Combining seasonal malaria chemoprevention with new therapeutics for malaria prevention

Lydia Braunack-Mayer, Josephine Malinga, Narimane Nekkab, Sherrie L Kelly, Jörg J Möhrle, Melissa A Penny

2024 IDM Annual Symposium, October 1st to 2nd

lydia.braunack-mayer@swisstph.ch; melissa.penny@thekids.org.au

Plasmodium falciparum malaria has a complex life cycle

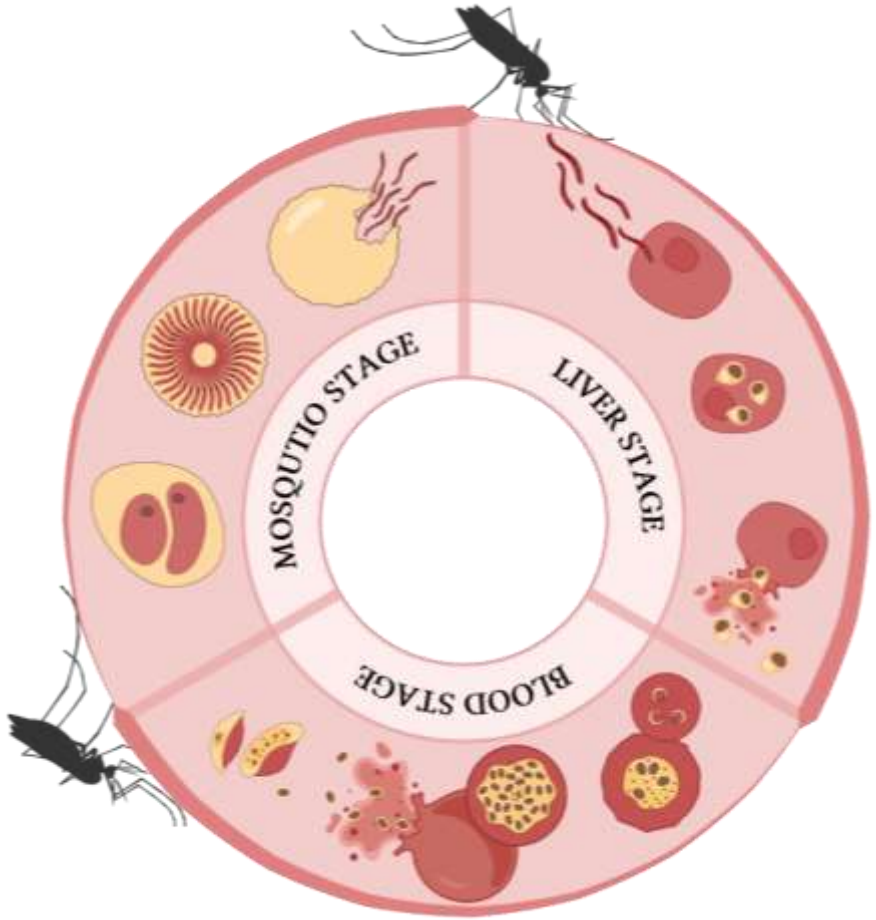
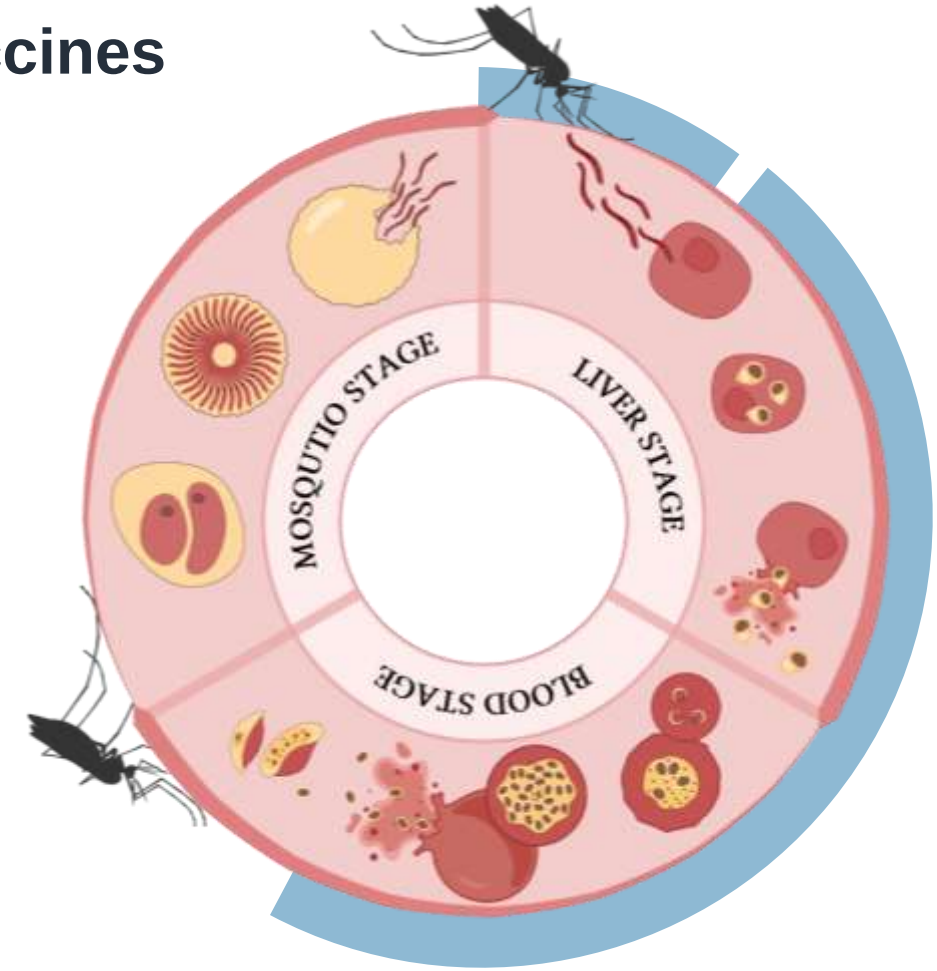


