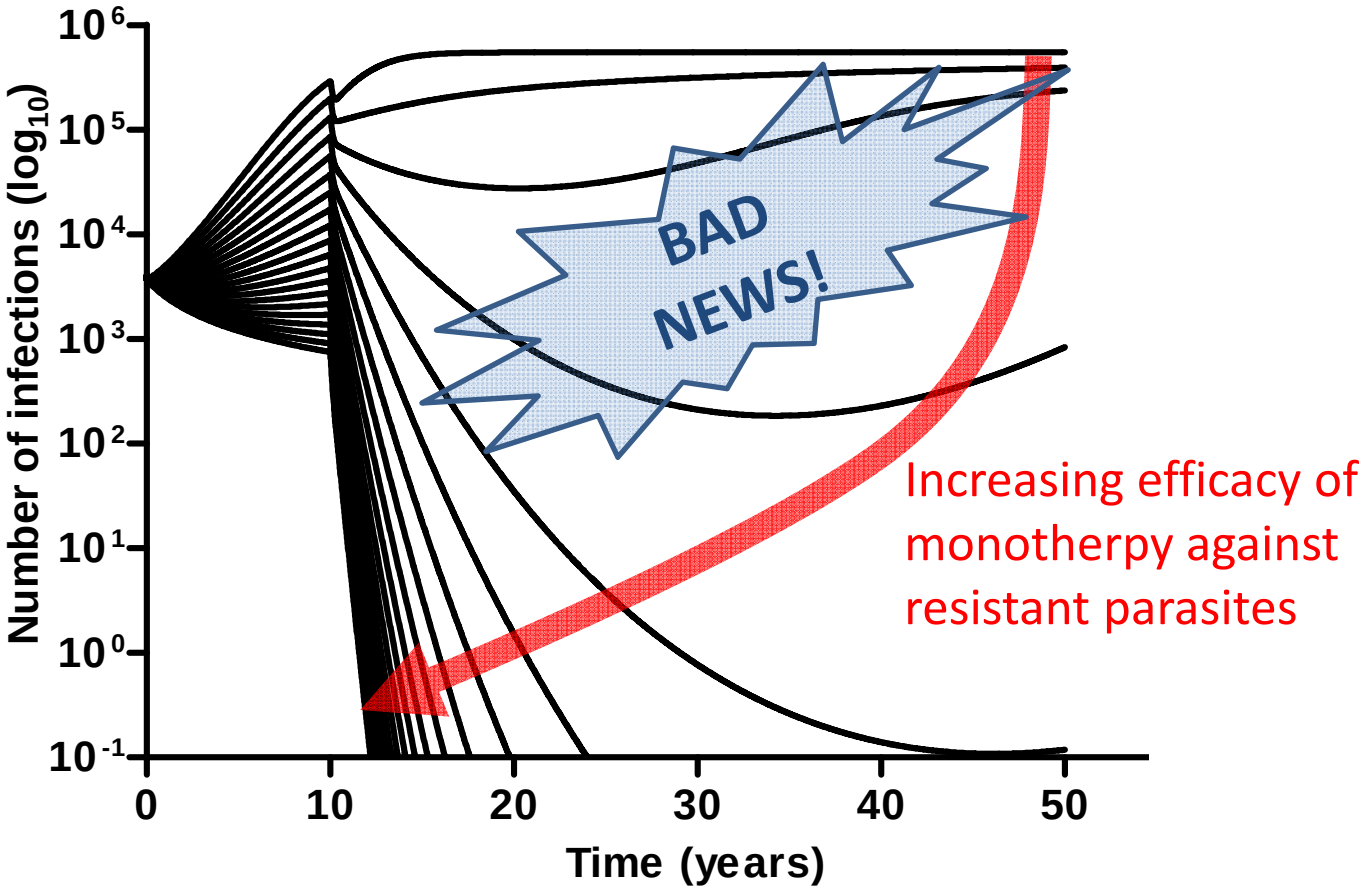
Continuation of artesunate monotherapy for treatment



