Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Associated Institute of the University of Basel

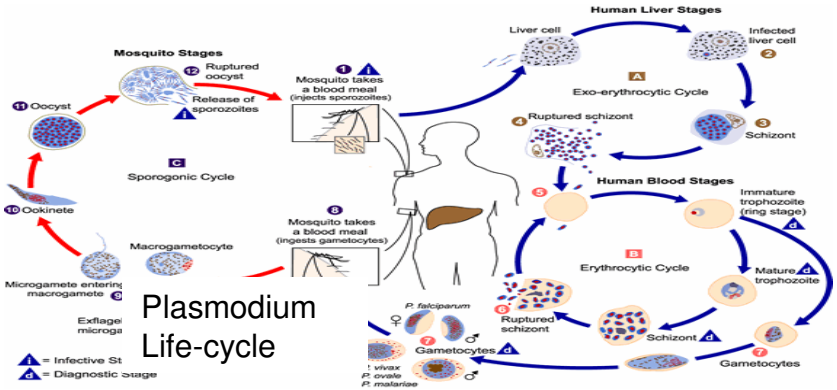
Dept of Epidemiology and Public Health
Biostatistics and Computational Sciences Unit

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

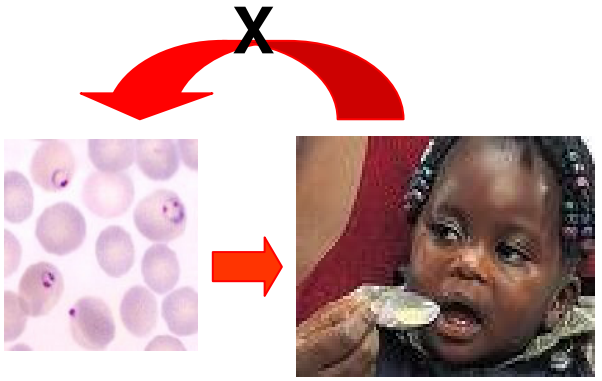
Swiss Meeting for Infectious Disease Dynamics
24 August 2011

Valerie Crowell
Swiss TPH

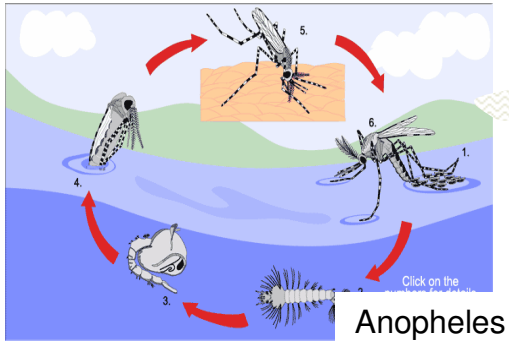
Malaria control- a highly dynamic system



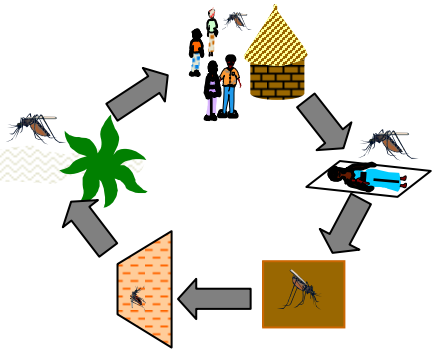
Plasmodium Life-cycle



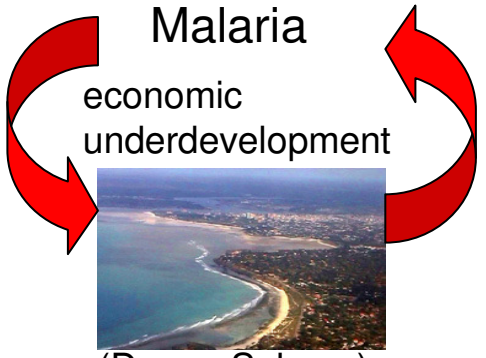
Effects of health systems



Anopheles Life-cycle



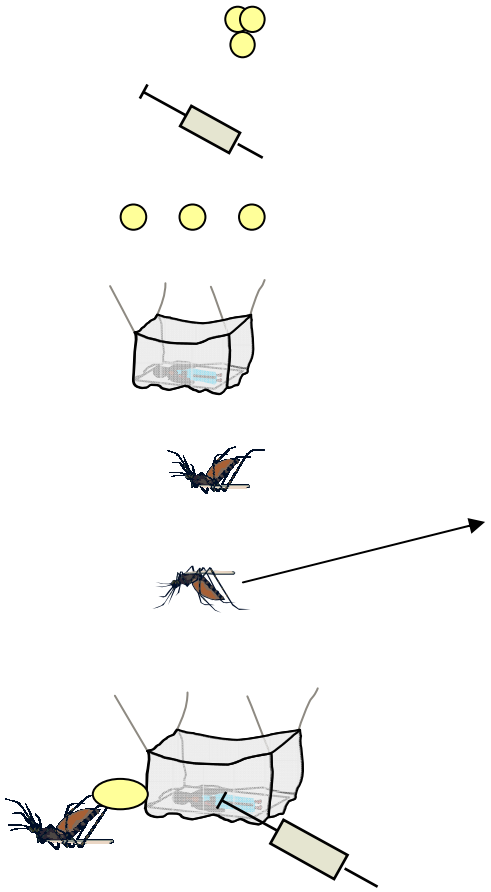
Anopheles feeding-cycle



(Dar es Salaam)

