Mathematical Modelling of the Elimination of Artemisinin Resistant Malaria

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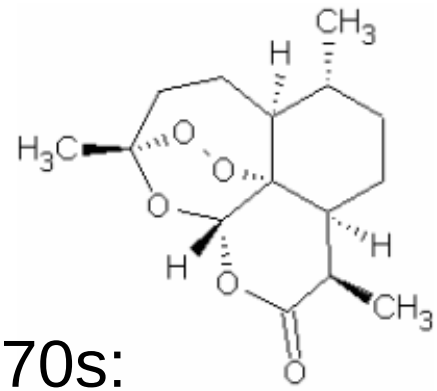
WELLCOME TRUST - MAHIDOL UNIVERSITY-OXFORD TROPICAL MEDICINE RESEARCH PROGRAMME

Introduction

Artemisia annua

Zhāng Jī (150-219 AD)



1970s:

- Artemisinins
- Most effective antimalarials

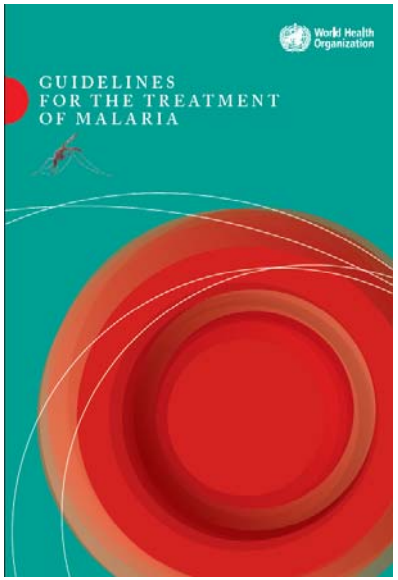
Mid 1970s: introduced to Cambodia

Introduction

- 2006

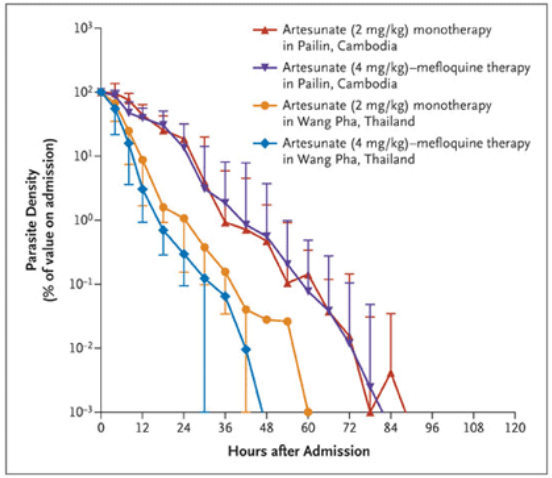
  WHO Guidelines

  – Artemisinins first-line treatment for malaria worldwide



- 2007

  – Artesunate resistance first confirmed in Pailin, Cambodia



Dondorp et al. 2009. NEJM;361:1714.

Introduction

- Pailin historic source of chloroquine and S/P resistance

- If artesunate resistance spreads from Cambodia then disaster for malaria control efforts worldwide

PLAN

- **Intensify malaria control and eliminate malaria in this region**

Challenge

- Many possible elimination strategies
- Many ways to deploy them
- Limited epidemiological data

Which would be the most effective way to eliminate artemisinin resistant malaria in western Cambodia?

Contribution of Mathematical Modelling

– Predict the impact of potential malaria control interventions alone and in combination

<u>BUT</u>

- Results needed quickly to be useful - interventions are being planned now!

– Simple and flexible approach
– Working closely with stakeholders to explore multiple scenarios quickly
– Feedback between model development and policy discussions