Switching from artesunate monotherapy to ACT for treatment of infected patients

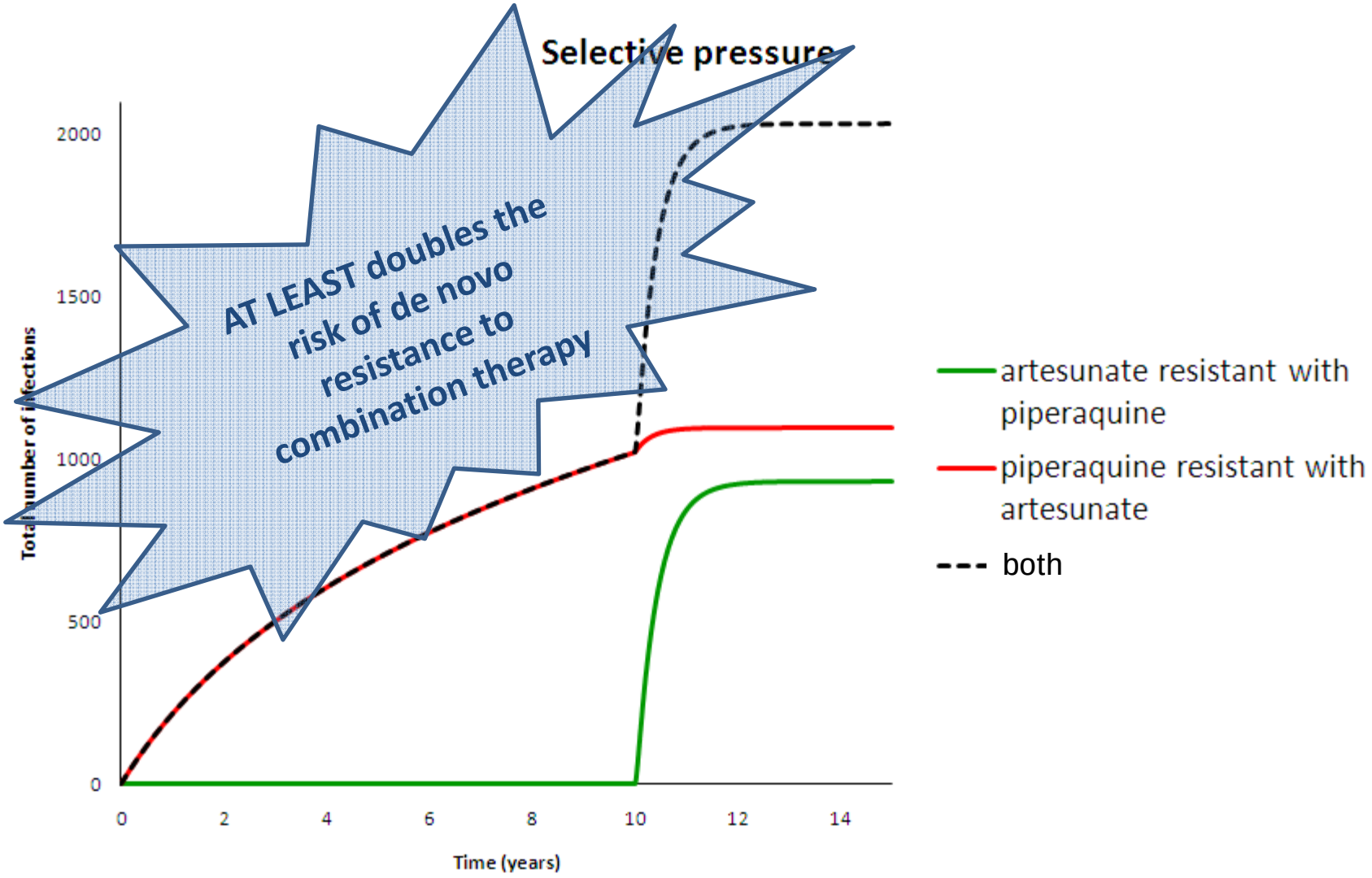


Three months of mass drug administration (MDA) of dihydroartemisinin/piperaquine followed by monotherapy



