Modelling competition dynamics of drug resistant malaria

Tamsin E. Lee and Melissa Penny
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Via a theoretical model: What dynamics have the strongest influence on the frequency of resistance within a population?

↓ Recombination  ↓ Suppression  ↑ Competitive release

How does this vary by setting and strategy?

~ 3%, ~ 15%, ~ 40% prevalence (all ages)
5%, 40%, 80% probability of being treated in two weeks
Overview

The model

The dynamics

Sensitivity analysis
The model
Adapted SIS model to include within host dynamics (not an explicit within-host model). Hosts carry a mix of sensitive and resistant parasitaemia.

**Input:** Parameters for key dynamics

**Output:** The proportion of resistant parasitaemia in the whole population
Multiple infections

\[ S \]

- \( I_S \) 0
- \( I_{RSS} \) 0.33
- \( I_{RS} \) 0.5
- \( I_{RRS} \) 0.67
- \( I_R \) 1

Suppression (untreated)
Competitive release (treated)
Demonstration

Infection time

Density transmitted to humans
Demonstration

R

S

Density transmitted to humans

Infection time

Infection time

Infection time
Demonstration

Density transmitted to humans

Infection time
Demonstration

R

S

Density transmitted to humans

Infection time

Infection time

Infection time
Within-host ↔ between-host

Mosquitoes

$R$

S

Density transmitted to humans

↓ Recombination

$R$

S

Density transmitted from humans
Within-host ↔ between-host

Mosquitoes

Density transmitted to humans

Transmission rate

Humans

Density transmitted from humans

Infected, untreated

↓Recombination

↓Suppression (Transmission rate)
Within-host ↔ between-host

Mosquitoes

R

S

Density transmitted
to humans

↓ Recombination

Humans

R

S

Infected, untreated

Max. prob. of being treated
Period treatment possible

↓ Suppression
(Transmission rate)

R

S

Density transmitted
from humans

↓ Competitive release

↑ Suppression
(Transmission rate)

R

S

Infected, treated

Drug efficacy
Drug half-life
Adherence

↓ Suppression
(Transmission rate)
**Within-host ↔ between-host**

**Mosquitoes**
- R (Infected)
- S (Untreated)
- Density transmitted to humans

**Humans**
- R (Infected, untreated)
- S (Infected, treated)

**Transmitting rates**
- Transmission rate

**Factors affecting transmission rate**
- Suppression (Transmission rate)
- Competitive release (Transmission rate)
- Drug efficacy
- Drug half-life
- Adherence

**Infection length**
- Reduction in S infection length
- Reduction in R infection length

**Other factors**
- Max. prob. of being treated
- Period treatment possible

**Additional factors**
- Recombination
Resistance added after 500 days (dashed line).
Proportion of resistant infections (without dynamics)

Medium transmission

High transmission

Time (years)

Resistant prop.
The dynamics
Recombination

None $\{0\}$ $\rightarrow$ $\{0.1\}$ $\rightarrow$ Maximum $\{1\}$
Suppression

None \{0\} \rightarrow \{0.004\} \rightarrow \text{Maximum} \{1\}
Suppression

None \{0\} \quad \rightarrow \quad \{0.004\} \quad \rightarrow \quad \text{Maximum \{1\}}
Competitive release $[\not\not SR] \rightarrow [SR] \Rightarrow [SRR]$
Competitive release $[\emptyset SR] \rightarrow [SR] \Rightarrow [SRR]$

None $\{0\}$  $\rightarrow$  $\{0.1\}$  $\rightarrow$  Maximum $\{1\}$
Sensitivity analysis
Sensitivity analysis (Single effects)

Med. transmission vs. High transmission

- **Suppression**
- **Recombination**
- **Comp. release**

Sensitivity (in direction of influence on resistance)
Sensitivity analysis (Total effects)

<table>
<thead>
<tr>
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<th>Med. transmission</th>
<th>High transmission</th>
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<tr>
<td>Suppression</td>
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Suppression
Recombination
Comp. release

Sensitivity (in direction of influence on resistance)
Main effects

Medium transmission

High transmission

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Dynamic effects (high transmission only)

Simulation

Comp. release | Recombination | Suppression

Dyn. (black) | Resistance (red)

0.0 0.5 1.0 | 0.000 0.005 0.010 0.015

Med. treatment

High treatment
Summary
Modelling multiple infections

Model within-host dynamics without explicitly modelling parasite density.

Can track:

**Dynamics** - ↓ recombination  ↓ suppression  ↑ competitive release

**Infection parameters** - *Infection length (S&R)*

**Treatment parameters** - *Treatment rate that changes in time, reduction in infection length (S & R)*

**Treatment parameters** - *Drug efficacy, drug half-life, adherence*
When there is little resistance in the population, competitive release dominates and thus resistance spreads.

When there is high resistance in the population, recombination and suppression have more influence, especially when transmission is high.

Treatment increases the proportion of resistant parasitaemia, with or without competitive release. However, the spread of resistance is greatly hindered by recombination, and failing that, suppression.
Acknowledgements

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