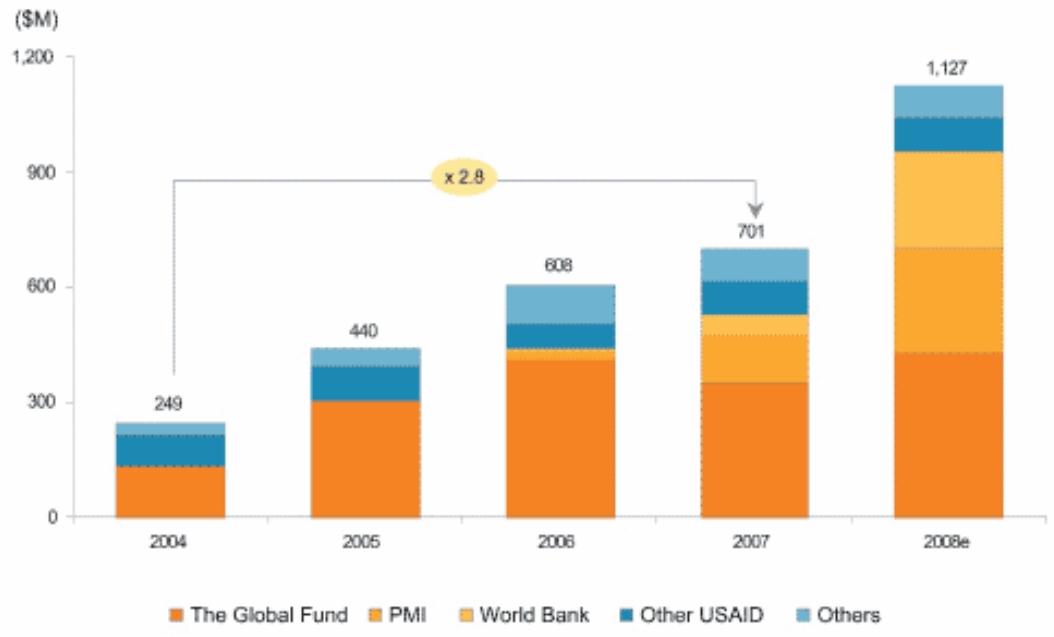
Interventions against malaria

- 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 I.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

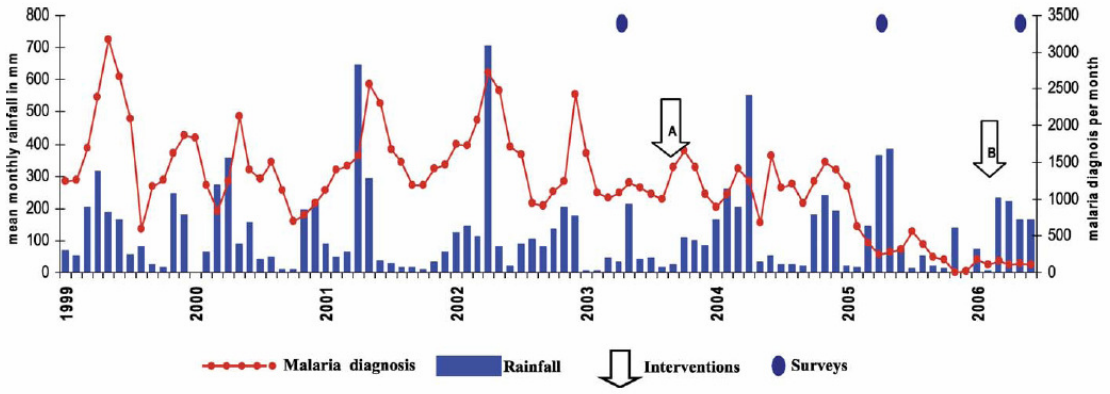
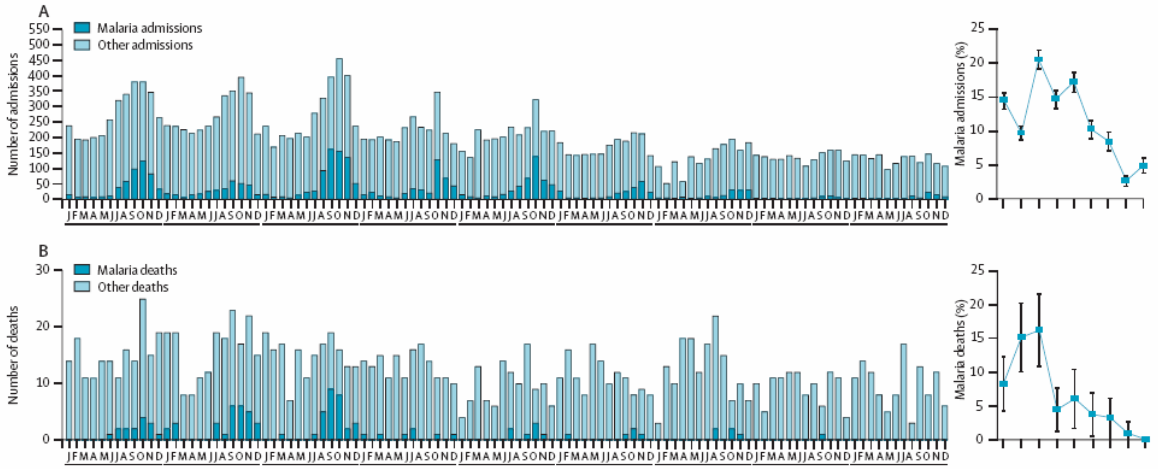


Figure 1. Malaria Interventions, Cross-Sectional Surveys, Monthly Rainfall, and Reported Clinical Malaria Diagnoses in Children under 5 Years of Age in North A District, Zanzibar

(A) Start of the implementation of artemisinin-based combination therapy for treatment of uncomplicated malaria in September 2003.
(B) Introduction of LLINs in February 2006. Promotion of ITNs started in January 2004; the use of conventional ITNs, however, remained low, until the introduction of LLINs. Outpatient data for 2006 are up to June.
doi:10.1371/journal.pmed.0040309.g001

Source: Bhattarai A, Ali AS, Kachur SP et al. Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar. *PLoS Med.* 2007;4:e309.

The Gambia



Source: Ceesay SJ, Casals-Pascual C, Erskine J et al. Changes in malaria indices between 1999 and 2007 in The Gambia: a retrospective analysis. *Lancet.* 2008;372:1545-1554.

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

malERA
Malaria Eradication Research Agenda

UCSF Global Health Group
Malaria Elimination Group guidance and evidence for malaria elimination

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?