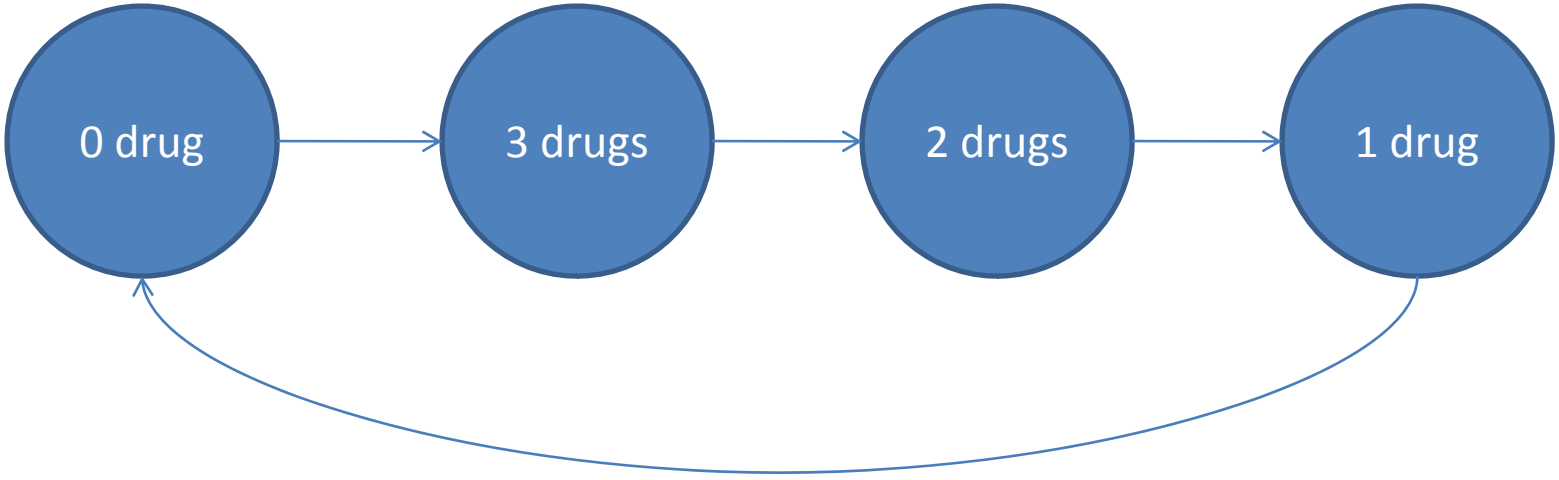
Switching from artesunate monotherapy to ACT

FURTHER CONSIDERATIONS



Other strategies currently being analysed

- Combination of screening and treatment with malarone (atovaquone + proguanil) and primaquine coupled with long term switch to ACT (DHA + piperaquine)



Complexities and why the simple model is conservative

- **Immunity**
  - In general, immunity should result in lower spread of resistance and greater chance of elimination given a mass treatment intervention
  - This model is conservative in that it assumes no immunity
- **Survival disadvantage of resistant parasites**
  - This will result in lower transmission of resistant parasites and thus a greater chance of elimination
  - This model is conservative in that it assumes no survival disadvantage
- **Vector dynamics**
  - We model vector dynamics with one constant, β. in reality it is of course far more complex and seasonal
  - This model is conservative in that we looked at seasonality briefly and concluded that an intervention timed at the low transmission period was likely to be more effective
- **Spatial heterogeneity**
  - This has the potential for improved planning of interventions and should be investigated further

Modelling Messages (1)

- To eliminate artemisinin resistant malaria **we must eliminate malaria**
- A short-term intervention has limited increases in effect if sustained for longer than three months
- A long-term switch will be just as effective as a mass intervention
- If a long term switch is not implemented, MDA can result in elimination but **only** if resistant infections still respond to treatment
- Sustained intervention over **many years** is required for elimination
- Adding a transmission blocking intervention decreases the time to elimination

Modelling Messages (2)

- Possible drawbacks:
  - Increased risk of emergence of de novo resistance to combination therapy
  - Incomplete elimination could result in a highly resistant parasite population
- Are they truly **RESISTANT**? Recent clinical and experimental evidence and individual-based modelling indicate “tolerance” rather than “resistance”. The implications for transmission advantage need to be determined to calibrate the predictive models.
- Modelling also indicates that changing the dosing regimen can accelerate parasite clearance to original levels (soon to be tested in field trials).