Figure created with BioRender.com

Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

Therapeutics for preventing *Plasmodium falciparum* malaria act at different stages in the parasite life cycle

RTS,S and R21 vaccines



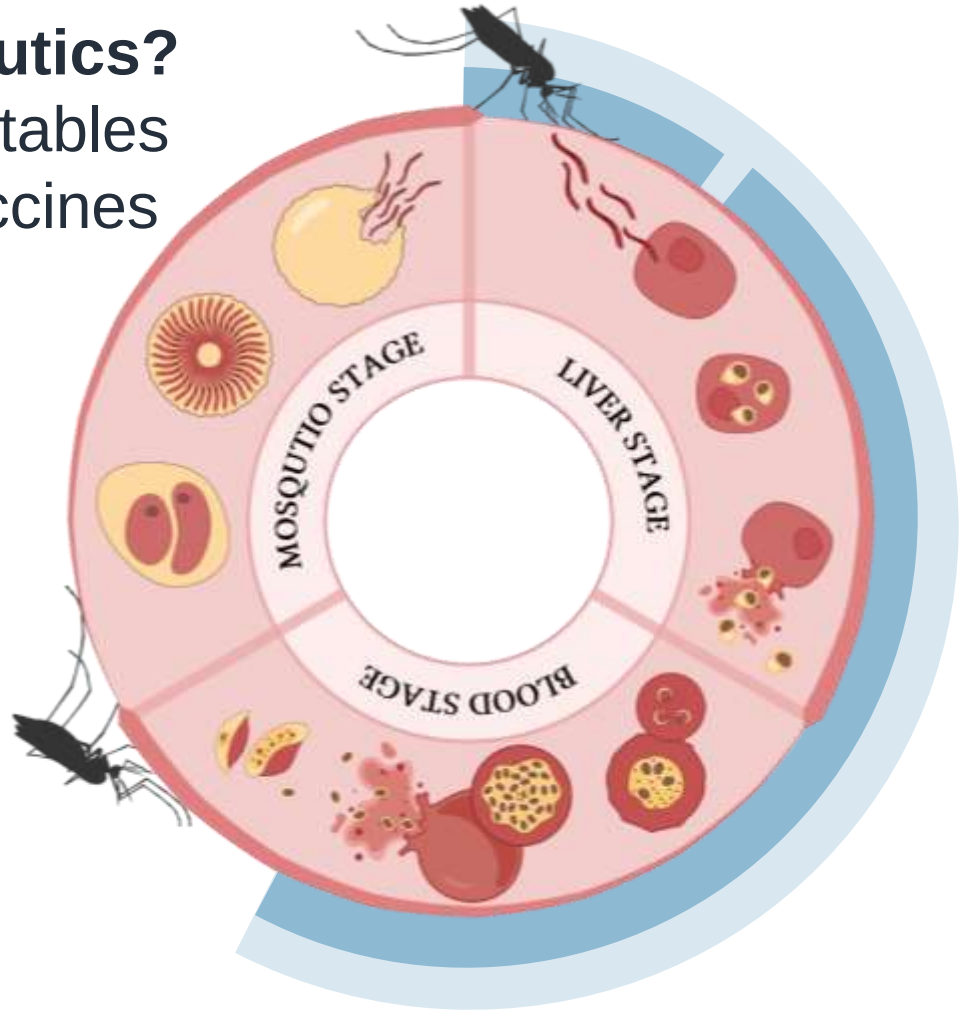
chemoprevention drugs e.g. SP-AQ

Figure created with BioRender.com

Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

What properties should new prevention therapeutics have for use in combination with malaria chemoprevention?

multi-stage therapeutics?
e.g. long-acting injectables and combination vaccines



chemoprevention drugs e.g. SP-AQ

Figure created with BioRender.com

Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

We modelled the essential properties for a new therapeutic used in combination with seasonal malaria chemoprevention

Aim

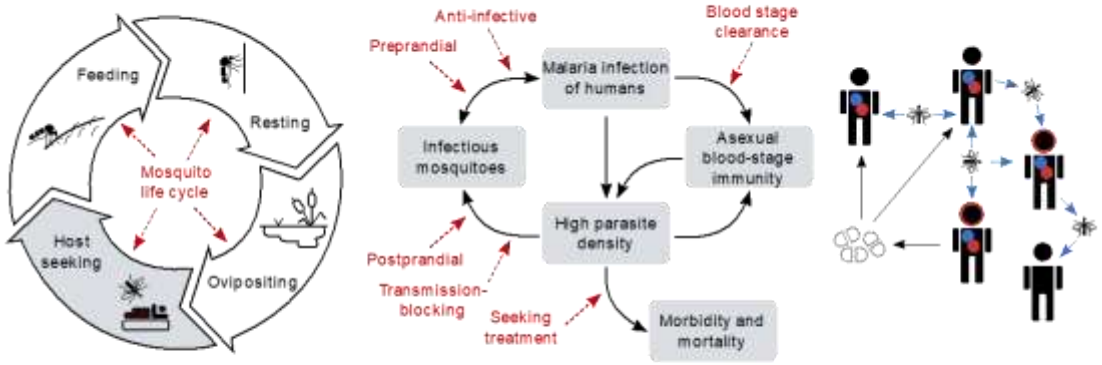
Understand the essential properties needed for a **new vaccine or injectable** to successfully **combine with seasonal malaria chemoprevention (SMC)**

Approach

- Used an individual-based malaria transmission model, **OpenMalaria**
- Simulated the effectiveness of both **single-stage** and **multi-stage therapeutics:**
  - Pre-liver stage therapeutics
  - Blood stage therapeutics
  - Pre-liver and blood stage therapeutics

OpenMalaria

Individual-based stochastic simulator of malaria epidemiology and control (*Plasmodium falciparum*) available at https://github.com/SwissTPH/openmalaria/wiki



Within-host + intervention dynamics *within* population models

OpenSource C++ developed and in use since 2006
Many applications, validated, updated calibrations, and used by many groups

