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

Epidemiology and Public Health
Health Systems Research and Dynamical Modelling

Building on Success – Malaria Control and Elimination
Swiss TPH Winter Symposium 2016

Defining success for next generation malaria vaccines

Melissa Penny, Basel 8th December 2016

2000-2015 reduction in malaria incidence and mortality

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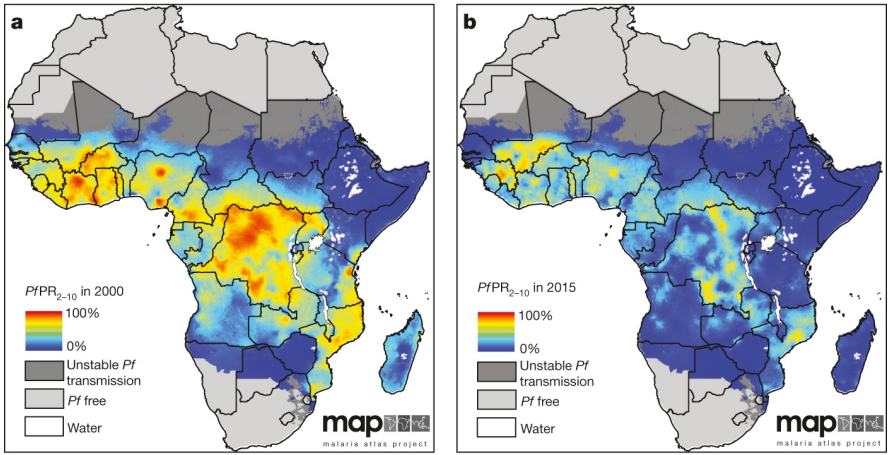
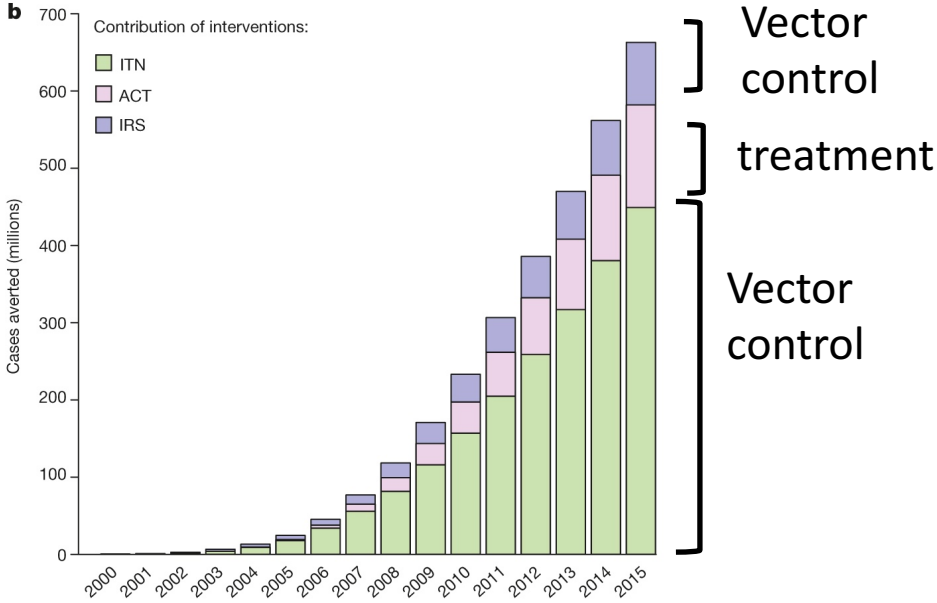
Reduction in malaria prevalence



2000 2015

Bhatt et al (2015) *The effect of malaria control on Plasmodium Falciparum in Africa between 2000 and 2015*, **Nature, 526**:207

Malaria incidence averted



Elimination?

- 2015-2030 targets: 90% case reduction, eliminate in 35 countries
- Success will not be simple continuations of current tools and intervention mixes. New tools will be required
- Drug and insecticide resistance

Framework for tools for elimination

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Region/geographic tailored intervention mixes – based on epidemiology and capacity

Reduce transmission
- Vector control
- Prophylaxis
- Vaccines

Clear infections
- Case-management
- Diagnostics
- Drugs
- Campaigns and reactive case detection and treatment

Prevent reintroduction
- Surveillance and response
- Case management

Available tools (present + 10years)

Combinations will be required

- Drugs
  - Single encounter radical cure
  - Prophylaxis
- Diagnostics
- Future vaccines
- Vector control
  - Insecticide Treated Nets
  - Indoor Residual Spraying
  - Larval controls, source management
  - Novel push-pull
- Logistics support
- Modelling and quantitative analysis

Designing new malaria vaccines

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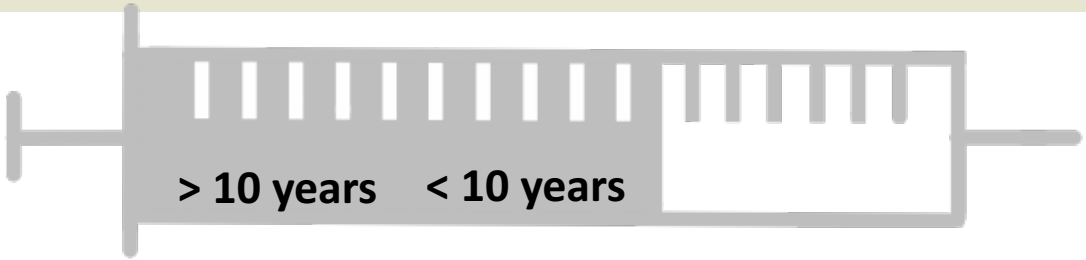


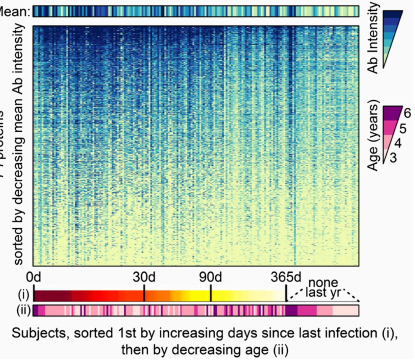
Discovery → Preclinical → Early clinical → Clinical → Implementation