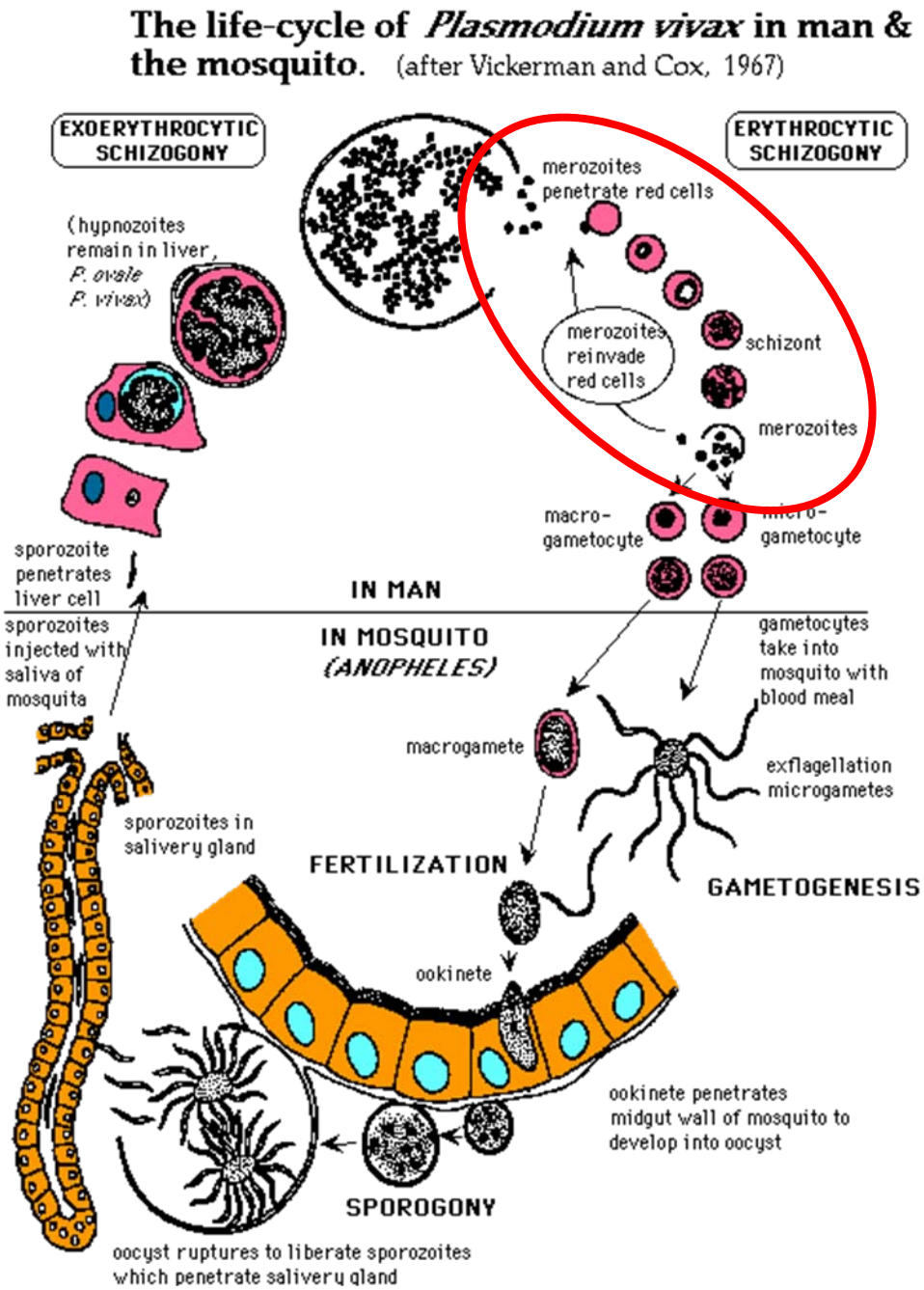
Any Questions?