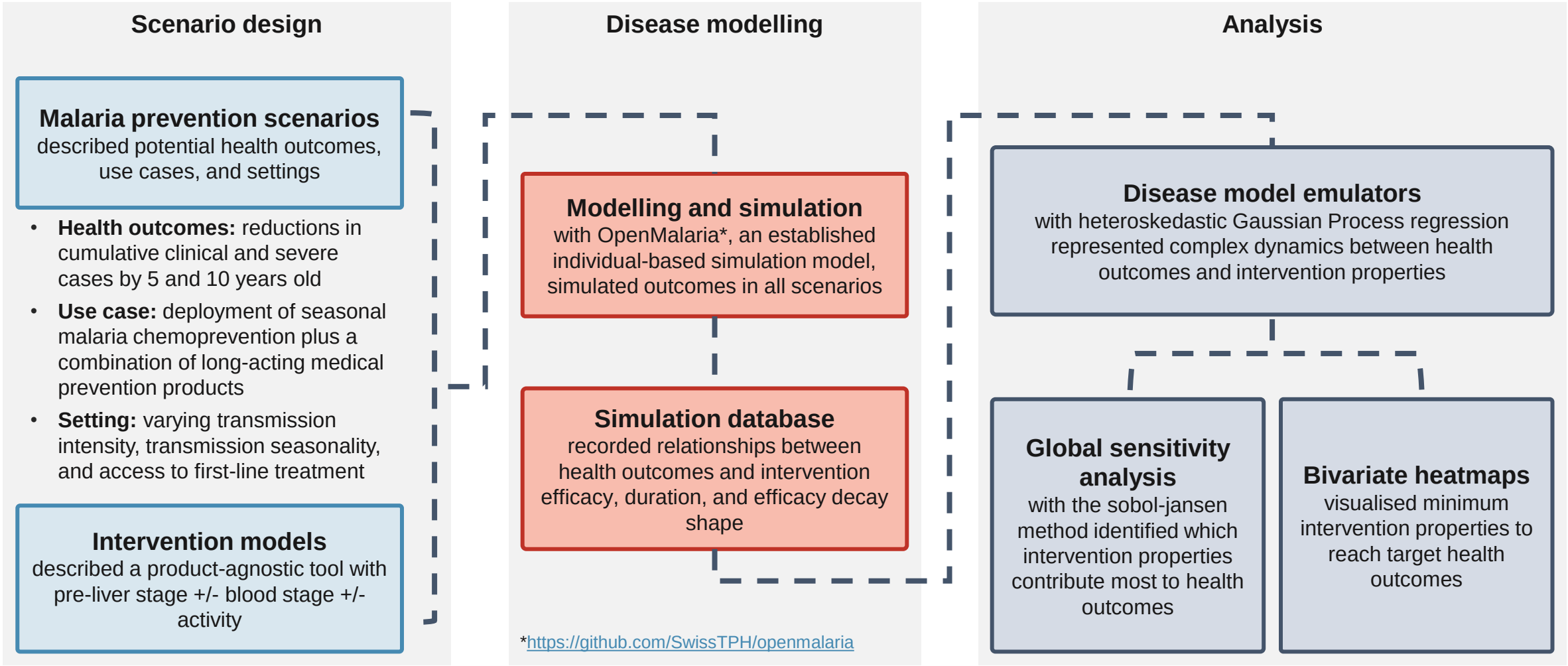
https://github.com/SwissTPH/openmalaria/wiki

Swiss TPH | The KIDS Research Institute Australia | The University of Western Australia

Figure created with BioRender.com

Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

Our target product profile modelling framework links therapeutic profiles with likely public health outcomes