Methods

Population dynamic mathematical model

$$\dot{S}_{dn} = b_d P - \frac{(1-\rho)\beta S_{dn}}{}$$

$$\dot{L}_{rdn} = \frac{(1-\rho)\beta S_{dn} \sum_{n\in N}\sum_{d\in D}}{P}$$

$$\dot{B}_{rdn} = \gamma L_{rdn} - (\sigma + \nu_{B,rdn}$$

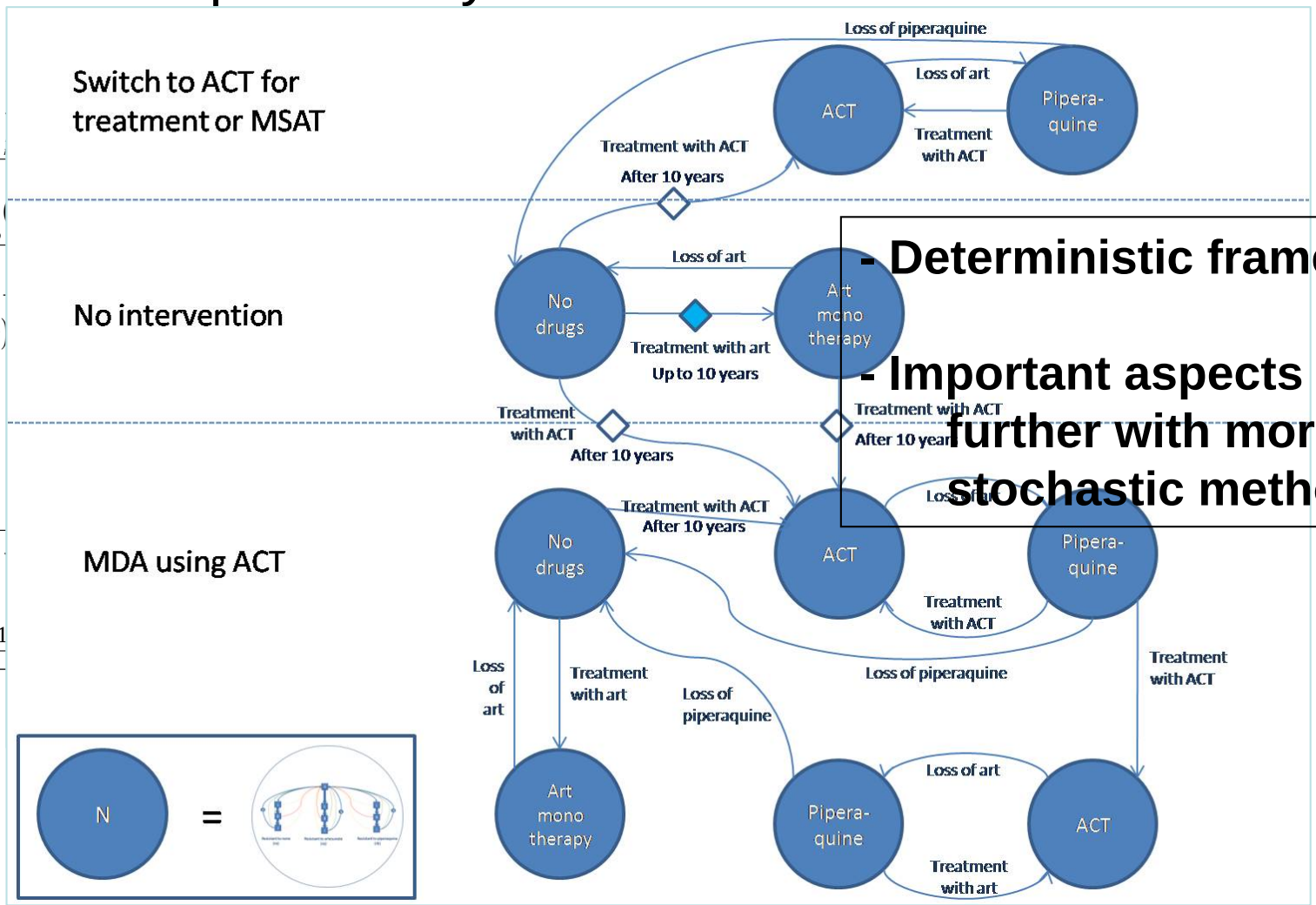
$$\dot{I}_{rdn} = \sigma B_{rdn} - (\nu_{I,rdn} + \mu)$$

$$r \in R = \{none, a, b\},$$

$$\mathbf{b} = (\mu \quad 0 \quad 0 \quad 0)$$

$$\mathbf{c} = (0 \quad c_a \quad c_b)$$

$$\mathbf{X} = \begin{pmatrix} 0 & \frac{1}{x_a} & \frac{1}{x_b - \\ 0 & -\frac{1}{x_a} & 0 \\ 0 & 0 & -\frac{1}{x_b - \\ 0 & 0 & 0 \end{pmatrix}$$



- **Deterministic framework**
- **Important aspects explored further with more detailed stochastic methods**

Maude RJ et al. Malaria J. 2009 ; 8:31.