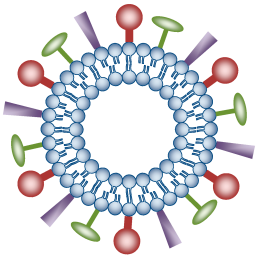
Research and discovery
Antigen discovery

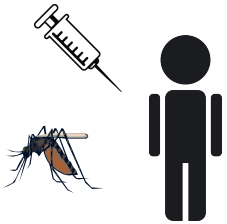
Potency
Toxicology
Schedule
Delivery system
Adjuvant
Mechanism of action

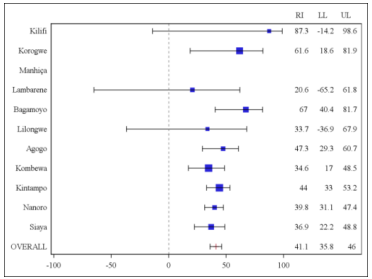
Route of immunization
Dose/intervals
Target groups
Adjuvant
Efficacy: challenge studies
Trial Design

Phase II/III efficacy
Trial design
Health Impact assessment
Economics/cost-effectiveness









Designing new malaria vaccines

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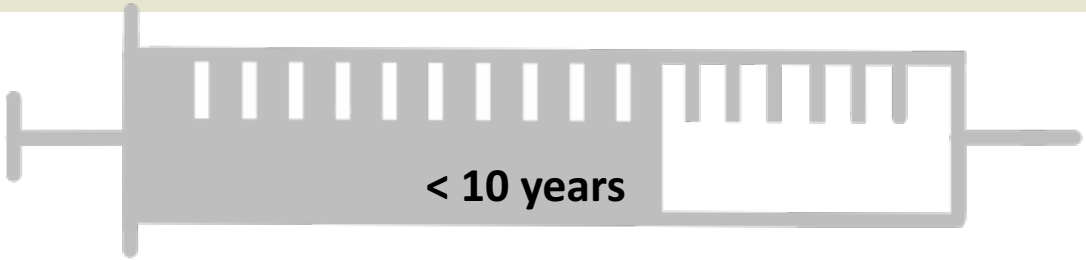

Discovery → Preclinical → Early clinical → Clinical → Implementation

Discovery	Preclinical	Early clinical	Clinical	Implementation
Research and discovery Antigen discovery	Potency Toxicology Schedule Delivery system Adjuvant Mechanism of action	Route of immunization Dose/intervals Target groups Adjuvant Efficacy: challenge studies Trial Design	Phase II/III efficacy Trial design Health Impact assessment Economics/cost-effectiveness	

Modelling and simulation to inform development

Modelling and simulation: frameworks for decisions

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Observable / Data / early knowledge of interventions

- Natural history of malaria
- Mechanisms of action of new interventions
- Early estimates of impact/protection and action
- Efficacy from later trials

Model-based frameworks

Different model types

- static
- spatial
- deterministic
- stochastic
- compartmental
- Individual-based models

Potential impact

- Guide thinking on malaria dynamics
- Explore minimum properties required of new tools (e.g. efficacy, duration)
- Test scenarios/strategies: estimate impact of new tools for different target ages, coverage, roll-out. What coverage is required to meet health goals?
- Explore combinations to find mixes that optimise over various criteria
- Effectiveness of interventions in the real world and impact beyond trials
- Economic analysis

Simulation model of malaria epidemiology and control

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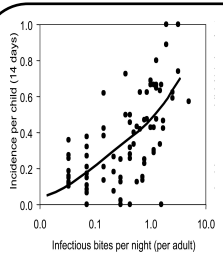
OpenMalaria: Individual-based stochastic simulator of malaria epidemiology and control

open source:

https://github.com/SwissTPH/openmalaria/wiki



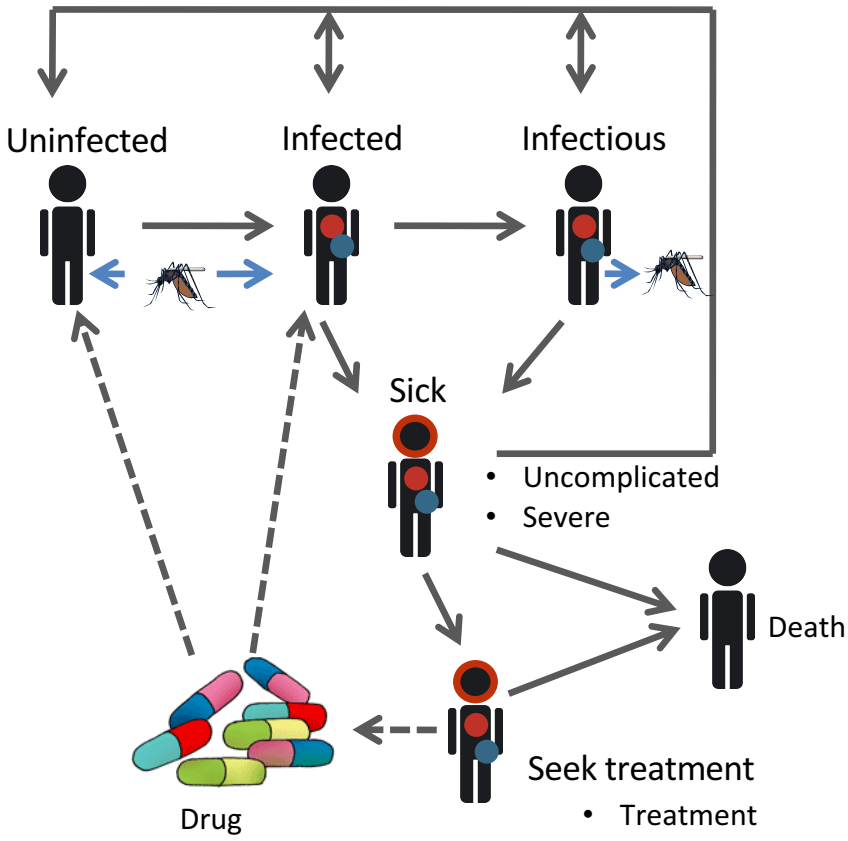
Calibrated by formal fitting to data from field studies.