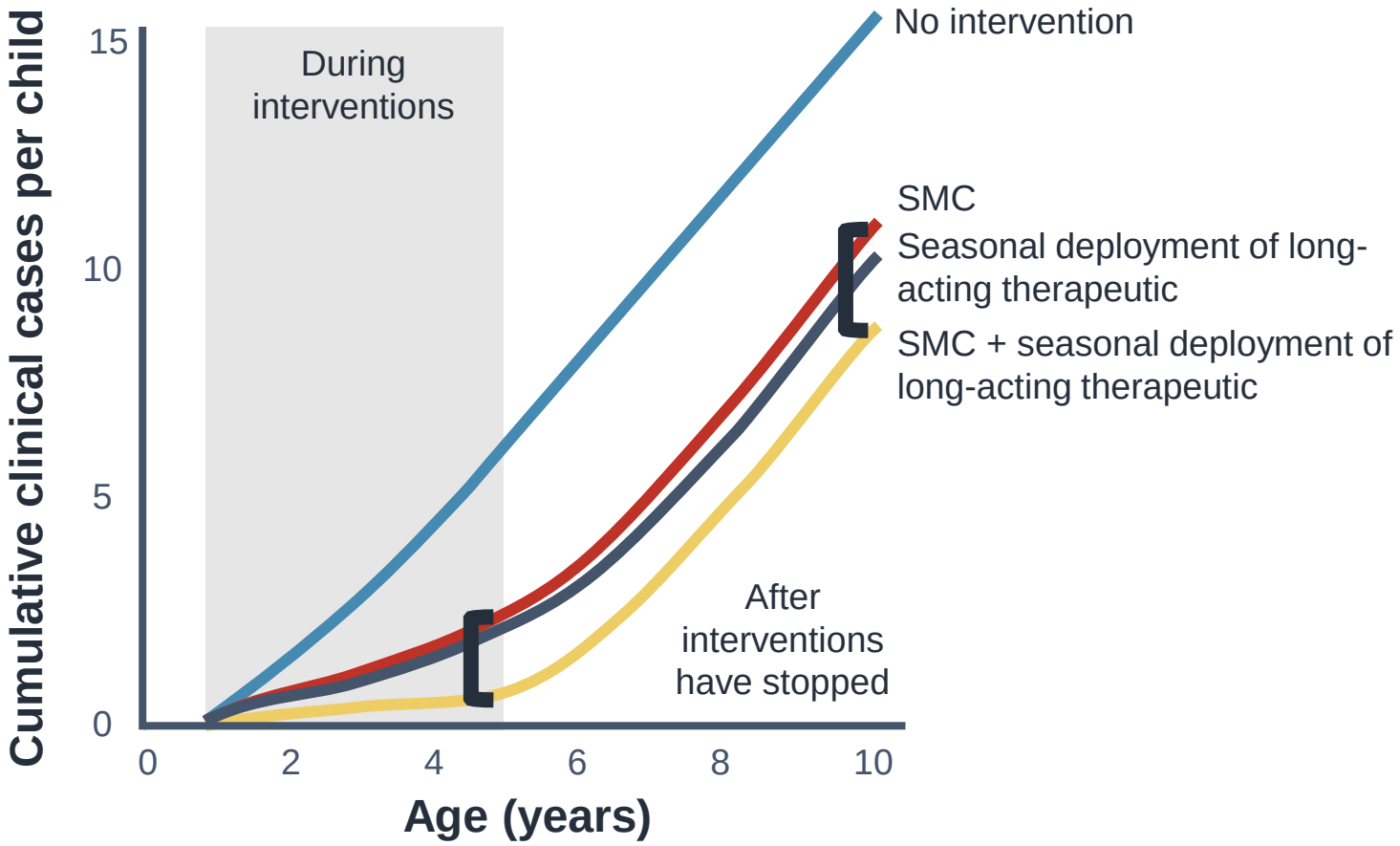
Our target product profile modelling framework links therapeutic profiles with likely public health outcomes

Scenario design

Malaria prevention scenarios
described potential health outcomes, use cases, and settings

- **Health outcomes:** reductions in cumulative clinical and severe cases by 5 and 10 years old
- **Use case:** deployment of seasonal malaria chemoprevention plus a combination of long-acting medical prevention products
- **Setting:** varying transmission intensity, transmission seasonality, and access to first-line treatment

Illustrative model outputs



Our target product profile modelling framework links therapeutic profiles with likely public health outcomes

