Can we depend on case management to prevent re-establishment of P. falciparum malaria, after local interruption of transmission?

Swiss Meeting for Infectious Disease Dynamics
24 August 2011

Valerie Crowell
Swiss TPH
Malaria control - a highly dynamic system

Effects of health systems

Malaria economic underdevelopment
(Dar es Salaam)

Anopheles feeding-cycle

Plasmodium Life-cycle

Anopheles Life-cycle
Interventions against malaria

- Case management
- Vaccines
- Intermittent treatment
- Insecticide Treated Nets
- Indoor Residual Spraying
- Larval control (source reduction or larviciding)
- Repellents/Deterrents
- Integrated control (combinations)
International funding for malaria is increasing...

Figure 1.6: Evolution of international funding disbursements for malaria

Source: World Malaria Report 2008. Geneva, World Health Organization, 2008 (Government, UN Agencies, Bilaterals, EU); GFATM website; PMI operational plans; USAID website; World Bank Booster Program (see appendix on methodology)
...contributing to reductions in malaria burden

Zanzibar


The Gambia

Can (eventual) malaria eradication now be envisaged?

October 17, 2007

Bill and Melinda Gates Call for New Global Commitment to Chart a Course for Malaria Eradication
World Health Organization Definitions

**Eradication**: permanent reduction to zero of the worldwide incidence of infection caused by a specific agent as a result of deliberate efforts. Intervention measures are no longer needed once eradication has been achieved.

**Elimination**: interrupting local mosquito-borne malaria transmission in a define geographical area - **ie, zero incidence of locally contracted cases**, although imported cases will continue to occur. Continued intervention measures are required.
Countries: malaria-free, eliminating, or controlling?

Locally-acquired malaria cases in the U.S., 1957–2002

FIGURE 1. Number of locally acquired malaria cases, by year—United States, 1957–2003

The U.S. is classified as malaria-free, but local transmission still occurs

Imported malaria in Singapore in 2005

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Short Report: A Large Cluster of Imported Plasmodium falciparum Malaria among Nigerian Expatriate Students

Mei L. Kang*, Liyang Hsu, and Asok Kurup
Department of Internal Medicine, Infectious Diseases Unit, Singapore General Hospital, Singapore

Abstract. Singapore reported the elimination of malaria in 1982, but this country remains vulnerable to imported malaria. We describe a large cluster of 16 cases of imported Plasmodium falciparum malaria in visiting Nigerian students. More than half were asymptomatic and diagnosed only on screening. Although early diagnosis and treatment of patients averted local transmission of disease, our report illustrates the vulnerability of malaria-free countries to the introduction of malaria in this age of increasing globalization and ease of travel.

"There were no reports of local transmission of P. falciparum malaria resulting from this large cluster of imported infection in the subsequent months. We believe that early diagnosis, treatment, and screening of the asymptomatic students prevented local transmission of the infection."
Imported and endemic malaria in the Caribbean

"For the first time in fifty years, Jamaica (211 cases) is listed as both an endemic and a non-endemic country (CAREC, 2007)."


Chandy C. John, Melissa A. Riedesel, Ng’wena G. Magak, Kim A. Lindblade, David M. Menge, James S. Hodges, John M. Vulule, and Willis Akhwale

Figure 1. Malaria incidence and number of patients seen at health dispensaries in 2 highland areas of western Kenya, April 2003–March 2008. A) Monthly incidence of malaria/1,000 persons in Kipsamoite. B) Monthly incidence of malaria/1,000 persons in Kapusiwa. C) No. patients who came to the Kipsamoite health dispensary. D) No. patients who came to the Kapusiwa health dispensary. Gaps in panels A and B indicate that no data were collected during these periods. Arrows indicate when indoor residual spraying was conducted in the 2 areas.
Can interruption of transmission be maintained (and how)?