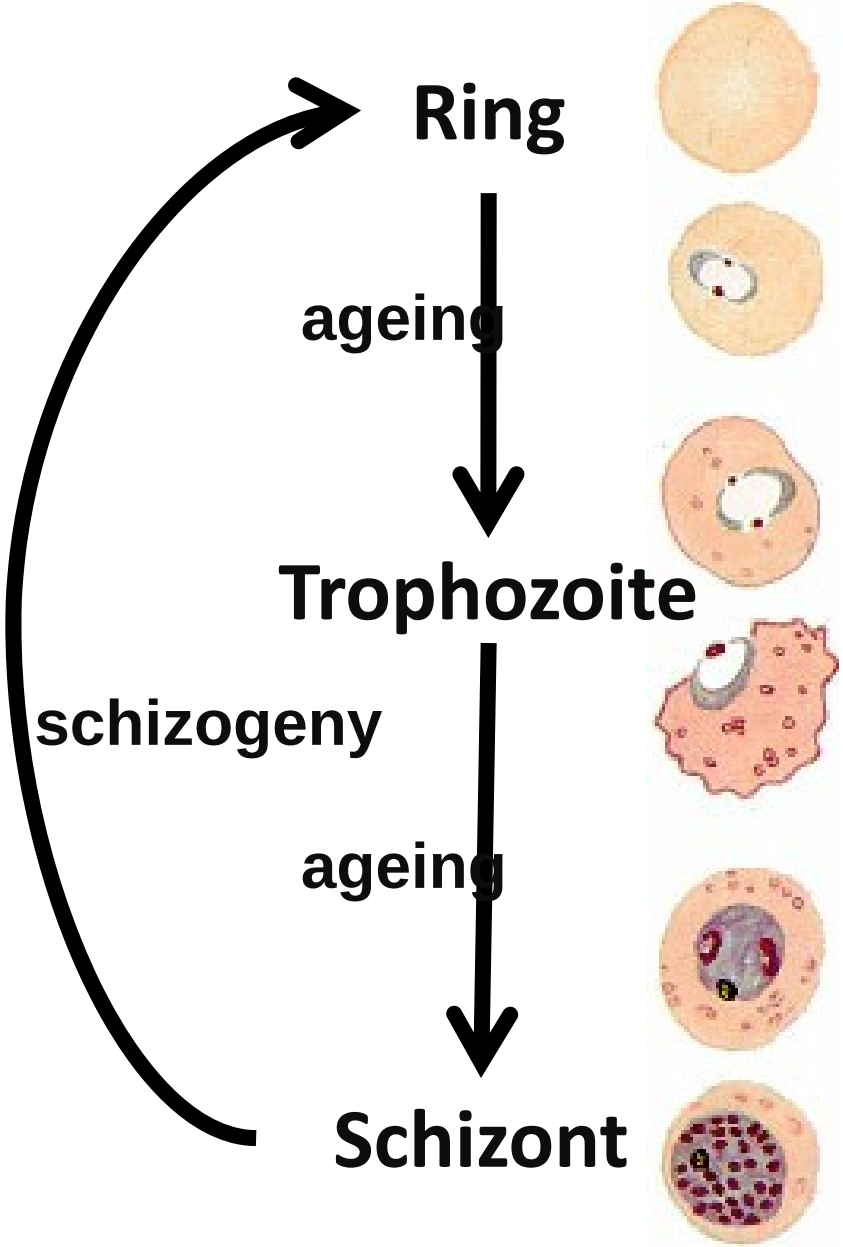
Intra-host dynamic model to examine the impact of different dose regimes on artemisinin resistance

The Challenge

- Standard treatment using artesunate involves the administration of the drug every 24 hours.
  - The drug acts on the
    - ring (aged 6-21 hours)
    - trophozoite (aged 22-30 hours)
    - schizont (aged 30-44 hours) stages.
- Resistance has been observed in the form of increased clearance times and occurrence of recrudescence

- **BIG QUESTION**: Can the dosing regime be altered to effectively treat individuals infected with resistant parasites?