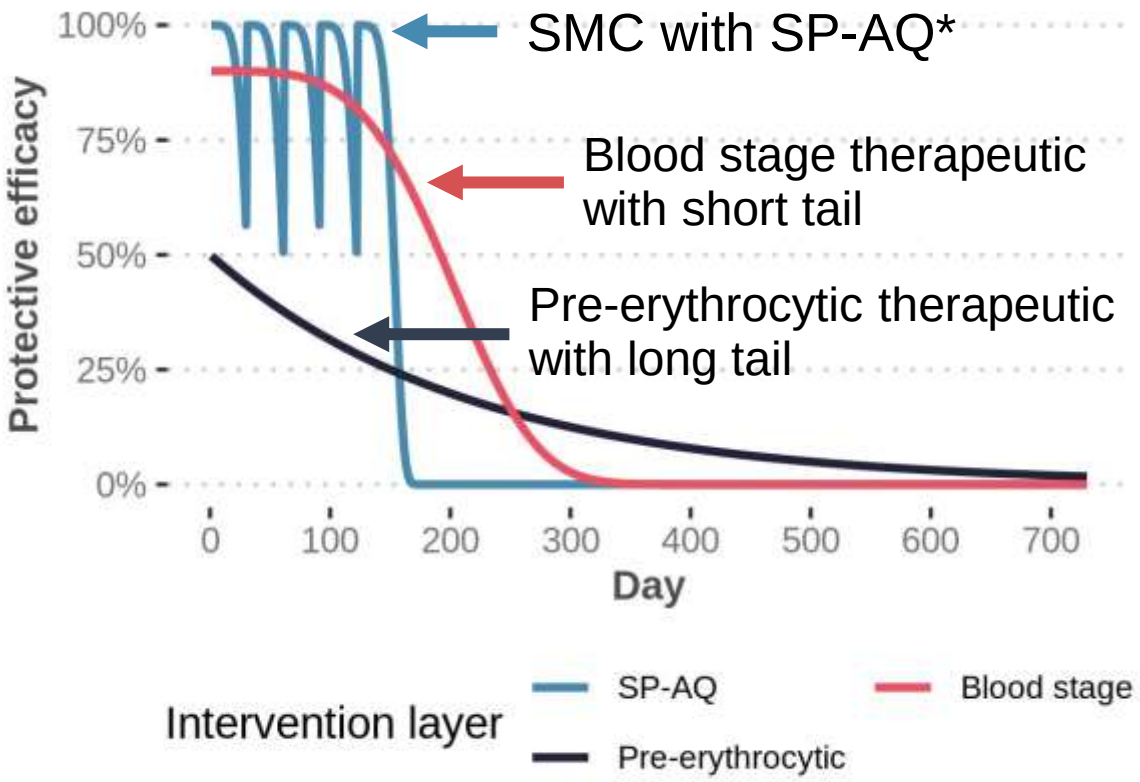
Scenario design

Malaria prevention scenarios
described potential health outcomes, use cases, and settings

- **Health outcomes:** reductions in cumulative clinical and severe cases by 5 and 10 years old
- **Use case:** deployment of seasonal malaria chemoprevention plus a combination of long-acting medical prevention products
- **Setting:** varying transmission intensity, transmission seasonality, and access to first-line treatment

Intervention models
described a product-agnostic tool with pre-liver stage +/- blood stage +/- activity

Illustrative therapeutic profiles



*SP-AQ: Sulfadoxine-Pyrimethamine + Amodiaquine. SP-AQ models assume pre-erythrocytic protection combined with blood stage and liver stage parasite clearance at the time of administration

Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

Our target product profile modelling framework links therapeutic profiles with likely public health outcomes