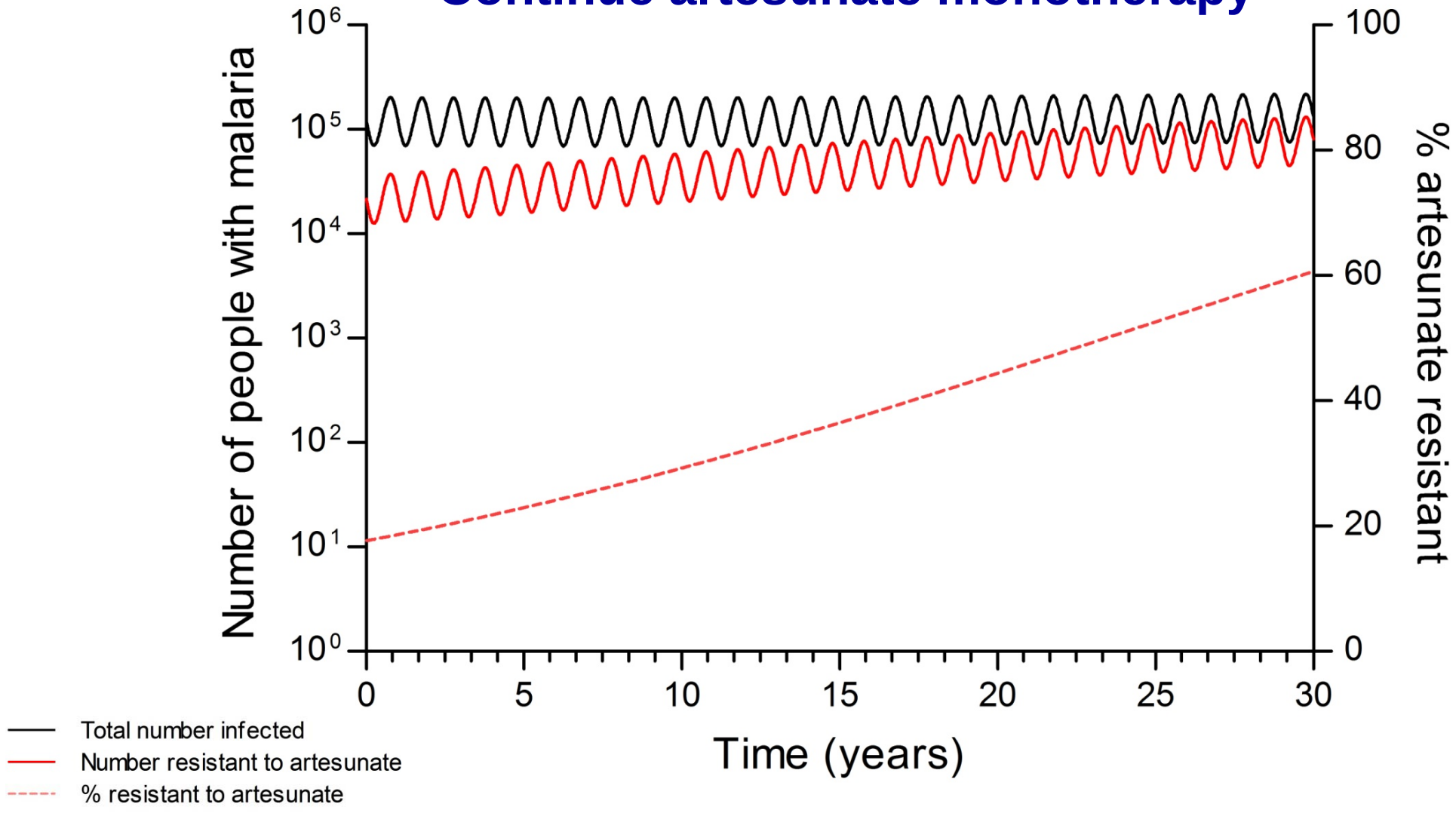
Strategies considered

- Replacing artesunate monotherapy with ACT
- ACT vs atovaquone/proguanil +/- primaquine
- Mass screen and treat (MSAT)
- Mass drug administration (MDA)
- Insecticide treated bednets

Maude RJ et al. Malaria J. 2009 ; 8:31.