- Parasite densities
- Infectiousness
- Number of infections
- Immunity
- Drug level

- Infectiousness
- Mosquito density
- Feeding cycle
- Parasite development
- Seasonality

- Health system
- Drugs & quality
- Adherence
- Compliance

- Drugs
- Vector Control
- Vaccine
- Mass treatment



Designing new malaria vaccines

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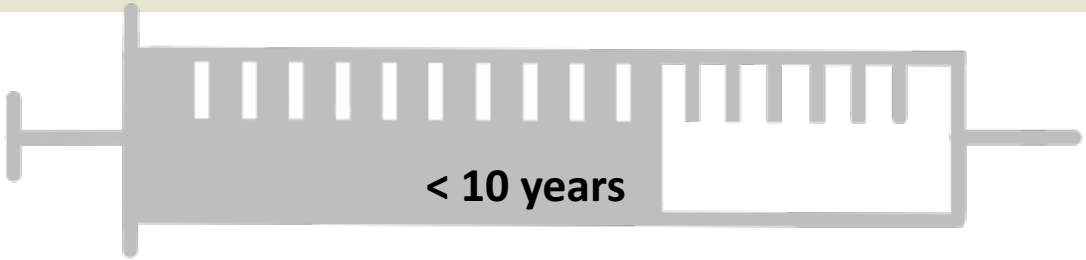

Discovery → Preclinical → Early clinical → Clinical → Implementation

Phase II/III efficacy
Trial design

Health Impact assessment
Economics/cost-effectiveness

Example: modelling to estimate RTS,S impact

The GSK malaria vaccine RTS,S/AS01

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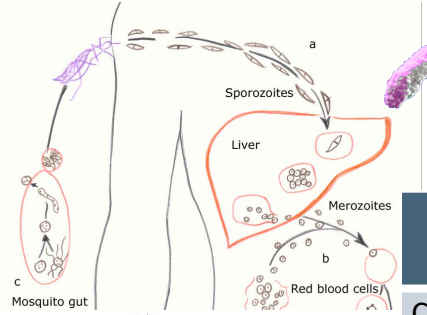
Genetically engineered central CS-tandem repeat fused with S-antigen of HBs

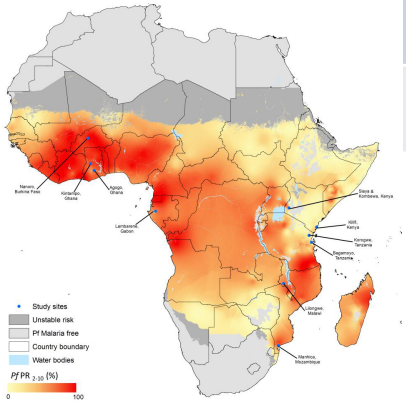


Circumsporozoite protein

RTS,S/AS01 Phase III
Vaccine efficacy (VE) against clinical disease (32 months post dose 3)

	VE in children [95% CI] 3 doses	VE in infants [95% CI] 3 dose	VE in children [95% CI] 4 doses	VE in infants [95% CI] 4 doses
Clinical malaria	35·2% [30·5 to 39·5]	20·3% [13·6 to 26·5]	43·9% [39·7 to 47·8]	20·3% [13·6 to 26·5]
Severe malaria	4·5% [–20·6 to 24·5]	7·9% [–23·3 to 31·2]	34·9% [15·6 to 50·0]	11·9% [-18·3 to 34·5]

The RTS,S Clinical Trials Partnership (2015) *Lancet*



Infants 6-12 weeks of age: **7100**
Children 5-17 months of age: **8900**
11 centers in 7 African countries

Moderately efficacious vaccine

- EMA positive scientific opinion
- WHO recommendation: **pilot implementations before wider country level introduction**… to ensure that **4 doses** of malaria vaccine can be given …… in **3-5 distinct epidemiological settings** in sub-Saharan Africa, at subnational level , covering moderate-to-high transmission settings

RTS,S clinical development

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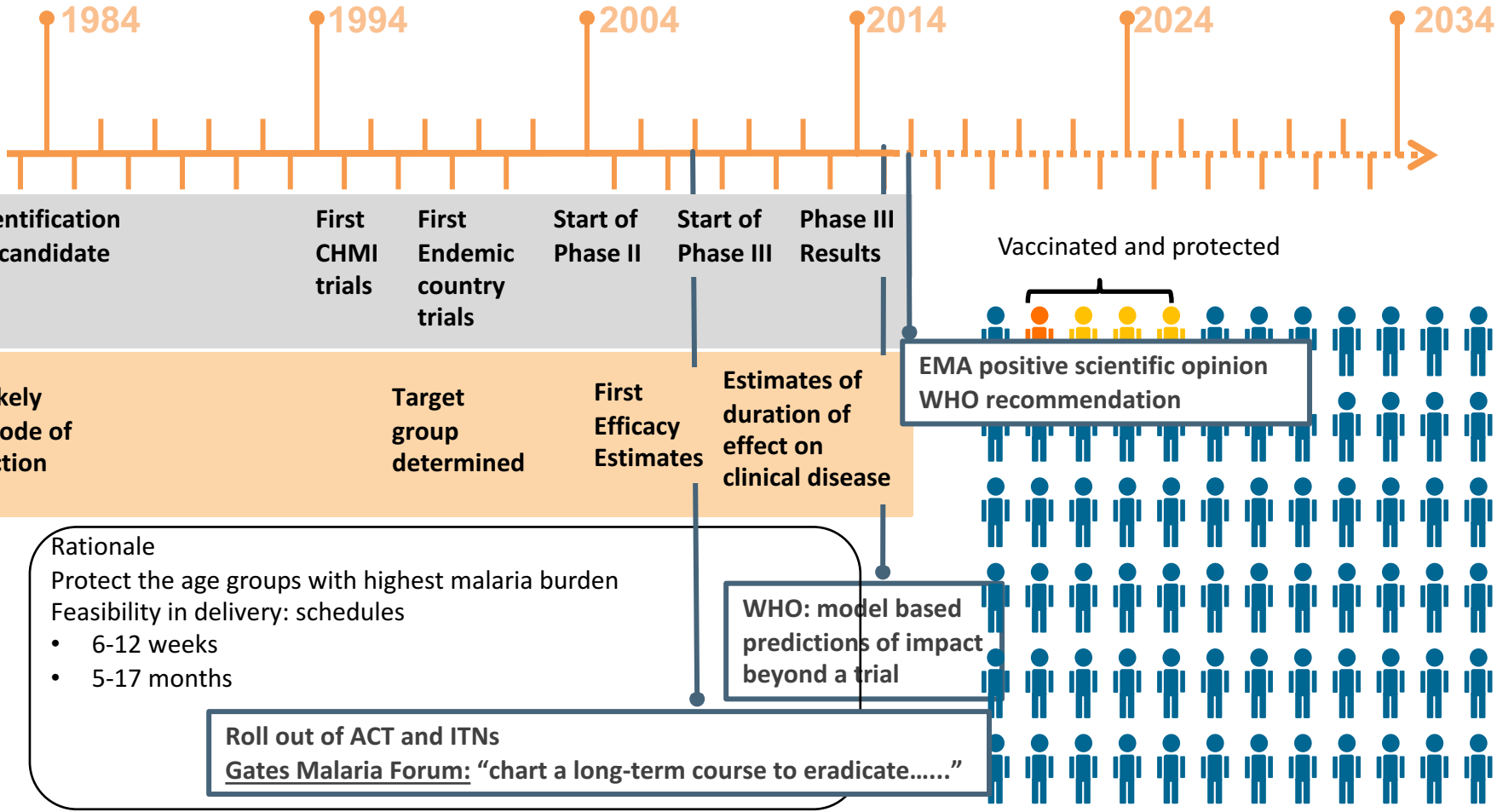