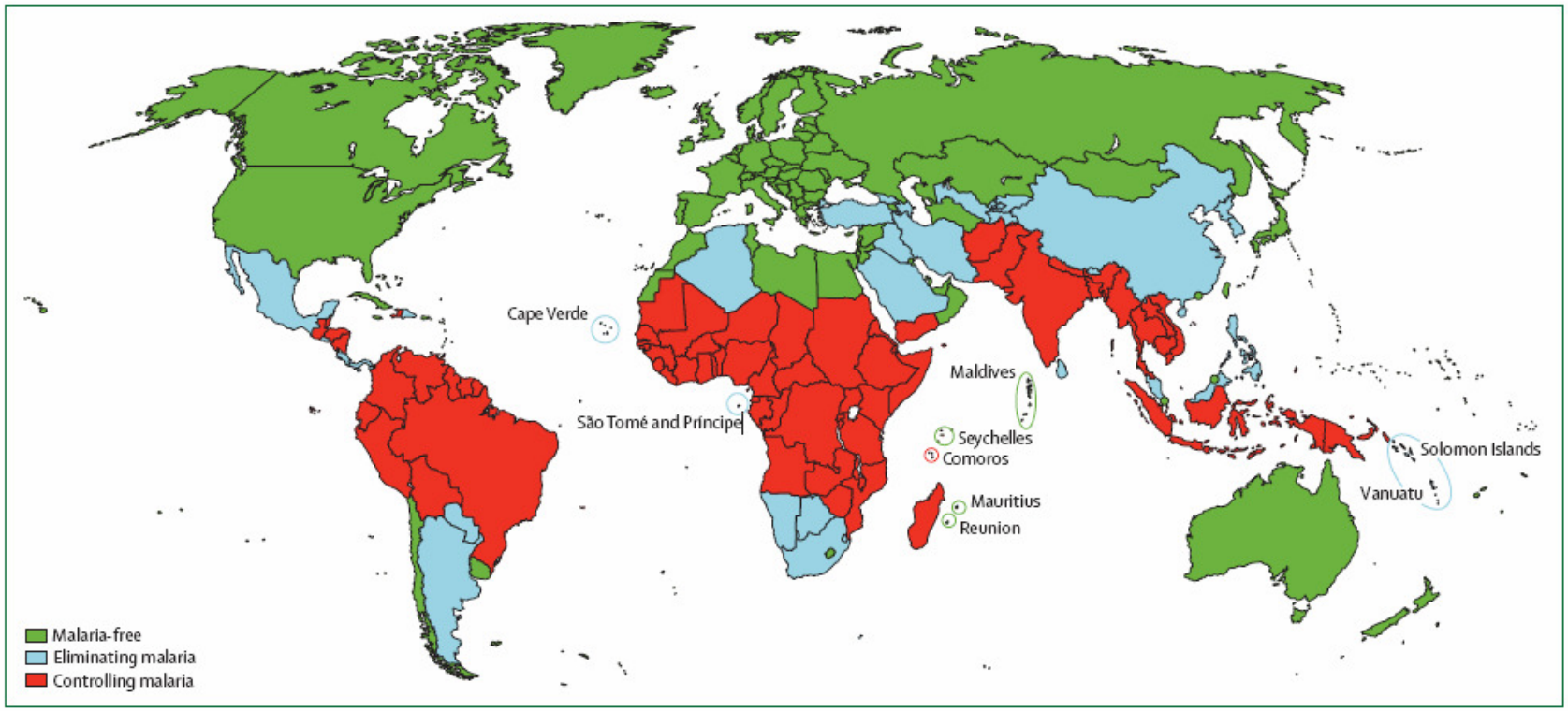
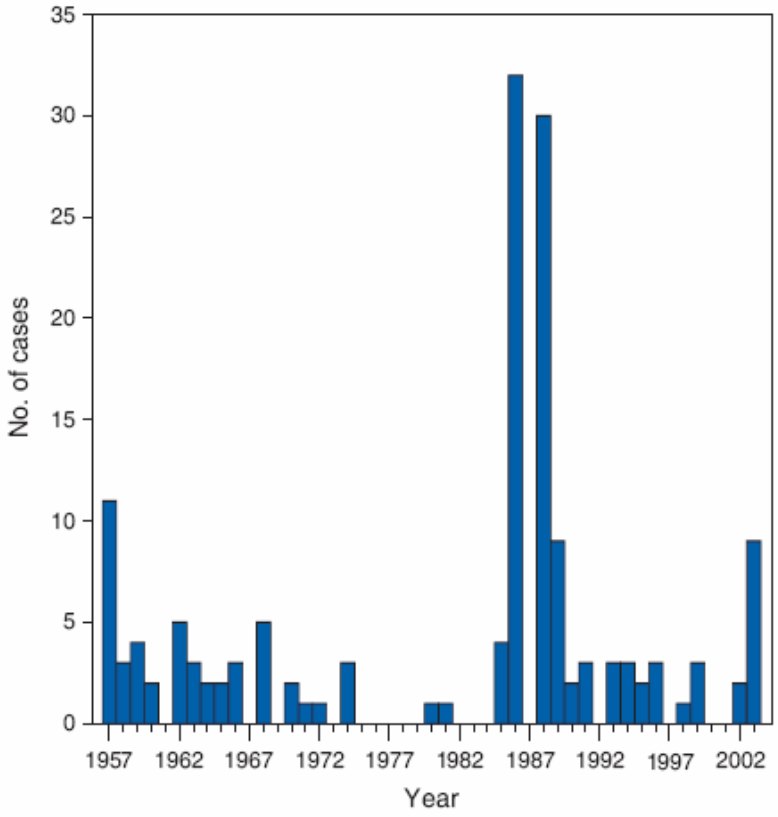


Figure 1: Categorisation of countries as malaria free, eliminating malaria, or controlling malaria, 2010

Source: Feachem RG, Phillips AA, Hwang J, Cotter C, Wielgosz B. Greenwood BM, Sabot O, Rodriguez MH, Abeyasinghe RR, Ghebreyesus TA, Snow RW. **Shrinking the malaria map: progress and prospects.** Lancet. 2010 Nov 6;376(9752):1566-78.

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

Source: Filler SJ, MacArthur JR, Parise M, Wirtz R, Eliades MJ, Dasilva A, Steketee R: **Locally acquired mosquito-transmitted malaria: a guide for investigations in the United States.** *MMWR Recomm Rep* 2006 , **55**(RR-13)**:**1-9.