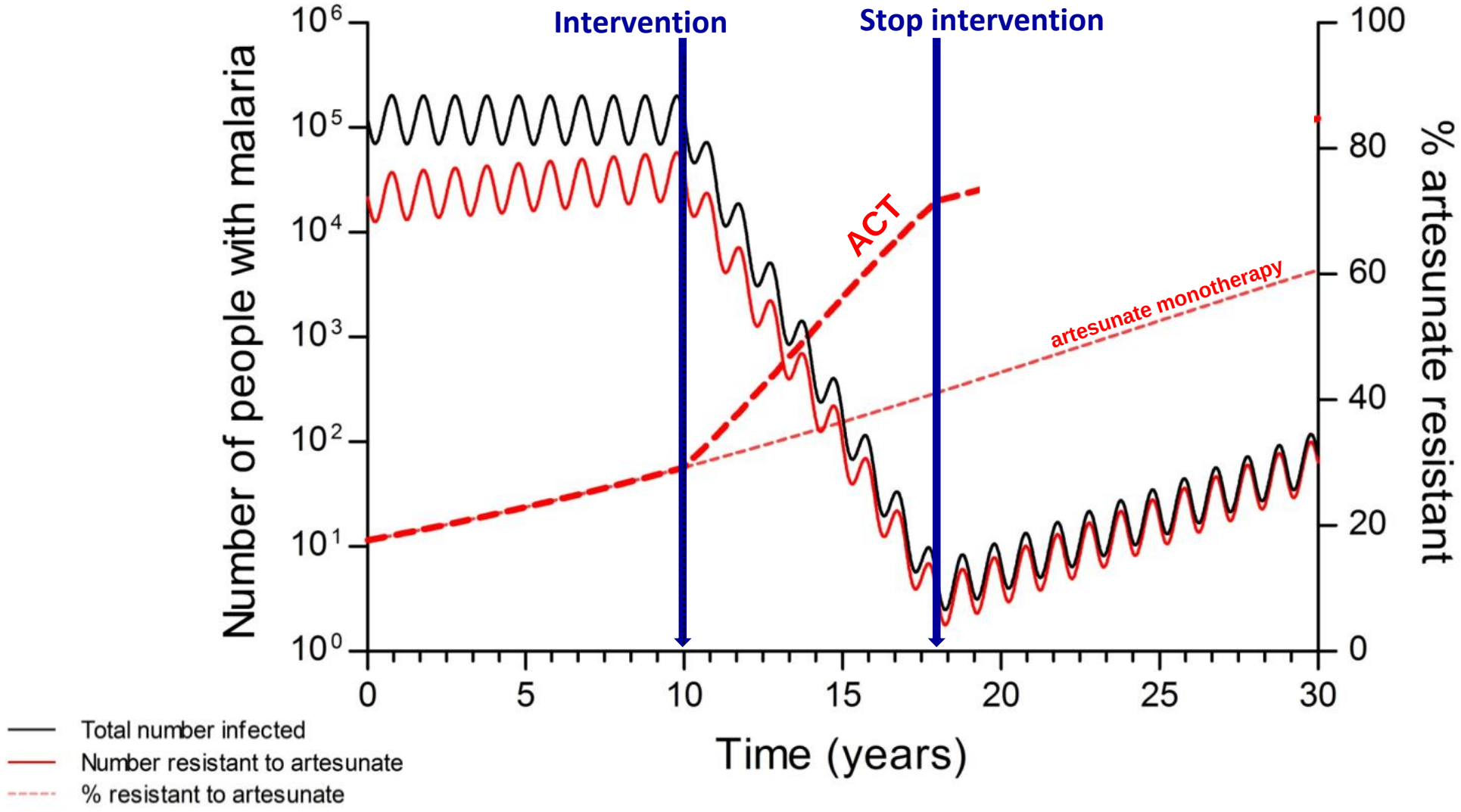
Results

Continue artesunate monotherapy



Maude RJ et al. Malaria J. 2009 ; 8:31.