Ensemble approach to modeling health impact

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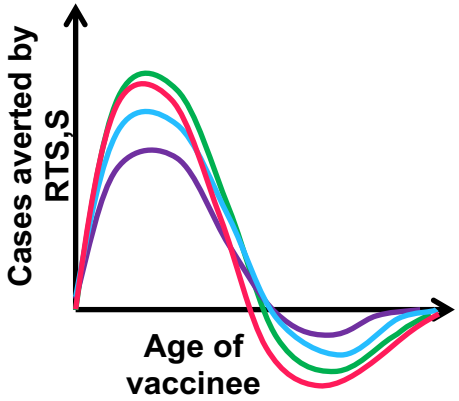
INTELLECTUAL VENTURES

gsk GlaxoSmithKline Vaccines



- **No one 'perfect' model**
- Differences reflect modeling choices and uncertainty in calibration data
- Ensemble approach allows exploration of outcome ranges

WHO requested predictions for:

- **Defined target age group or schedule**
- Realistic **coverage** of children
- **Harmonised** inputs and outputs
- Expected **effectiveness**: % and number events averted
- **cost-effectiveness** (& comparison with interventions & vaccines)
- Role in addition to high coverage of insecticide treated nets and routine treatment

WHY?:

- Understand impact beyond the trial (control settings). Trial **not powered** to evaluate impact against severe disease and mortality, especially in low-moderate transmission settings.

What was not simulated:

- Indicate impact outside of tested age Potential of alternative vaccine delivery or integration into other programs

Dynamical modeling is informed by trial data to project future public health impact

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Clinical Trial Setting

- **High** treatment rates
- **High** insecticide treated net (ITN) use
- Limited transmission settings
- **< 5 year** follow-up
- **Data:** Vaccine efficacy

DATA

Assessed Vaccine Properties

Calibrated Malaria Models

- Trial data
- Historical data

SIMULATIONS

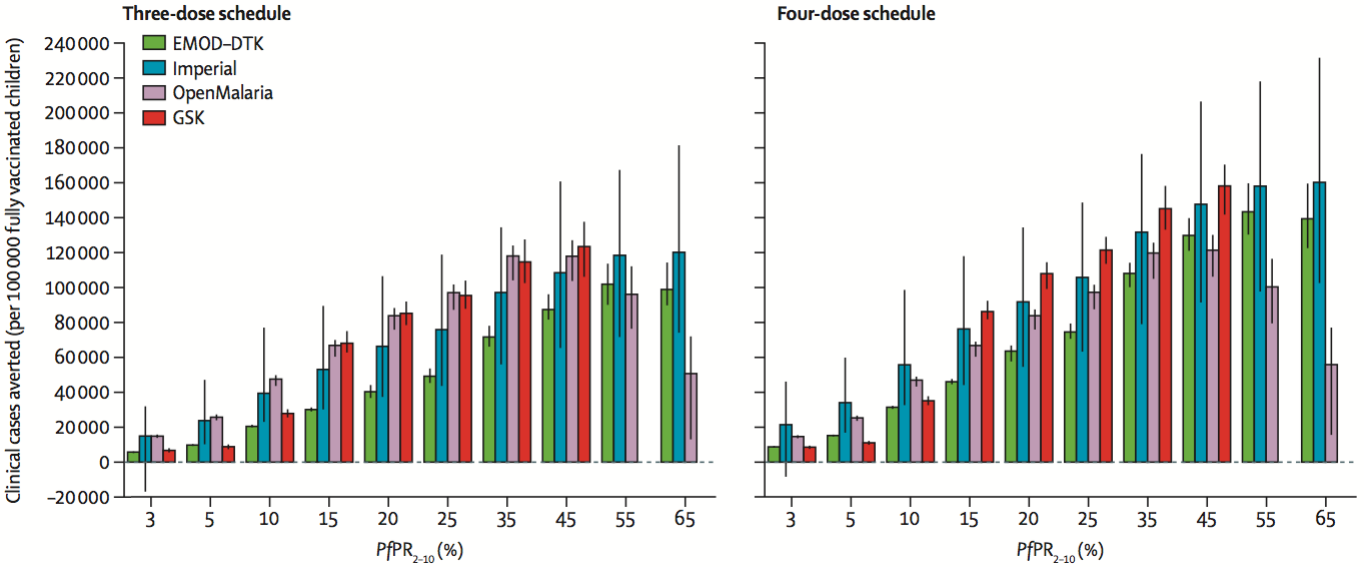
Future Use Case

- **Range** of treatment rates
- **Range** of ITN use
- Broad spectrum of transmission settings
- **> 5 year** impact
- **Mortality impact**
- **Delivery strategy:** Vaccination at 6-9 months, 27 months