Imported malaria in Singapore in 2005

Am. J. Trop. Med. Hyg., 77(4), 2007, pp. 790–792

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

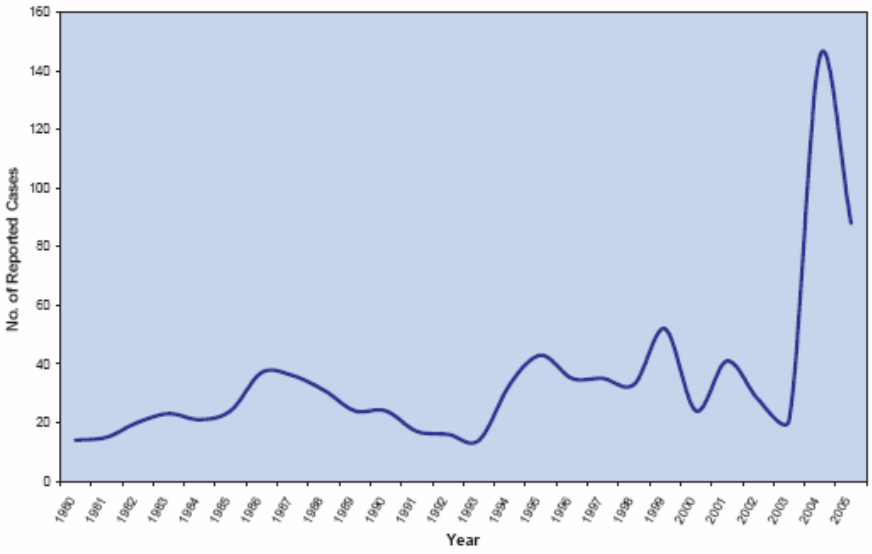


Fig. 2a: Confirmed cases of malaria (imported) by year, all CAREC member countries, 1980–2005.

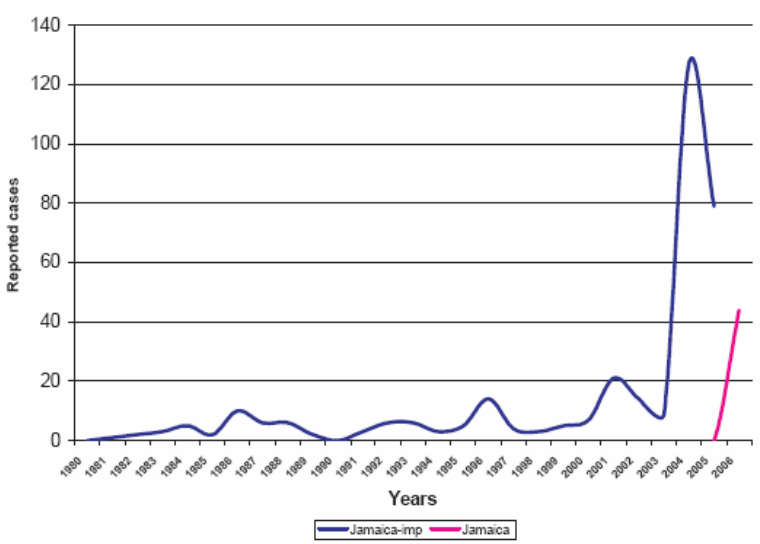


Fig. 2c: Reported cases of indigenous and imported malaria in Jamaica.

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

Source: Rawlins SC, Hinds A, Rawlins JM. **West Indian Med J 2008; 57 (5): 462**

Possible Interruption of Malaria Transmission, Highland Kenya, 2007–2008

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

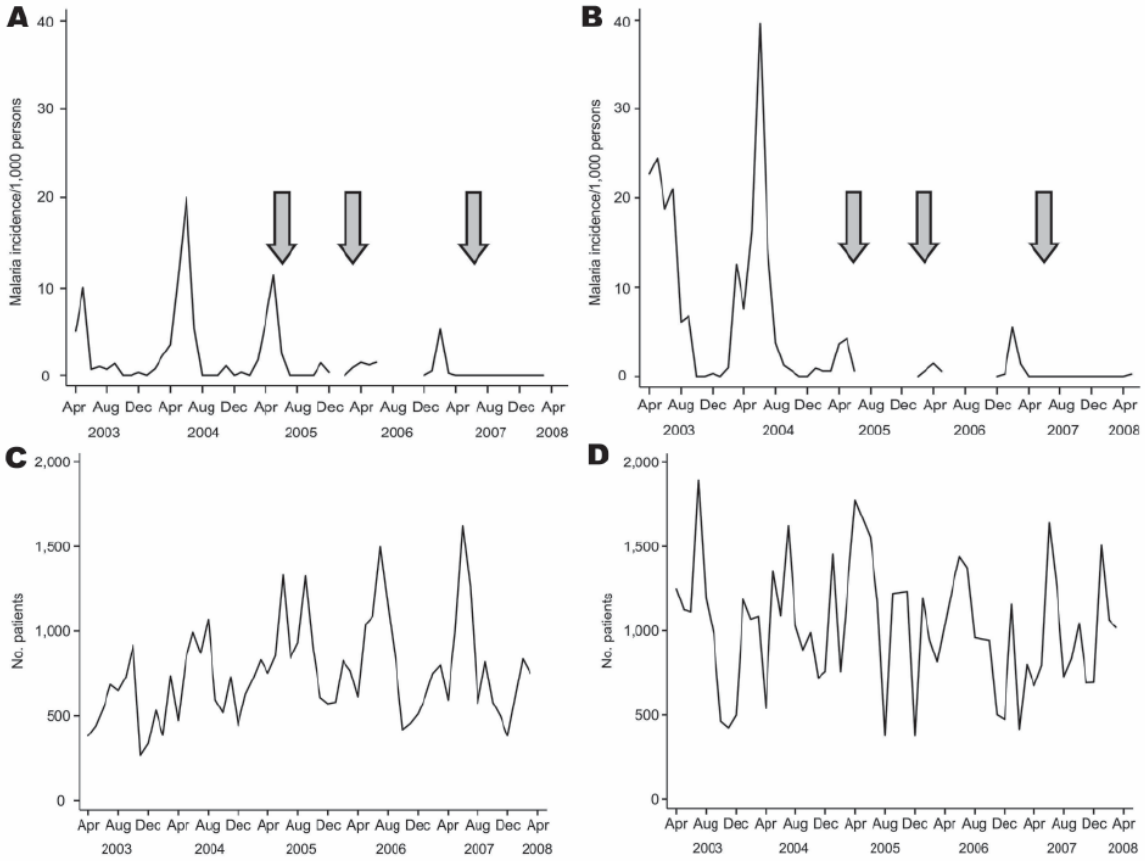
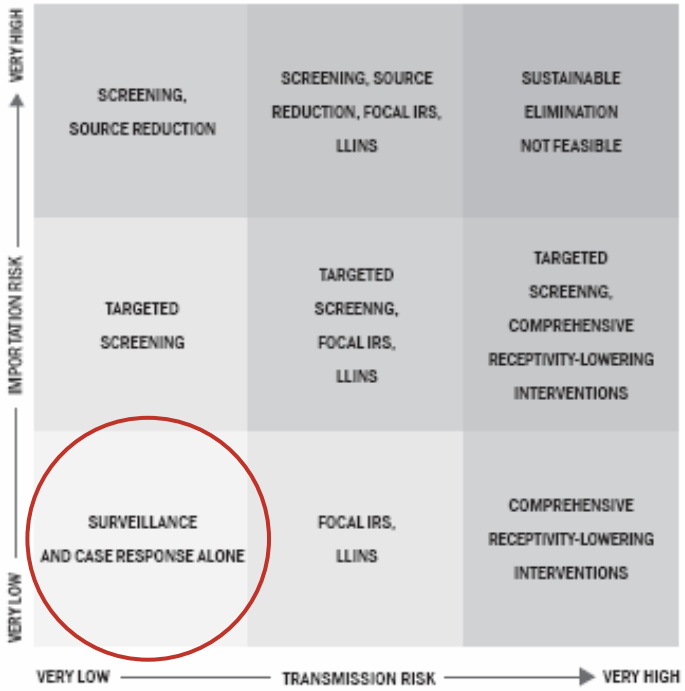