Most effective intervention = replace artesunate monotherapy with high coverage ACT



Maude RJ et al. Malaria J. 2009 ; 8:31.

Conclusions: Last Man Standing is Most Resistant

- Can eliminate artemisinin-resistant malaria by switching treatment to effective ACTs with high coverage

  (even better when combined with bed nets)

BUT

- ACTs will increase the proportion of artemisinin-resistant infections
- Therefore critical that ensure complete elimination of ALL malaria
- Failure to do so would worsen the problem and lead to more rapid spread of resistance

Maude RJ et al. Malaria J. 2009 ; 8:31.

Challenge

If use ACTs to control artemisinin-resistant malaria…

…how can we maximise their impact to ensure elimination?

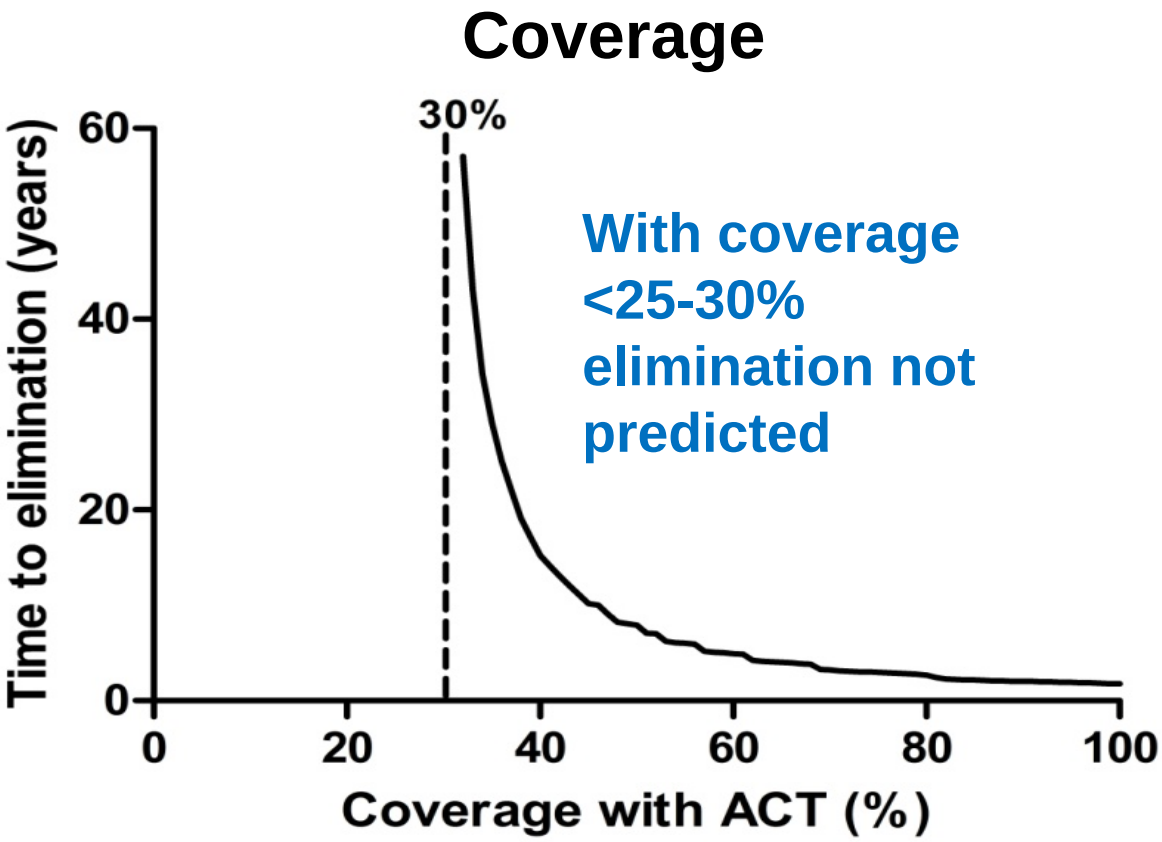
Modelling

Model can be used to explore:

- How should ACT be given?