Predicted public health impact: generic transmission settings

Model predictions: follow-up 15 years

Clinical cases averted per 100,000 fully vaccinated children



***Pf*PR$_{2-10}$ 10-65%, 4 dose schedule:**

*Avert between **8% and 29% of clinical cases in children less than 5 years old***

*Avert median **116,482 (31,448-160,236) clinical cases for every 100,000** fully vaccinated children*

Penny, Verity, Bever, Sauboin *et al.* (2016) "Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models" *Lancet*

Public health impact – age shift of clinical disease

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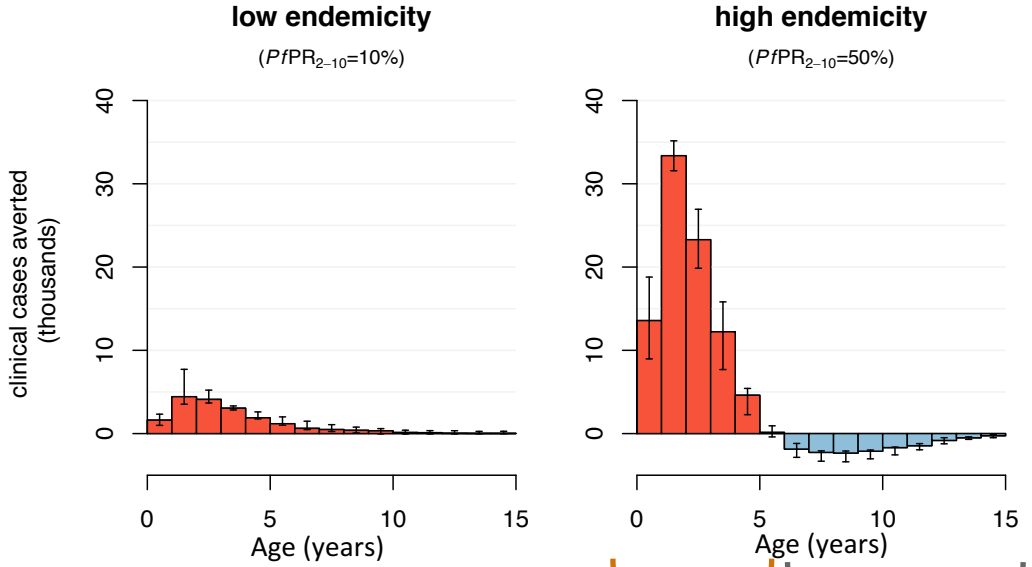
Clinical cases averted per 100,000 fully vaccinated children by age



Penny, Verity, Bever, Sauboin *et al.* (2016) "Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models" *Lancet*

Cost-effectiveness range and comparison with other malaria preventative interventions

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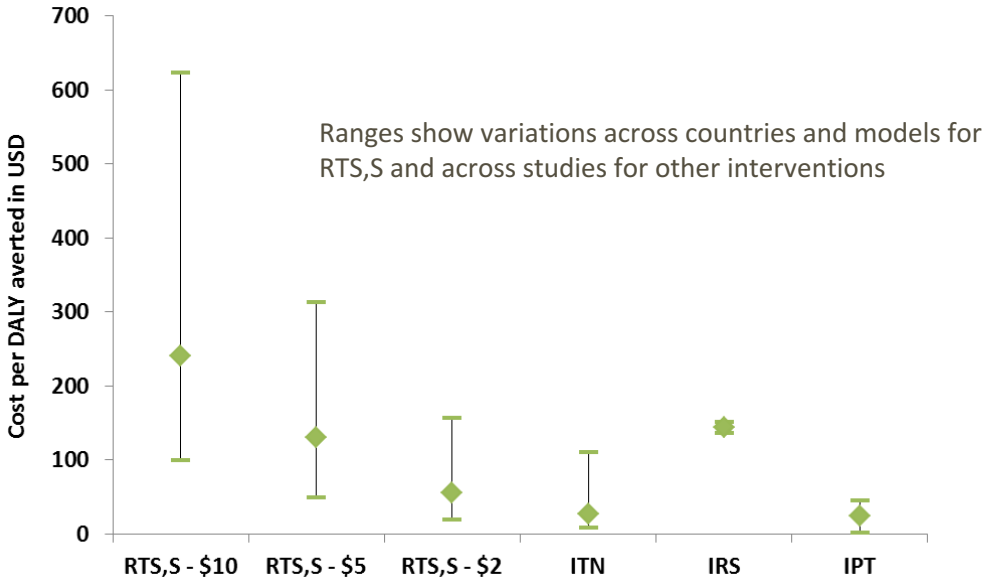
WHO and GAVI perspective: comparison to other interventions

- Vaccine price range tested from $2 to $10 per dose
- Cost-effectiveness estimates for other malaria interventions from literature[1]
- Cost-effectiveness estimates from the literature have been made in a different context than current modeling work



1. White et al. 2011 (Malaria Journal) ITN: Insecticide-Treated Nets; IRS: Indoor Residual Spraying; IPT: Intermittent Preventive Treatment

RTS,S is likely to have positive impact with potential for substantial public health benefits, but that careful consideration of the cost-effectiveness compared to other interventions should be made in the context of local priorities and health systems.

Penny, Verity, Bever, Sauboin *et al.* (2016) "Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine: a systematic comparison of predictions from four mathematical models" *Lancet*

Country-level or sub-national perspective: estimates of RTS,S impact and cost-effectiveness

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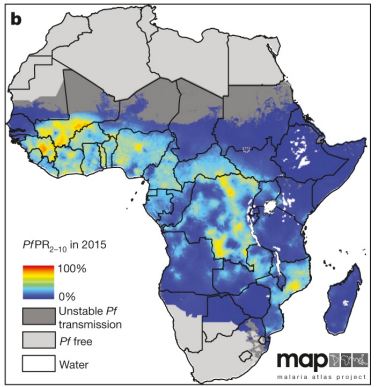
Country-specific inputs