The life-cycle of *Plasmodium vivax* in man & the mosquito. (after Vickerman and Cox, 1967)
EXOERYTHROCYTIC SCHIZOGONY
ERYTHROCYTIC SCHIZOGONY
(hypnozoites remain in liver, *P. ovale* *P. vivax*)
merozoites penetrate red cells
merozoites reinvade red cells
schizont
merozoites
macro-gametocyte
micro-gametocyte
sporozoite penetrates liver cell
IN MAN
IN MOSQUITO (ANOPHELES)
sporozoites injected with saliva of mosquita
gametocytes take into mosquito with blood meal
macrogamete
exflagellation microgametes
sporozoites in salivery gland
FERTILIZATION
GAMETOGENESIS
ookinete
ookinete penetrates midgut wall of mosquito to develop into oocyst
SPOROGONY
oocyst ruptures to liberate sporozoites which penetrate salivery gland


Ring
ageing
Trophozoite
schizogeny
ageing
Schizont

Modelling approach

- Base model for an individual patient (without drug) must include:
  - A distribution of ages of parasite at admission
  - Ageing of each parasite in time
  - Schizogeny at age 48 hours
- Model outputs
  - Graphs

demo_1

Characterising Resistance

- Reduction in efficacy at
  - ring stage
  - trophozoite stage
  - schizont stage
- Reduction in duration of drug effect at
  - ring stage
  - trophozoite stage
  - schizont stage
- Any combination of the above

Drugs

- Drug action graphs
  - Example: treat every 24 hours for 7 days
- Model outputs
  - Graphs
  - parasite reduction ratio at 24 hours
  - parasite reduction ratio at 48 hours
  - clearance time
  - recrudescence
  - minimum parasite load

demo_2

output	value
prr24	600
prr48	10^5
clearance	30 hours
recrudescence	no
min parasites	0.5