Figure 1. Malaria incidence and number of patients seen at health dispensaries in 2 highland areas of western Kenya, April 2003–March 2008. A) Monthly incidence of malaria/1,000 persons in Kipsamoite. B) Monthly incidence of malaria/1,000 persons in Kapsisiywa. C) No. patients who came to the Kipsamoite health dispensary. D) No. patients who came to the Kapsisiywa 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?

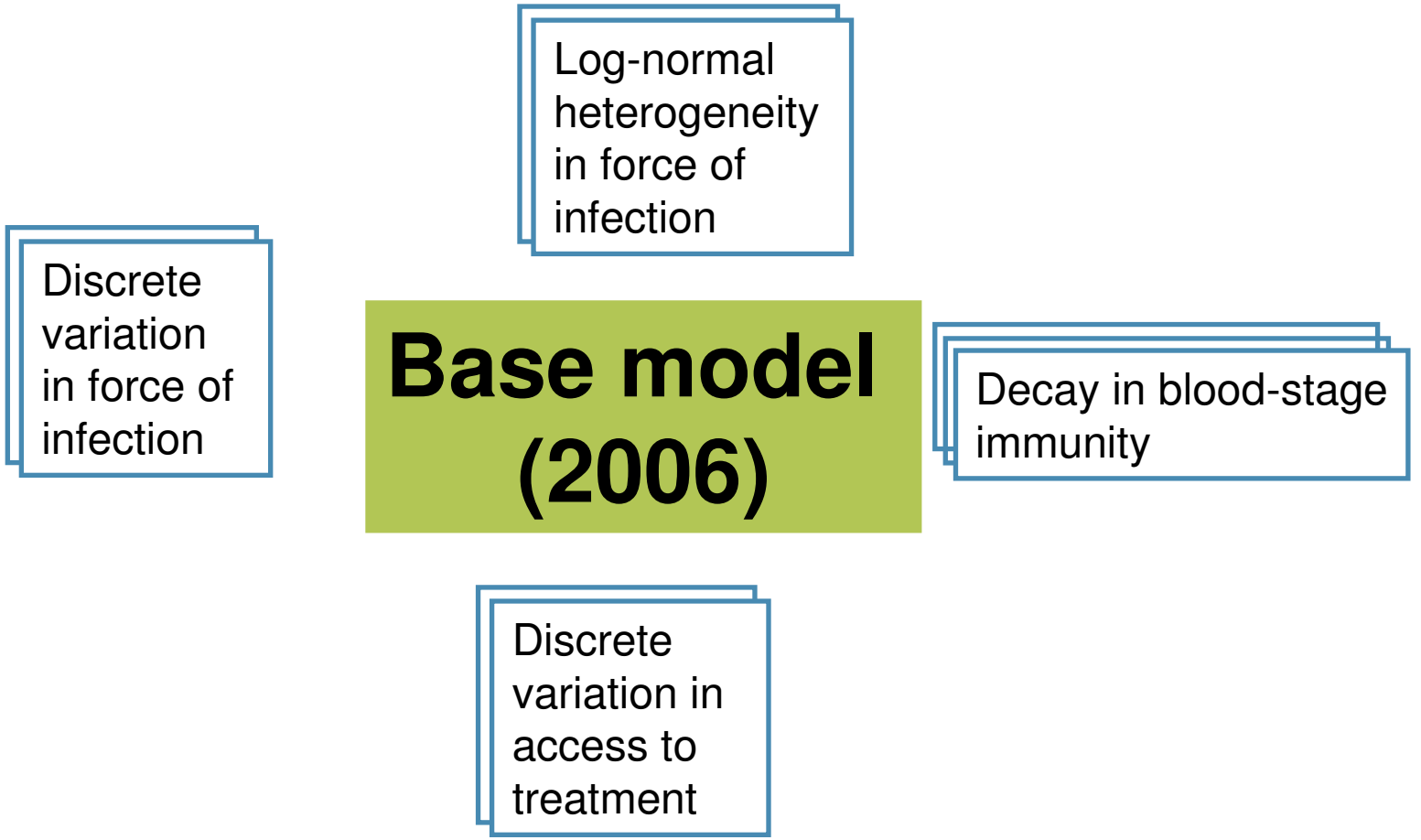
FIGURE 4: VARYING CONTROL MEASURE REQUIREMENTS FOR SUSTAINABLE ELIMINATION ACCORDING TO RELATIVE LEVELS OF OUTBREAK RISK AND IMPORTATION RISK (ADAPTED FROM COHEN ET AL., 2009)