- What are most important attributes of a partner drug?
  - (target product profiles of current and future ACT partner drugs)

How to Give ACT

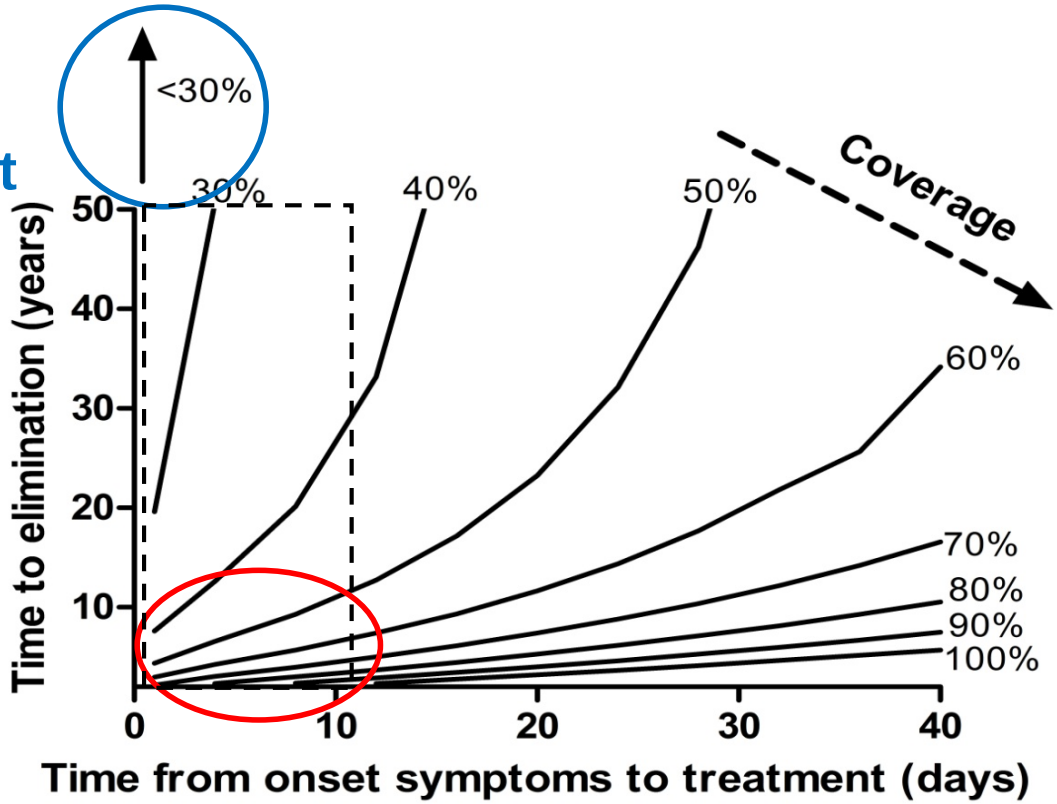


Aim for:

- **Coverage >50%**

How to Give ACT

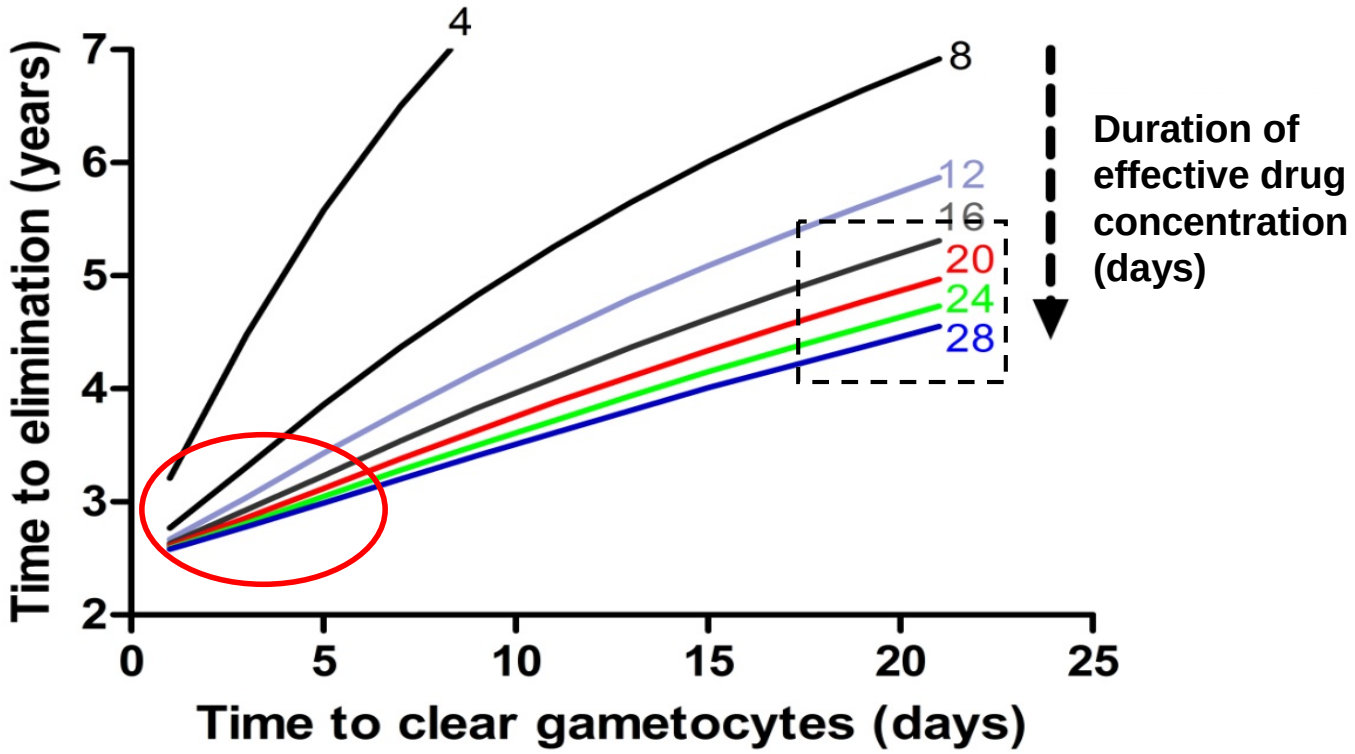
With coverage <25-30% elimination not predicted



Aim for:

- **Coverage >50%**
- **Early treatment**

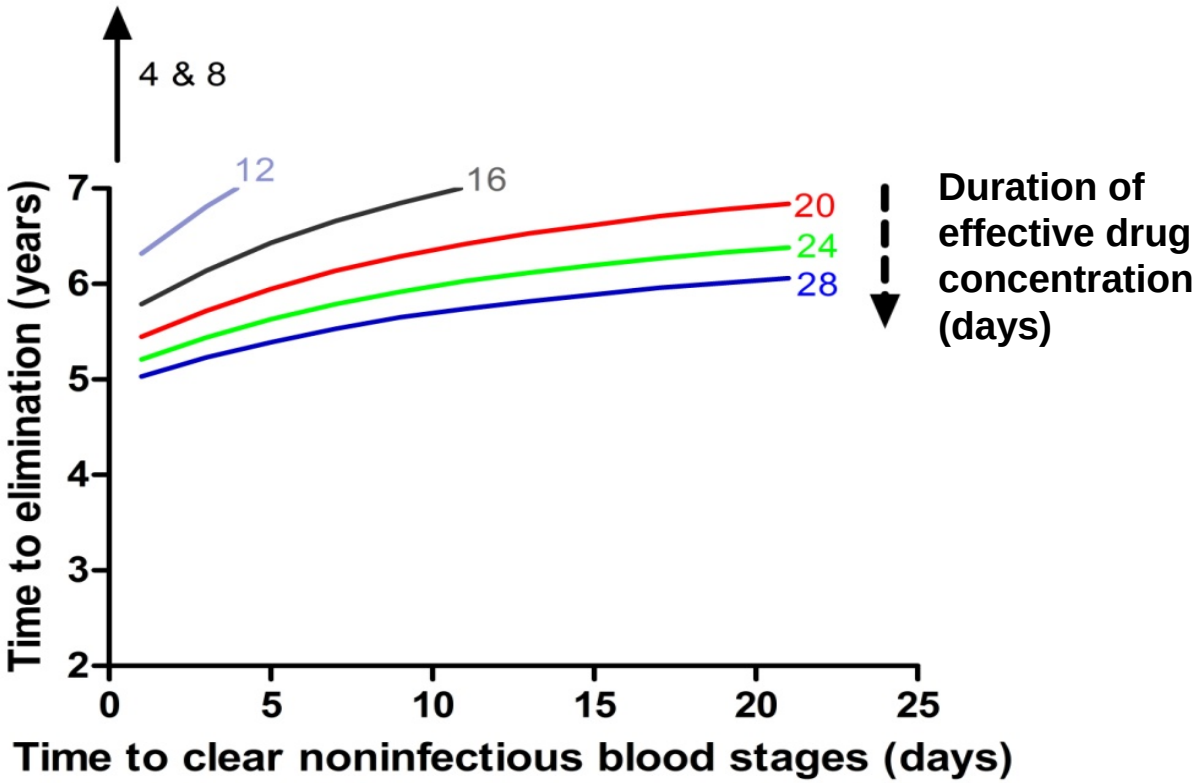
Target Product Profiling - gametocytes



Aim for: **Rapid action against gametocytes**

Duration of effective concentration >12 days but increases risk of partner drug resistance

Target Product Profiling – asexual stages



Activity against noninfectious blood stages less important

Aim for: **Duration of effective concentration >20 days but increases risk of partner drug resistance**

Conclusions

Eliminating artemisinin-resistant malaria with ACTs:

How to Give ACT:

Increasing coverage has the greatest predicted impact

- **>50% coverage**
- **Early treatment**

Target Product Profiling of partner drug:

Activity against gametocytes more important than asexual stages

- **Rapid action against gametocytes**
- **Duration of effective concentration >12-20 days**

(but shorter if high risk of resistance to partner drug)

Next steps…

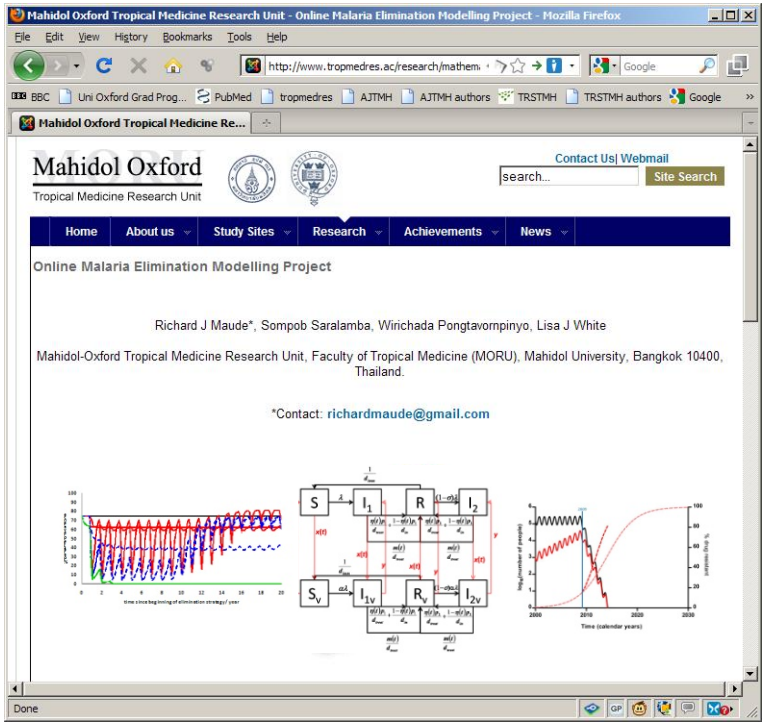
- Web-based collaborative malaria elimination model

  www.tropmedres.ac/elimination

- Other drugs and control measures

- Individual-based model of drug action

- Spatial modelling



Acknowledgements

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Any questions?