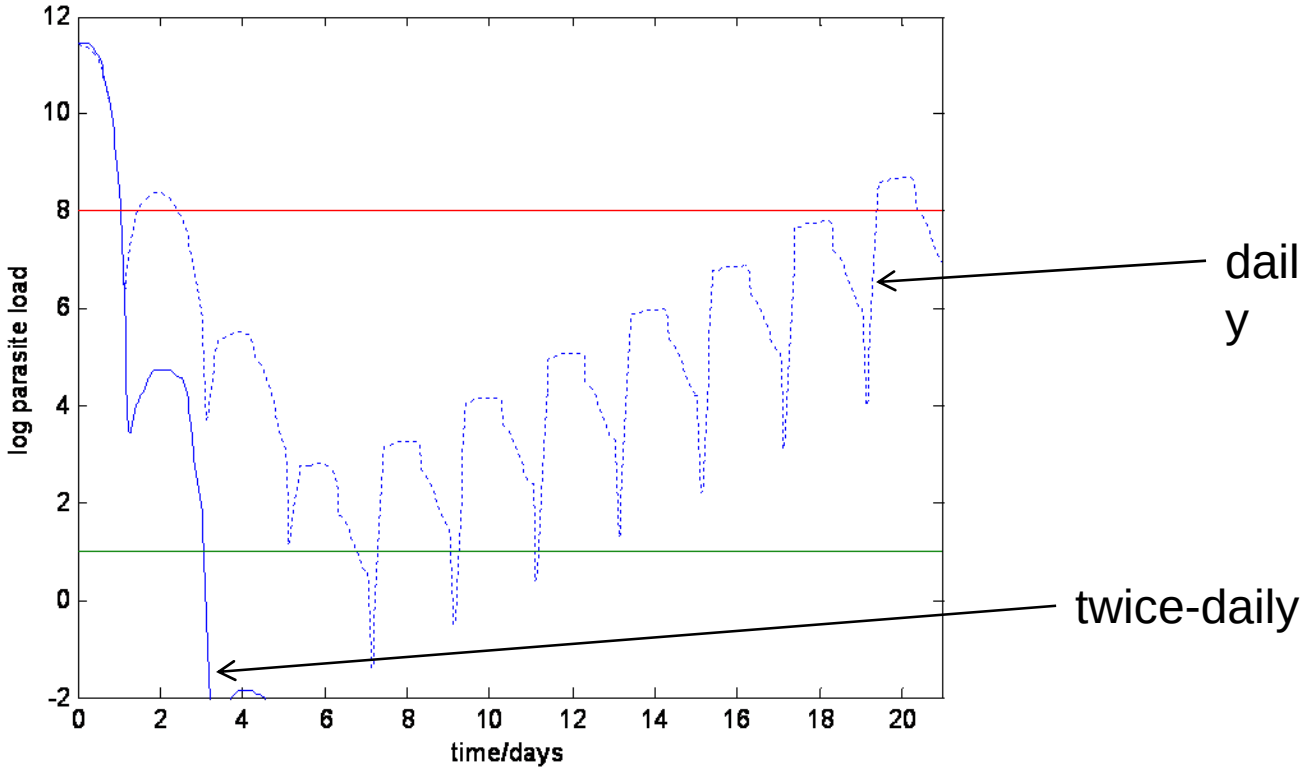
Modelling resistance

- Types of resistance
  - Reduced effect on any stage
  - Reduced duration of effect at any stage
- Example: drug has no effect on ring stages

output	value
prr24	600
prr48	1000
clearance	66 hours
recrudescence	20 days
min parasites	300

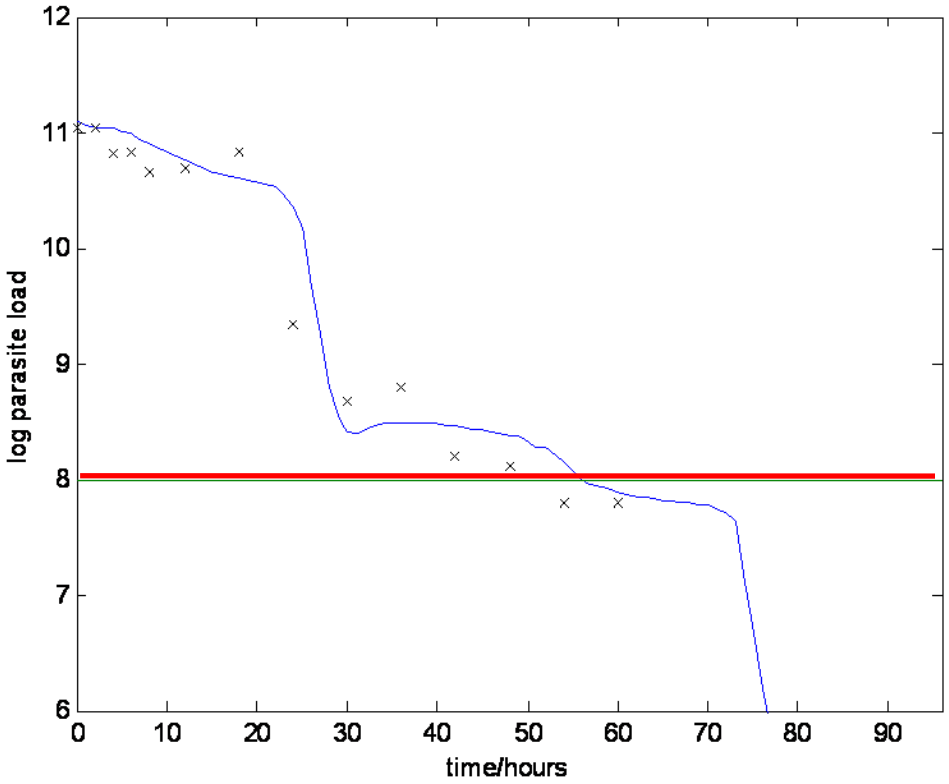
Changing the dosing regime – WORKS!