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



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

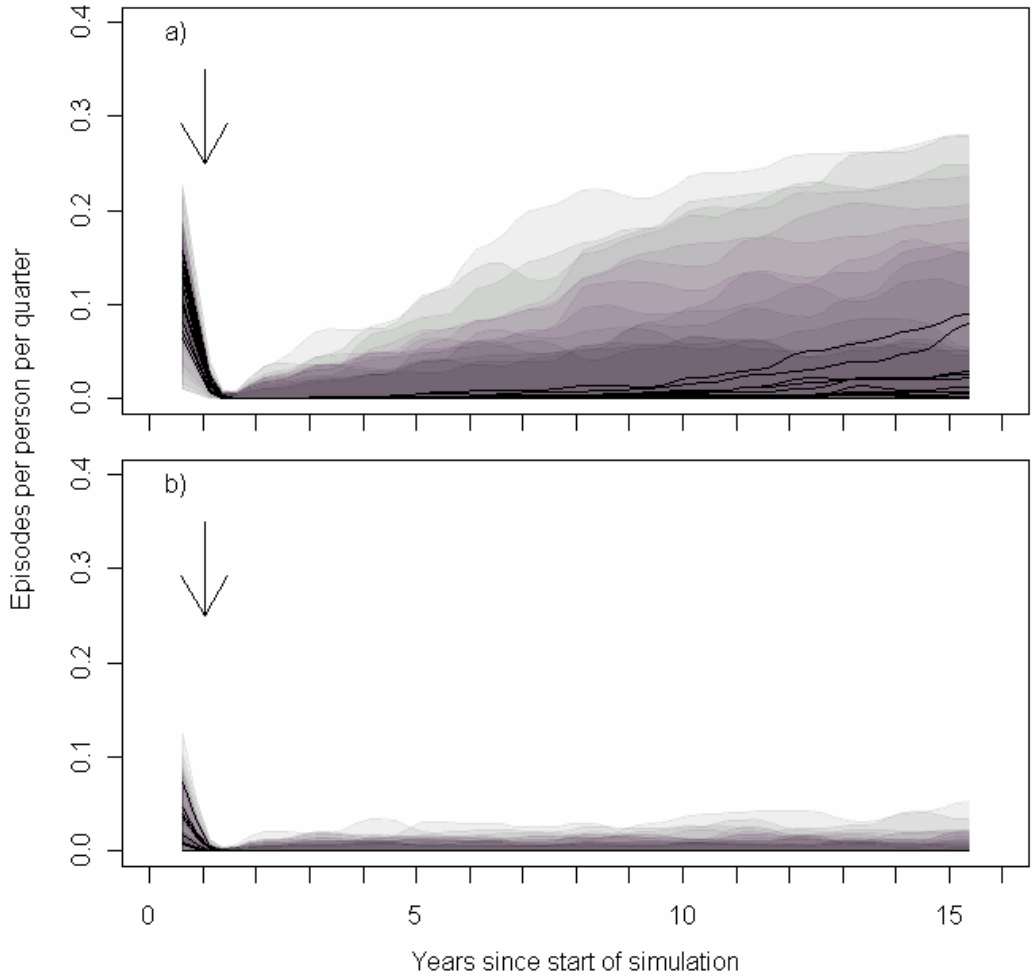
–100 runs

- Population size 1,000 individuals

- East African pattern of seasonality

- At year 5, interrupt transmission by mass treatment and uninfecting vectors

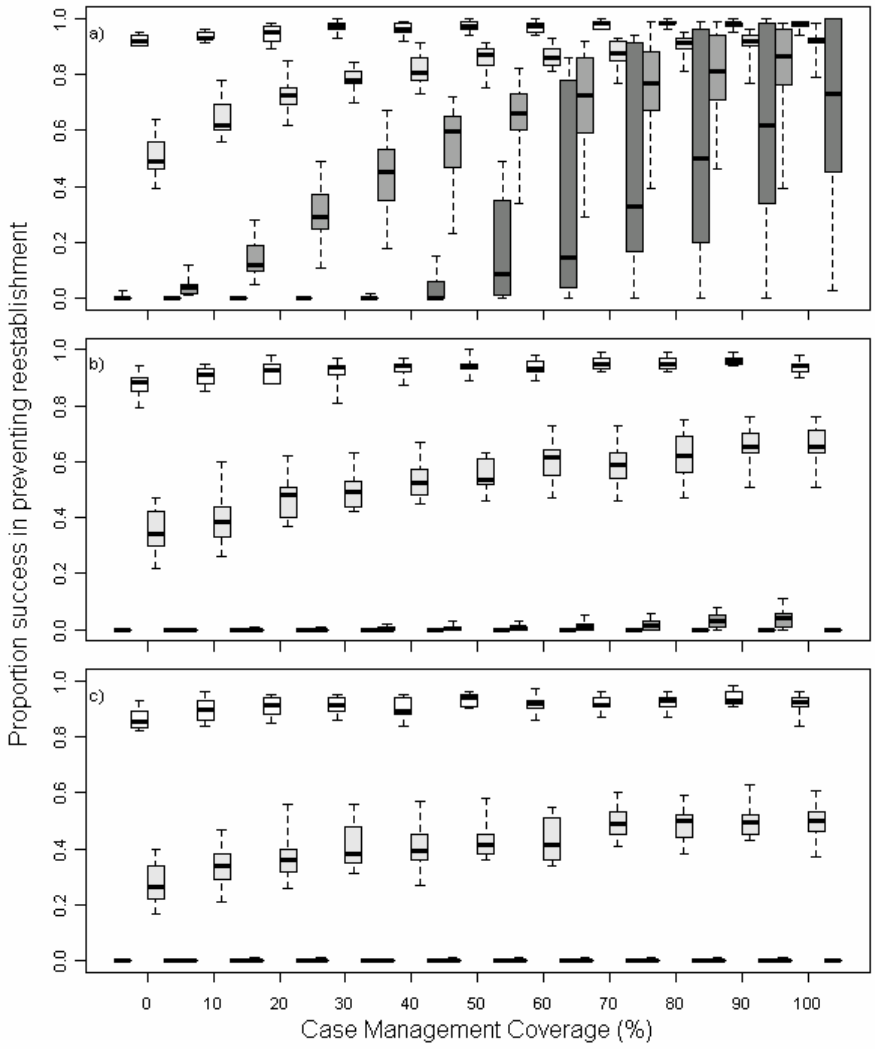
Simulation results, smoothed by sub-model