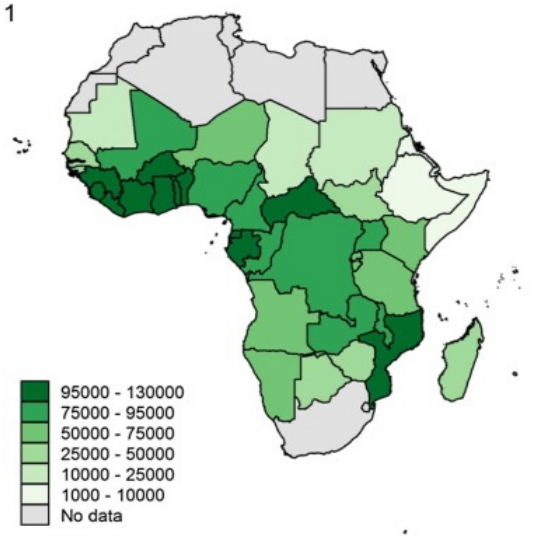


map malaria atlas project

+ Demographics
+ Mix of prevalence levels
+ Seasonality
+ Access to care & cost of illness
+ DTP coverage
+ Cost of vaccination

+ models

country-level estimates



Cumulative number of clinical cases averted per 100,000 vaccinated (at year 10 following vaccine introduction)

Galactionova *et al.* (2016) "*Country specific predictions of the cost-effectiveness of malaria vaccine RTS,S/AS01 in endemic Africa*" Vaccine

Success for RTS,S and future vaccines

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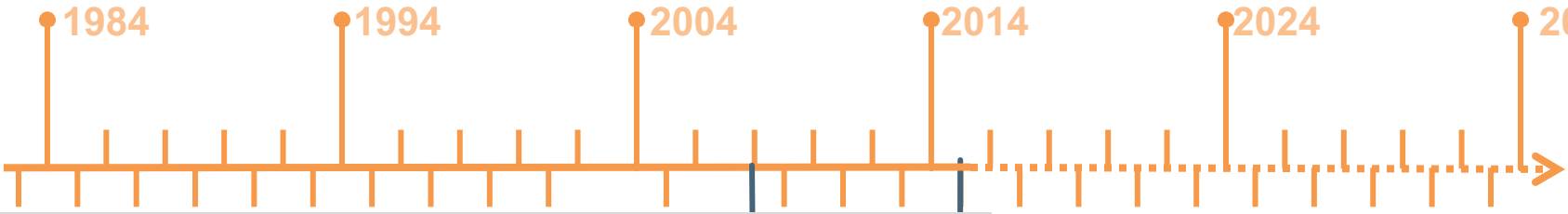

Identification of candidate

First CHMI trials

First Endemic country trials

Start of Phase II

Start of Phase III

Phase III Results

Next generation malaria vaccines CHMI/trials

Likely mode of action

Target group determined

First Efficacy Estimates

Estimates of duration of effect on clinical disease

Next generation malaria vaccines

Target/schedules/elimination goals

WHO: model based predictions of impact beyond a trial

Reference period for modelling of next generation malaria vaccines

Roll out of ACT and ITNs

Gates Malaria Forum: "chart a long-term course to eradicate……"

Modelling to guide thinking for future malaria vaccines

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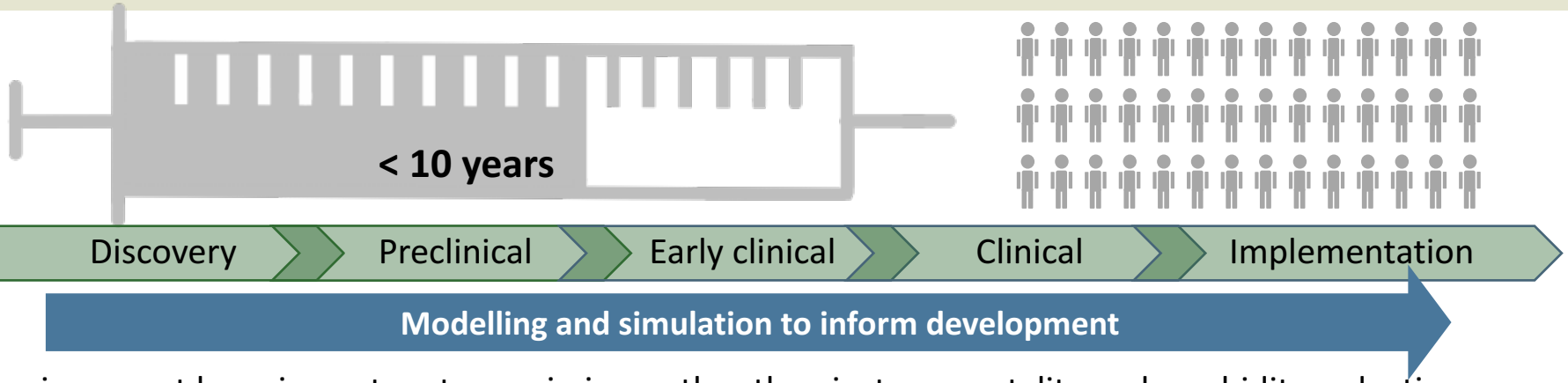

Vaccines must have impact on transmission, rather than just on mortality and morbidity reduction

- Immunogenicity and immune correlates (White et al (2015) Lancet Inf. Dis.)
- Prioritization of **target product profiles** (combinations, doses, trade off between efficacy, duration of protection, coverage)
- immunization **schedules and delivery routes** (and feasibility)
- **target demographic groups**
- Dosing (and feasibility)
- Settings (prevalence, seasonality, health systems)
- TPP for Mass vaccination: high-risk populations (pregnant women)
- Use of Controlled human malaria infection and models for candidate prioritization

