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

Reduction in malaria prevalence

2000

2015


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

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 + 10 years)
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

Discovery
- Research and discovery
- Antigen discovery

Preclinical
- Potency
- Toxicology
- Schedule
- Delivery system
- Adjuvant
- Mechanism of action

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

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

Implementation

> 10 years  < 10 years
Designing new malaria vaccines

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

Modelling and simulation to inform development
Modelling and simulation: frameworks for decisions

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

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

*Open source:* [https://github.com/SwissTPH/openmalaria/wiki](https://github.com/SwissTPH/openmalaria/wiki)

- **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**

Calibrated by formal fitting to data from field studies.

---

**Drug**

- **Uninfected**
- **Infected**
- **Infectious**

- **Sick**
  - Uncomplicated
  - Severe

- **Death**
  - Treatment
  - Hospitalised

**Seek treatment**
Designing new malaria vaccines

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

< 10 years
The GSK malaria vaccine RTS,S/AS01

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

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

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

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

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

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

Identification of candidate
First CHMI trials
First Endemic country trials
Start of Phase II
Start of Phase III
Phase III Results

Likely mode of action
Target group determined
First Efficacy Estimates
Estimates of duration of effect on clinical disease

Rationale
Protect the age groups with highest malaria burden
Feasibility in delivery: schedules
• 6-12 weeks
• 5-17 months

Vaccinated and protected

EMA positive scientific opinion
WHO recommendation

WHO: model based predictions of impact beyond a trial

Roll out of ACT and ITNs
Gates Malaria Forum: “chart a long-term course to eradicate......”
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

**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

**Swiss TPH**
Predicted public health impact: generic transmission settings

Model predictions: follow-up 15 years

Clinical cases averted per 100,000 fully vaccinated children

PfPR$_{2.10}$ 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

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

Vaccinated children not becoming infected

Vaccine protection worn off, left with lower immunity compared to non-vaccinated

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

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
- 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

Country-specific inputs

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

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

- **Identification of candidate**
- **First CHMI trials**
- **First Endemic country trials**
- **Start of Phase II**
- **Start of Phase III**
- **Phase III Results**

**Likely mode of action**
- Target group determined
- First Efficacy Estimates
- Estimates of duration of effect on clinical disease

**Roll out of ACT and ITNs**
- Gates Malaria Forum: “chart a long-term course to eradicate......”

**WHO: model based predictions of impact beyond a trial**

**Next generation malaria vaccines**
- CHMI/trials
- Target/schedules/elimination goals

**Reference period for modelling of next generation malaria vaccines**
Vaccines must have impact on transmission, rather than just on mortality and morbidity reduction

- 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

Ideal elimination vaccine

Duration of protection

Foreseeable: vaccine with shorter duration of protection vaccine

Booster

Booster

Malaria

Malaria

Malaria

Rain

Rain

Rain

Adapted from BMGF and PATH-MVI
Role for elimination: example transmission effects

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

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?

Penny et al. (2008) Plos One
Predictions of transmission blocking vaccine effects over time

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

Example effect on clinical incidence and probability to interrupt transmission

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

Smith et al. (2008) Trends in Parasitology
Challenges for modelling close-to-elimination

*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

Other important tools for innovating new interventions:

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

Available tools (present + 10 years)

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
Acknowledgements

With many thanks to WHO Advisory Committee the RTS,S Clinical Trials Partnership and Clinical trial units, and vaccinated children and their families.

Swiss TPH

Melissa Penny
Katya Galactionova
Peter Pemberton-Ross
Nicolas Maire
Olivier Briet
Tom Smith
Marcel Tanner
Malaria modelling team at Swiss TPH

Christophe Sauboin
Nicholas Van de Velde

Imperial College London

Robert Verity
Michael White
Jamie Griffin
Azra Ghani

INSTITUTE FOR DISEASE MODELING

Caitlin Bever
Edward Wenger
Philip Eckhoff

London School of Hygiene & Tropical Medicine

Stefan Flasche
Mark Jit

PATH

Farzana Muhib
Deb Atherly
Carla Botting

With many thanks to WHO Advisory Committee the RTS,S Clinical Trials Partnership and Clinical trial units, and vaccinated children and their families.

Funding
PATH-Malaria Vaccine Initiative
Bill and Melinda Gates foundation