Lines: sub-model medians
Polygons: 95% probability intervals of sub-models

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

Model predictions, proportion success in preventing re-establishment



- 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)

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

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)

Model identifier	Description	Half-life of decay (years)		odds ratio	95% ci	
		$t_{1/2} = \frac{-\ln(2)}{\alpha_b}$	$t_{1/2} = \frac{-\ln(2)}{\alpha_c}$			
R0063	Mass action:$E_a(i,t)$ varies mainly between hosts	∞	∞	2.04	2.37	1.75
R0065	Mass action: $E_a(i,t)$ varies between and within hosts	∞	∞	1.89	2.20	1.63
R0068	Mass action: varies mainly within hosts	∞	∞	1.53	1.78	1.32
R0125	Fixed decay in immune proxies	10 [d]	∞	1.47	1.71	1.27
R0133	Estimation of both decay parameters	19	250	1.37	1.59	1.18
R0131	Estimation of decay in effective cumulative exposure	∞	1187	1.36	1.58	1.17
R0115	Fixed decay in effective cumulative exposure	∞	10 [d]	1.29	1.50	1.11
R0132	Estimation of decay in in immune proxies	14		1.29	1.49	1.11
R0670	Heterogeneity in susceptibility to comorbidity	∞	∞	1.22	1.41	1.05
R0121	Fixed decay in immune proxies	1000[d]	∞	1.18	1.37	1.02
R0111	Fixed decay in effective cumulative exposure	∞	1000[d]	1.14	1.33	0.98
R0674	Uncorrelated heterogeneities in access to treatment and susceptibility to comorbidity	∞	∞	1.04	1.21	0.89
R0678	Heterogeneity in access to treatment	∞	∞	0.87	1.02	0.75

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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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