• Chance that transmission remains interrupted depends largely on
  • vulnerability (risk of importation of infections)
  • receptivity (vectorial capacity)
  • case detection and treatment rate
• with important implications for malaria strategy
• Under which conditions can a policy of surveillance and case response alone be pursued?
Stochastic Simulation of Malaria Epidemiology & Control

- To provide predictions of likely health impacts and cost effectiveness of different strategies for controlling *Plasmodium falciparum* malaria across the range of transmission intensities found in countries with endemic malaria.
  - Investigate comprehensive set of interventions
  - Reliable and quantitative predictions
  - Cost-effectiveness → policy → local planners
- Discrete-time stochastic individual-based simulation
- Modular components
- Simulations via volunteer computing
- Impacts of different intervention strategies can be compared over long time horizons
- **Useful predictions**: eg Vaccines (Tediosi et al 2009, Penny et.al. 2008, Maire et.al. 2006)
Dealing with model uncertainty: ensembles

Base model (2006)

- Log-normal heterogeneity in force of infection
- Decay in blood-stage immunity
- Discrete variation in force of infection
- Discrete variation in access to treatment
Simulation strategy

Health system using ACT: p of accessing treatment for uncomplicated malaria in any five day period: 0-1.0, stepsize 0.1

Infection importation rate (only via human route): 0.02, 0.2, 2.0, 20.0 per 1000 pop per year

Pre-intervention EIR (transmission setting): 2, 20, 50

For each scenario:
- 14 different stochastic sub-models / parameterisations
- 100 runs
- Population size 1,000 individuals
- East African pattern of seasonality
- At year 5, interrupt transmission by mass treatment and uninfecting vectors
Simulation results, smoothed by sub-model

Top: EIR=2, IIR=2 per 1000 pa, CMC= 20%; Bottom: EIR=2, IIR=2 per 1000 pa, CMC= 80%

Lines: sub-model medians
Polygons: 95% probability intervals of sub-models
- Cases post-year 5.25 < threshold -> interruption maintained

- In low transmission settings, case management is important to prevent re-establishment at middle IIRs; where IIRs are > ~2 per 1,000 pop. p.a. maintaining interruption will be difficult without continued vector control

- In higher transmission settings, case management has a more moderate effect; except at extremely low IIRs, interruption will likely not be maintained

Top: EIR=2, Middle: EIR=20, Bottom: EIR=50. White bars: IIR= 0.02; Light gray bars: IIR= 0.2, Middle gray bars: IIR=2, Dark gray bars: IIR= 20
Predicted odds ratio that transmission remains interrupted (EIR= 2)

<table>
<thead>
<tr>
<th>Model identifier</th>
<th>Description</th>
<th>Half-life of decay (years)</th>
<th>odds ratio</th>
<th>95% ci</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$t_{1/2} = -\frac{\ln (2)}{\alpha_s}$</td>
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<tr>
<td>R0125</td>
<td>Fixed decay in immune proxies</td>
<td>$10^a$</td>
<td>$\infty$</td>
<td>4.57 4.02 5.21</td>
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<tr>
<td>R0132</td>
<td>Estimation of decay in immune proxies</td>
<td>14</td>
<td>$\infty$</td>
<td>4.31 3.79 4.90</td>
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<tr>
<td>R0115</td>
<td>Fixed decay in effective cumulative exposure</td>
<td>$\infty$</td>
<td>$10^a$</td>
<td>4.17 3.67 4.74</td>
</tr>
<tr>
<td>R0133</td>
<td>Estimation of both decay parameters</td>
<td>19</td>
<td>250</td>
<td>3.89 3.42 4.42</td>
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<tr>
<td>R0131</td>
<td>Estimation of decay in effective cumulative exposure</td>
<td>$\infty$</td>
<td>1187</td>
<td>2.42 2.14 2.74</td>
</tr>
<tr>
<td>R0065</td>
<td>Mass action: $E_a(i,t)$ varies between and within hosts</td>
<td>$\infty$</td>
<td>$\infty$</td>
<td>2.18 1.93 2.47</td>
</tr>
<tr>
<td>R0670</td>
<td>Heterogeneity in susceptibility to comorbidity</td>
<td>$\infty$</td>
<td>$\infty$</td>
<td>2.03 1.80 2.30</td>
</tr>
<tr>
<td>R0063</td>
<td>Mass action: $E_a(i,t)$ varies mainly between hosts</td>
<td>$\infty$</td>
<td>$\infty$</td>
<td>1.86 1.64 2.10</td>
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<tr>
<td>R0121</td>
<td>Fixed decay in immune proxies</td>
<td>$1000^a$</td>
<td>$\infty$</td>
<td>1.63 1.45 1.84</td>
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<td>R0068</td>
<td>Mass action: $E_a(i,t)$ varies mainly within hosts</td>
<td>$\infty$</td>
<td>$\infty$</td>
<td>1.44 1.27 1.62</td>
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<tr>
<td>R0111</td>
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<td>$\infty$</td>
<td>1000$^a$</td>
<td>1.30 1.15 1.46</td>
</tr>
<tr>
<td>R0674</td>
<td>Uncorrelated heterogeneities in access to treatment and susceptibility to comorbidity</td>
<td>$\infty$</td>
<td>$\infty$</td>
<td>0.63 0.56 0.71</td>
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<tr>
<td>R0678</td>
<td>Heterogeneity in access to treatment</td>
<td>$\infty$</td>
<td>$\infty$</td>
<td>0.56 0.50 0.63</td>
</tr>
</tbody>
</table>