- Dosing regime
  - Every 12 hours for a week

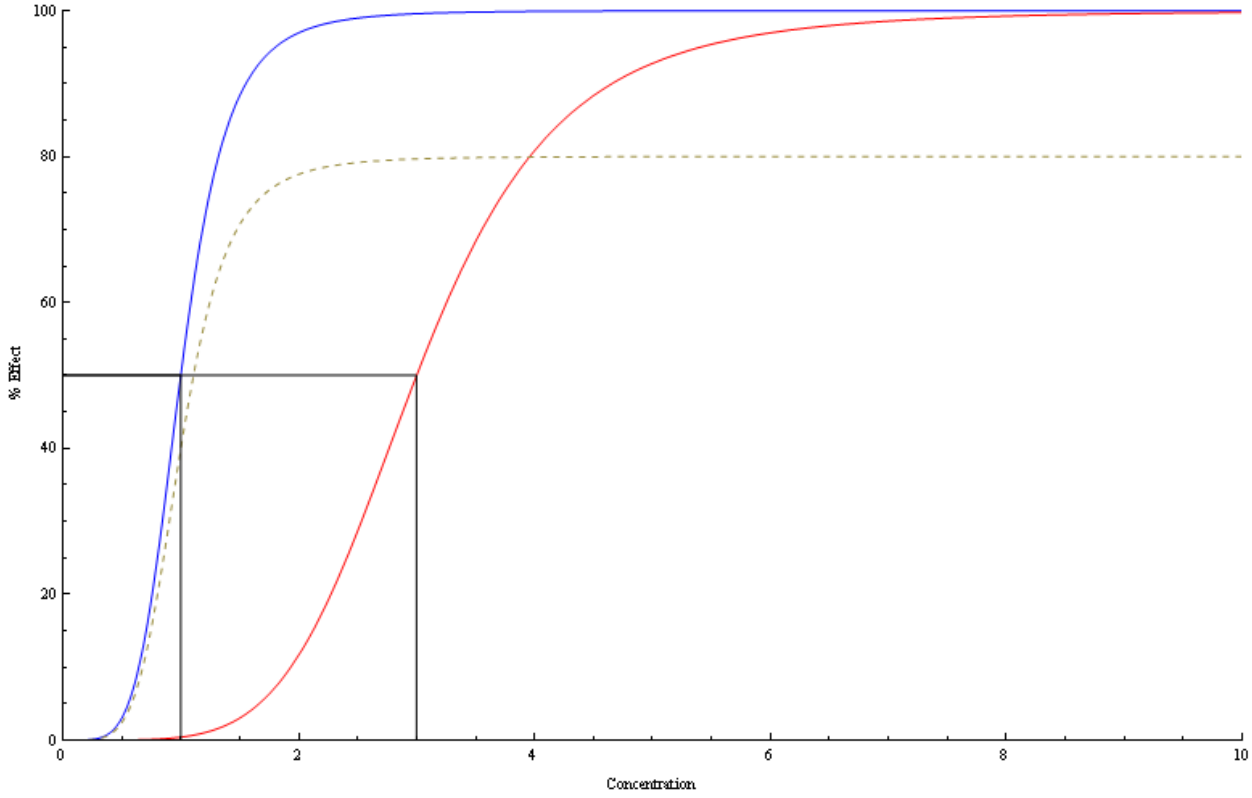


Can reproduce the data

- Patient 004
- Multiply parasites per μl by 50x80x1000



Incorporating PKPD



- Possible but not necessary for drugs with high dose and short half-life

Modelling messages

- The model can reproduce observations
- Much of the dynamics are not currently observed, but the model can predict this behaviour
- The model predicts that high clearance times are associated with
  - High initial parasite loads
  - Broad ranges of stages of parasite on admission
  - Resistance to drug
- The model predicts that increasing the frequency of doses will reduce clearance times and risk of recrudescence