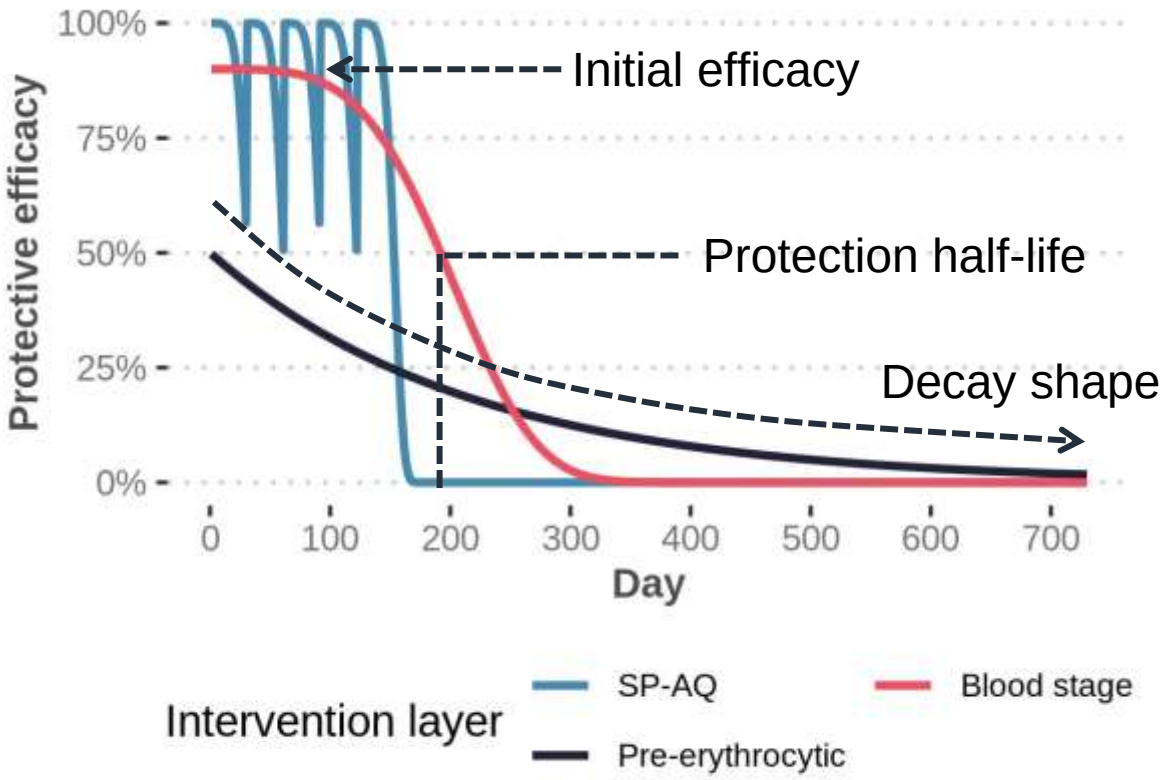
Scenario design

Malaria prevention scenarios
described potential health outcomes, use cases, and settings

- **Health outcomes:** reductions in cumulative clinical and severe cases by 5 and 10 years old
- **Use case:** deployment of seasonal malaria chemoprevention plus a combination of long-acting medical prevention products
- **Setting:** varying transmission intensity, transmission seasonality, and access to first-line treatment

Intervention models
described a product-agnostic tool with pre-liver stage +/- blood stage +/- activity

Illustrative therapeutic profiles



*SP-AQ: Sulfadoxine-Pyrimethamine + Amodiaquine. SP-AQ models assume pre-erythrocytic protection combined with blood stage and liver stage parasite clearance at the time of administration

Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

Our target product profile modelling framework links therapeutic profiles with likely public health outcomes

Scenario design

Malaria prevention scenarios
described potential health outcomes, use cases, and settings

- **Health outcomes:** reductions in cumulative clinical and severe cases by 5 and 10 years old
- **Use case:** deployment of seasonal malaria chemoprevention plus a combination of long-acting medical prevention products
- **Setting:** varying transmission intensity, transmission seasonality, and access to first-line treatment

Intervention models
described a product-agnostic tool with pre-liver stage +/- blood stage +/- activity

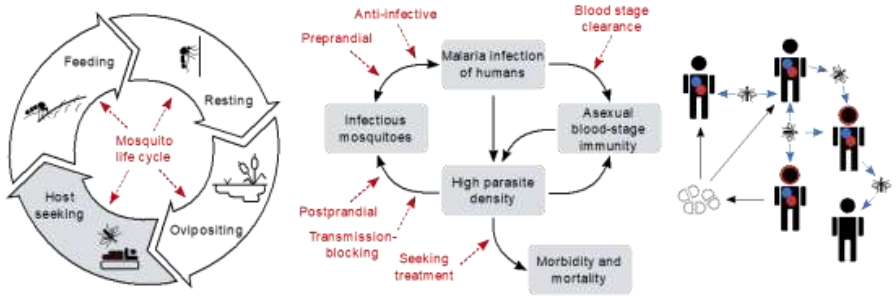
Disease modelling

Modelling and simulation
with OpenMalaria*, an established individual-based simulation model, simulated outcomes in all scenarios

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

OpenMalaria

Individual-based stochastic simulator of malaria epidemiology and control (*Plasmodium falciparum*) available at https://github.com/SwissTPH/openmalaria/wiki



Within-host + intervention dynamics *within* population models

OpenSource C++ developed and in use since 2006
Many applications, validated, updated calibrations, and used by many groups

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

Our target product profile modelling framework links therapeutic profiles with likely public health outcomes

Scenario design

Malaria prevention scenarios
described potential health outcomes, use cases, and settings

- **Health outcomes:** reductions in cumulative clinical and severe cases by 5 and 10 years old
- **Use case:** deployment of seasonal malaria chemoprevention plus a combination of long-acting medical prevention products
- **Setting:** varying transmission intensity, transmission seasonality, and access to first-line treatment

Intervention models
described a product-agnostic tool with pre-liver stage +/- blood stage +/- activity