Minimal and optimal properties, alternative deliveries

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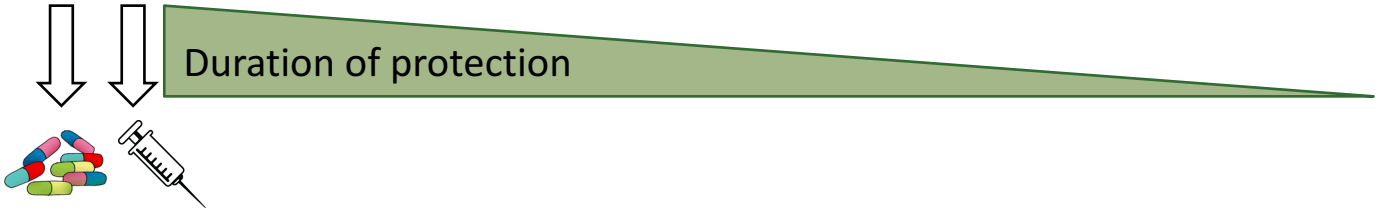
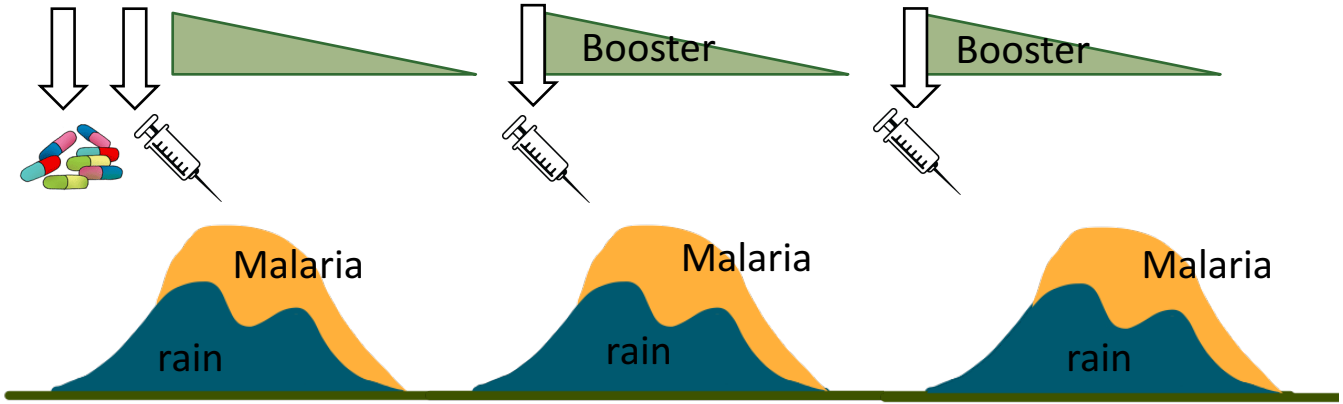
Ideal elimination vaccine



Foreseeable: vaccine with shorter duration of protection vaccine



Adapted from BMGF and PATH-MVI

Role for elimination: example transmission effects

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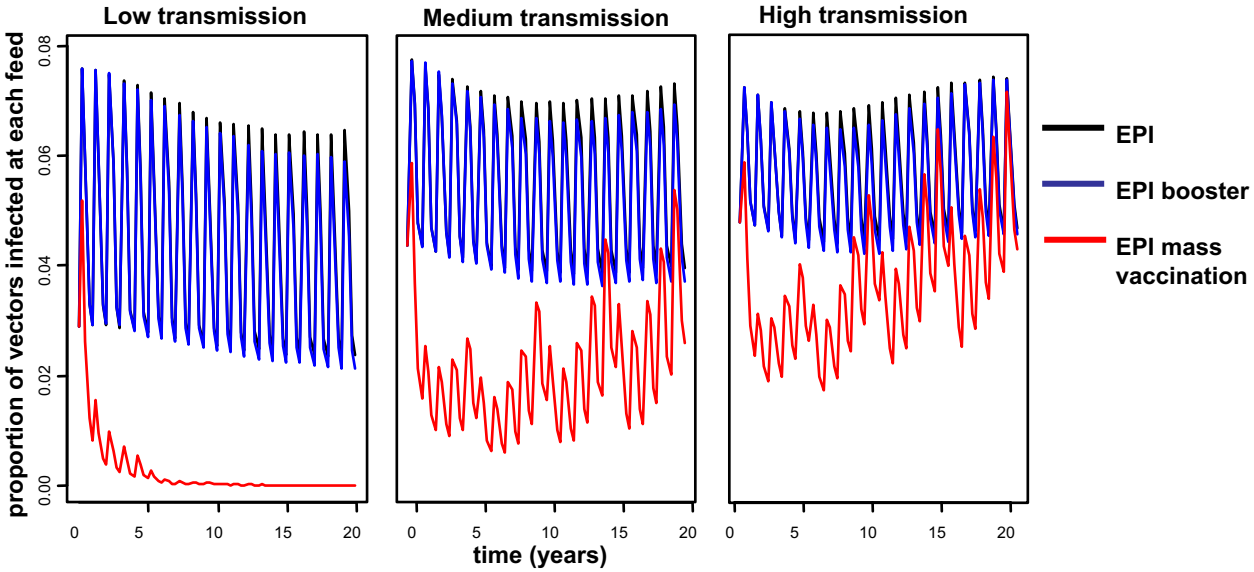
Pre-erythrocytic vaccines

- Observe some reduction of transmission with high initial efficacy (herd immunity when delivered via mass vaccination)
- Interruption of transmission for low transmission settings



Penny *et al.* (2008) Plos One

Modelling can guide thinking on:

- Coverage of mass vaccination to achieve success
- Longevity of protection required? = minimal and Target Product Profiles
- Determinants of success: minimum coverage level? minimum number of rounds?
- Cost savings?