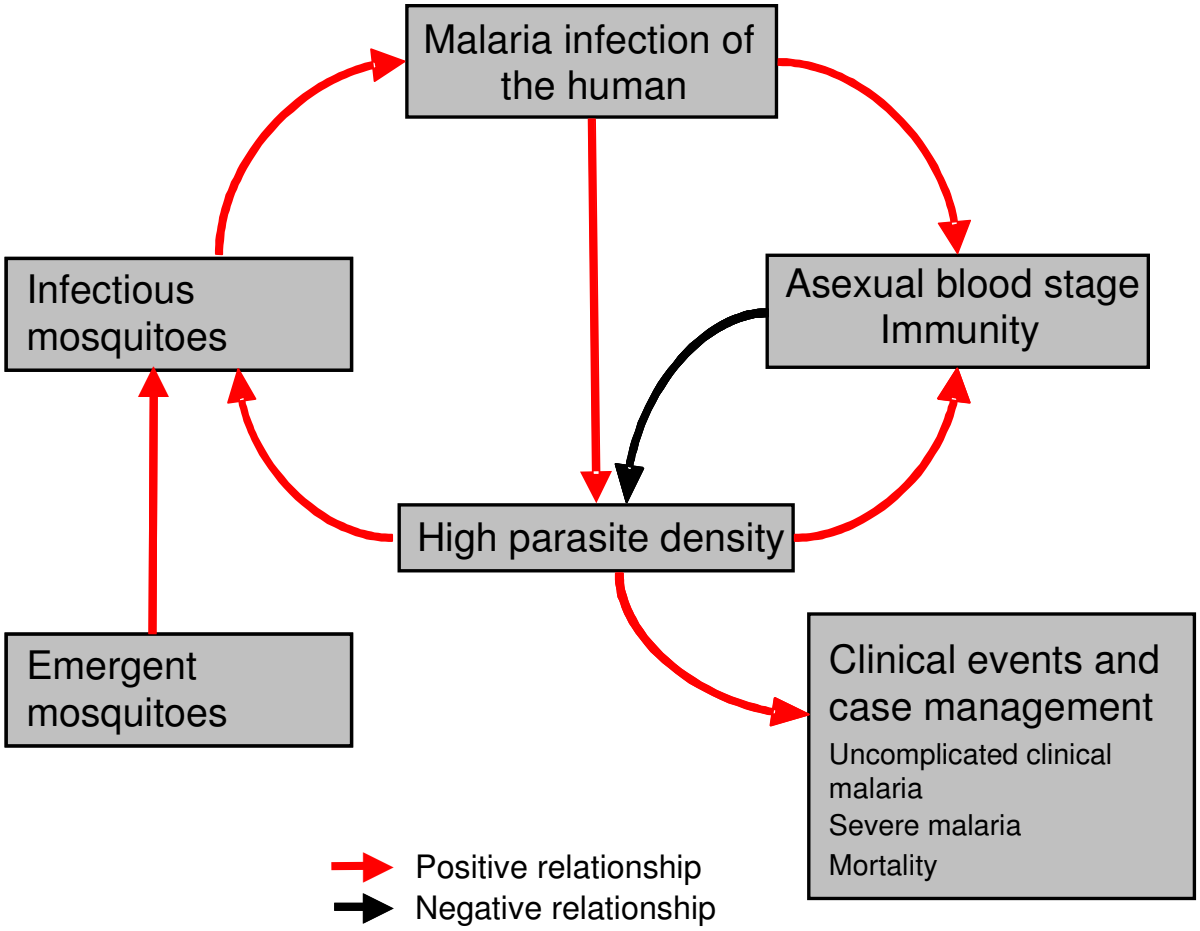
Up to 40% of public health expenditure

Indirect cost through lost productivity

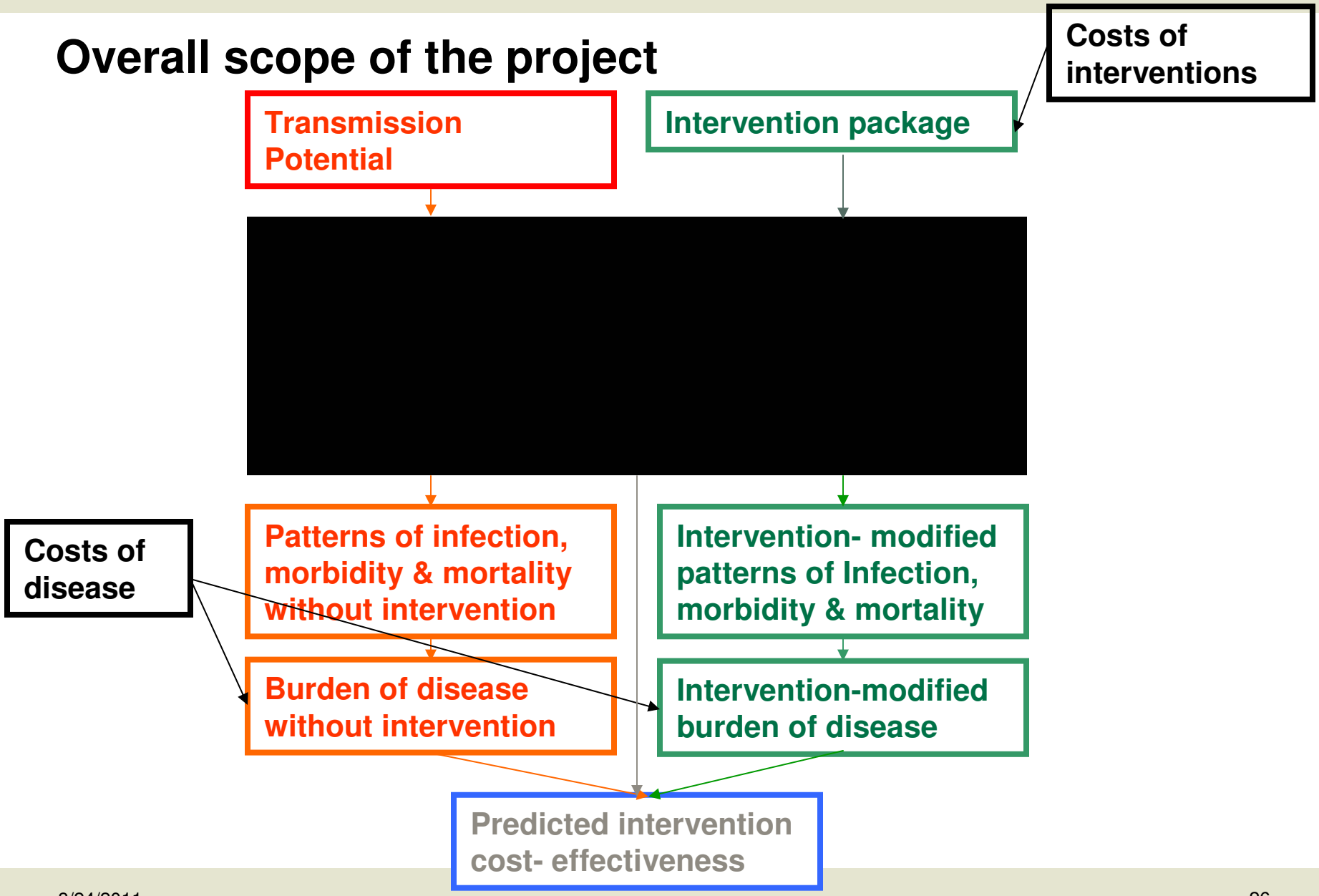
Many interventions possible, none perfect

Resource constrained context

Structure of malaria simulator

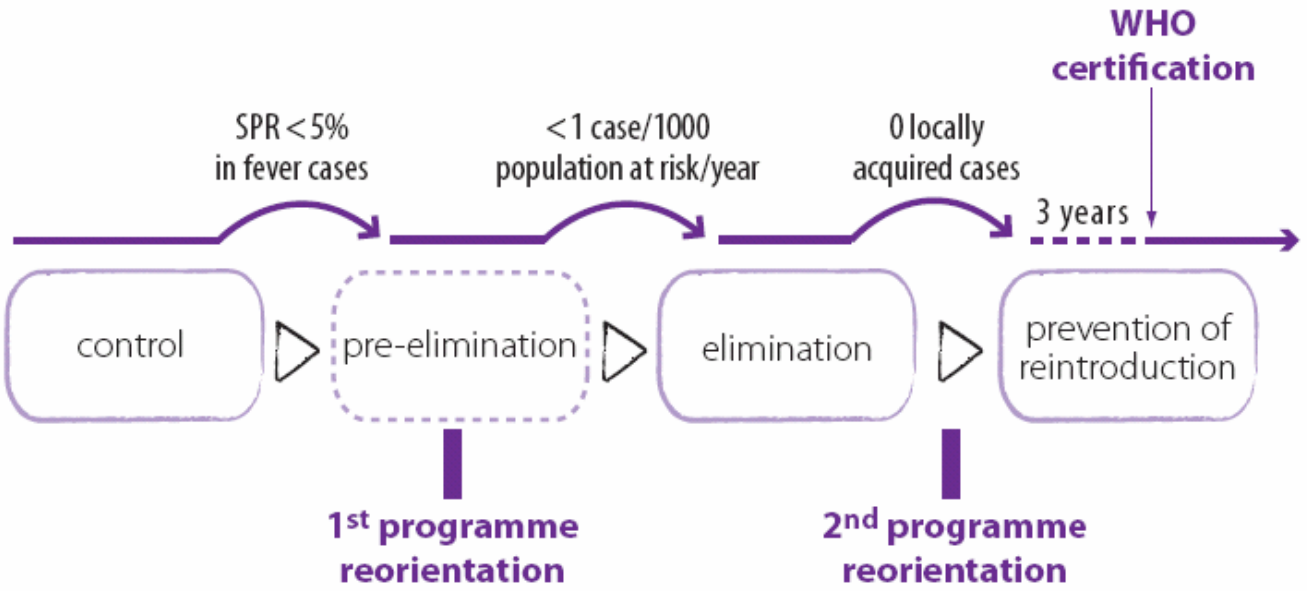


Overall scope of the project



Programme phases: from control to elimination

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



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.).