For each sub-model relative to the base model. $E_a(i,t)$ is the expected number of entomological inoculations, adjusted for age and individual factors. $a$ These parameters were fixed, in other models the decay parameters were estimated. Decays shorter than the shortest fixed values gave unacceptable fits to the data.
Predicted odds ratio that transmission remains interrupted (EIR= 20)

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<td>( \infty )</td>
<td>1.53</td>
</tr>
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<td>R0125</td>
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<td>10 (^d)</td>
<td>( \infty )</td>
<td>1.47</td>
</tr>
<tr>
<td>R0133</td>
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<td>19 (^a)</td>
<td>250</td>
<td>1.37</td>
</tr>
<tr>
<td>R0131</td>
<td>Estimation of decay in effective cumulative exposure</td>
<td>( \infty )</td>
<td>1187</td>
<td>1.36</td>
</tr>
<tr>
<td>R0115</td>
<td>Fixed decay in effective cumulative exposure</td>
<td>( \infty )</td>
<td>10 (^d)</td>
<td>1.29</td>
</tr>
<tr>
<td>R0132</td>
<td>Estimation of decay in in immune proxies</td>
<td>14</td>
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<td>1.29</td>
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<td>R0670</td>
<td>Heterogeneity in susceptibility to comorbidity</td>
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\[
\frac{1}{2} \ln(2) = \frac{-1 \ln(2)}{\alpha_b} \quad \frac{1}{2} \ln(2) = \frac{-1 \ln(2)}{\alpha_c}
\]
Issues to consider

Risk of re-establishment depends on:

- Population size
- Degree of connectedness between human populations
- Geographical and temporal heterogeneities in imported infections

Results need to be combined with evaluation of operational and financial feasibility
Current Research Team

**Applied Mathematics**
Melissa Penny (Swiss TPH)
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Marcel Tanner (Swiss TPH)

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Katherine Winter (LSTM)
Olivier Briet (Swiss TPH)

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Tom Smith (Swiss TPH)

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Michael Tarantino (Swiss TPH)
Tiago Antão (LSTM)
Henning Mortveit (VBI)

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Josh Yukich (Swiss TPH)
Lesong Conteh (LSHTM)
Valerie Crowell (Swiss TPH)

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Bill & Melinda Gates Foundation, PATH-MACEPA,
Swiss National Science Foundation
Background slides
Malaria

Endemic in most of the tropics
Large % of population can be infected
Acquired immunity prevents disease but not infection
~ 250 million illness episodes per year
Major cause of death
Up to 40% of public health expenditure
Indirect cost through lost productivity
Many interventions possible, none perfect
Resource constrained context
Structure of malaria simulator

- Malaria infection of the human
- Infectious mosquitoes
- Emergent mosquitoes
- Asexual blood stage
- Immunity
- High parasite density
- Clinical events and case management
  - Uncomplicated clinical malaria
  - Severe malaria
  - Mortality

Positive relationship
Negative relationship
Overall scope of the project

Transmission Potential

Intervention package

Costs of interventions

Patterns of infection, morbidity & mortality without intervention

Burden of disease without intervention

Intervention-modified patterns of infection, morbidity & mortality

Intervention-modified burden of disease

Predicted intervention cost-effectiveness

Costs of disease
Programme phases: from control to elimination

Figure 5. Malaria programme phases and milestones on the path to malaria elimination

- SPR <5% in fever cases
- <1 case/1000 population at risk/year
- 0 locally acquired cases
- WHO certification
- 3 years

SPR: slide or rapid diagnostic test positivity rate.

*a These milestones are indicative only: in practice, the transitions will depend on the malaria burden that a programme can realistically handle (including case notification, case investigation, etc.).