Predictions of transmission blocking vaccine effects over time

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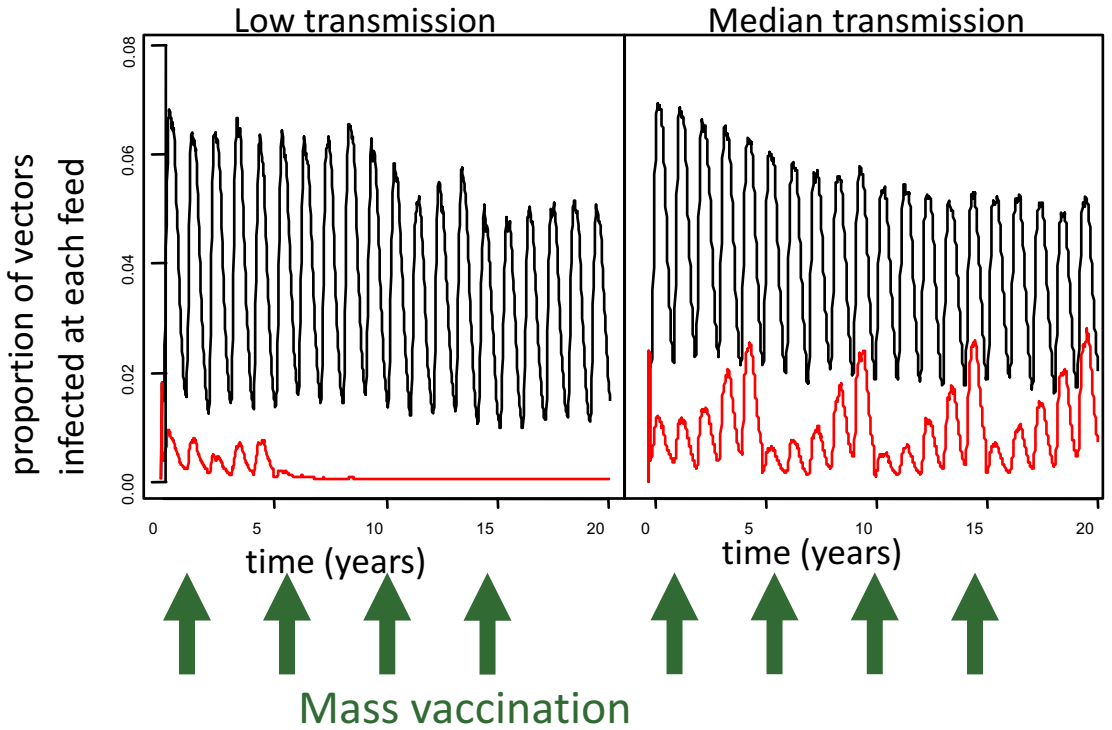
Transmission blocking vaccines

Possible to induce herd immunity and interrupt transmission when delivered via mass vaccination



Modelling can guide thinking on:

- How many rounds, coverage and timing of mass vaccination to achieve success?
- Longevity of protection required?
- Other intervention combinations to accelerate interruption of transmission

Penny *et al.* (2008) Plos One

Combination with other interventions

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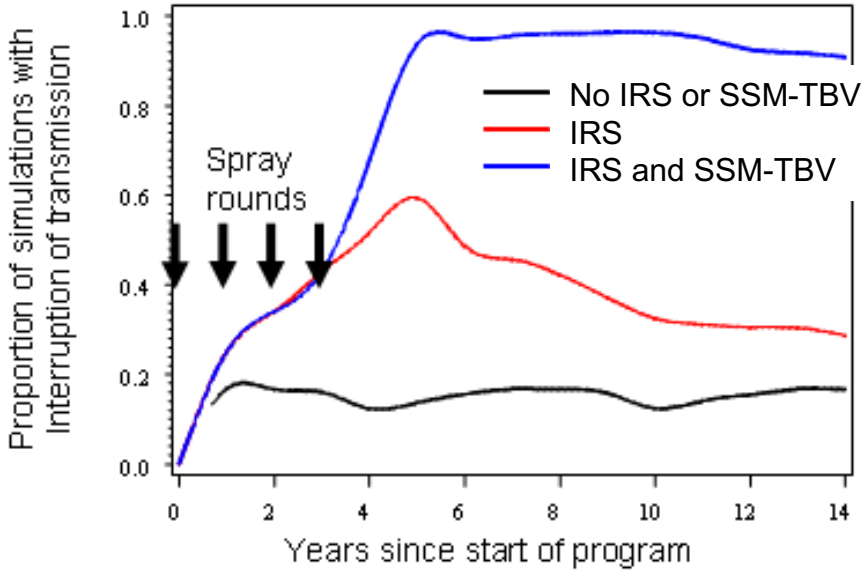
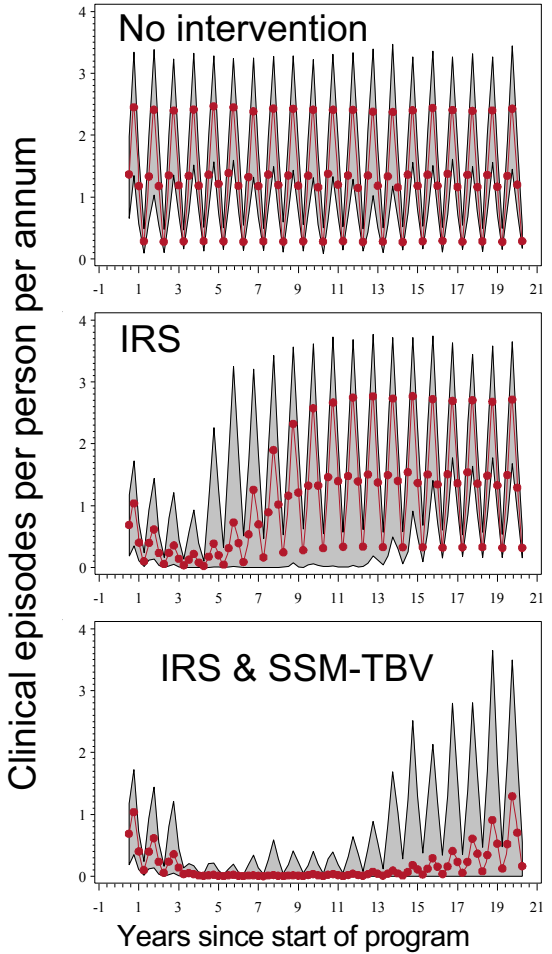
Example effect on clinical incidence and probability to interrupt transmission



Smith *et al.* (2008) Trends in Parasitology



- Profile of new interventions needed on top of existing interventions to achieve elimination
- Which settings?

Challenges for modelling close-to-elimination

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***Vivax* and other malaria species**

Low transmission and elimination settings

- Parasite diversity and parasite relatedness as transmission declines
- Incidence by age with changing population and individual immunity
- Data: most models designed and parameterised for hyper- and mesoendemic settings

Effects of population size and connectivity on the chances of elimination

- Connection between populations (movements of people/mosquitoes) make elimination more difficult
- Both population size and connectivity are hard to quantify

From defining success to achieving success

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Other important tools for innovating new interventions:

- Community
- Ideas
- Integration of all disciplines in the development pathway through to implementation

Available tools (present + 10years)

Combinations will be required

- Drugs
  - Single encounter radical cure
  - Prophylaxis
- Diagnostics
- New vaccines
- Vector control
  - Insecticide Treated Nets
  - Indoor Residual Spraying
  - Larval controls, source management
  - Novel push-pull
- Field logistics support
- Modelling and quantitative analysis

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