Disease modelling

Modelling and simulation
with OpenMalaria*, an established individual-based simulation model, simulated outcomes in all scenarios

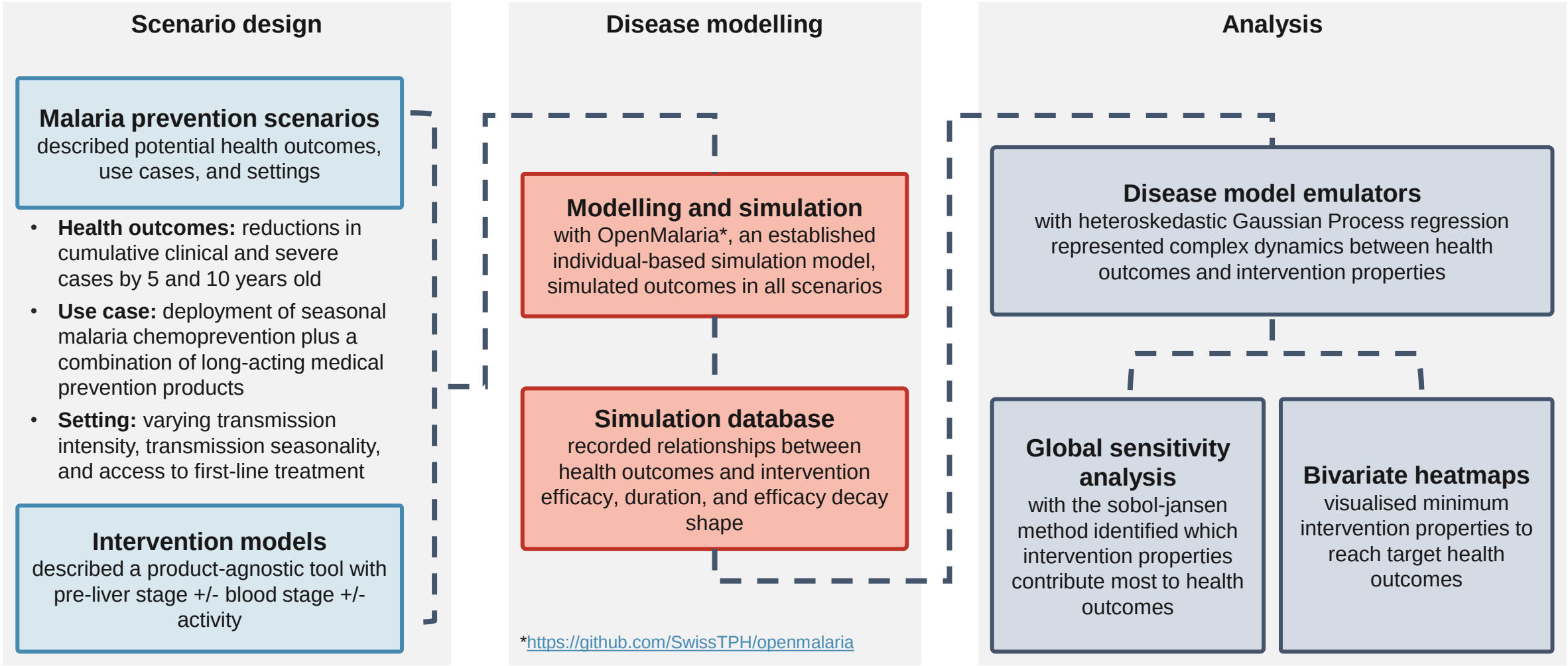
Simulation database
recorded relationships between health outcomes and intervention efficacy, duration, and efficacy decay shape

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

Illustrative simulation database

Simulation ID	Intervention inputs			Output
	Initial efficacy	Protection half-life (months)	Decay shape parameter	Reduction in cum. clinical incidence at 5 years old
1	73%	6	0.5	12%
2	76%	27	3	75%
3	75%	4	2.8	5%
4	80%	12	1	51%
5	90%	17	0.7	62%
6	97%	6	1.8	23%
7	77%	32	2.1	92%
8	83%	21	3.2	70%
9	92%	5	1.1	21%
10	76%	18	0.9	32%

Our target product profile modelling framework links therapeutic profiles with likely public health outcomes



Results confirm that the counterfactual matters for quantifying the benefit of a new intervention

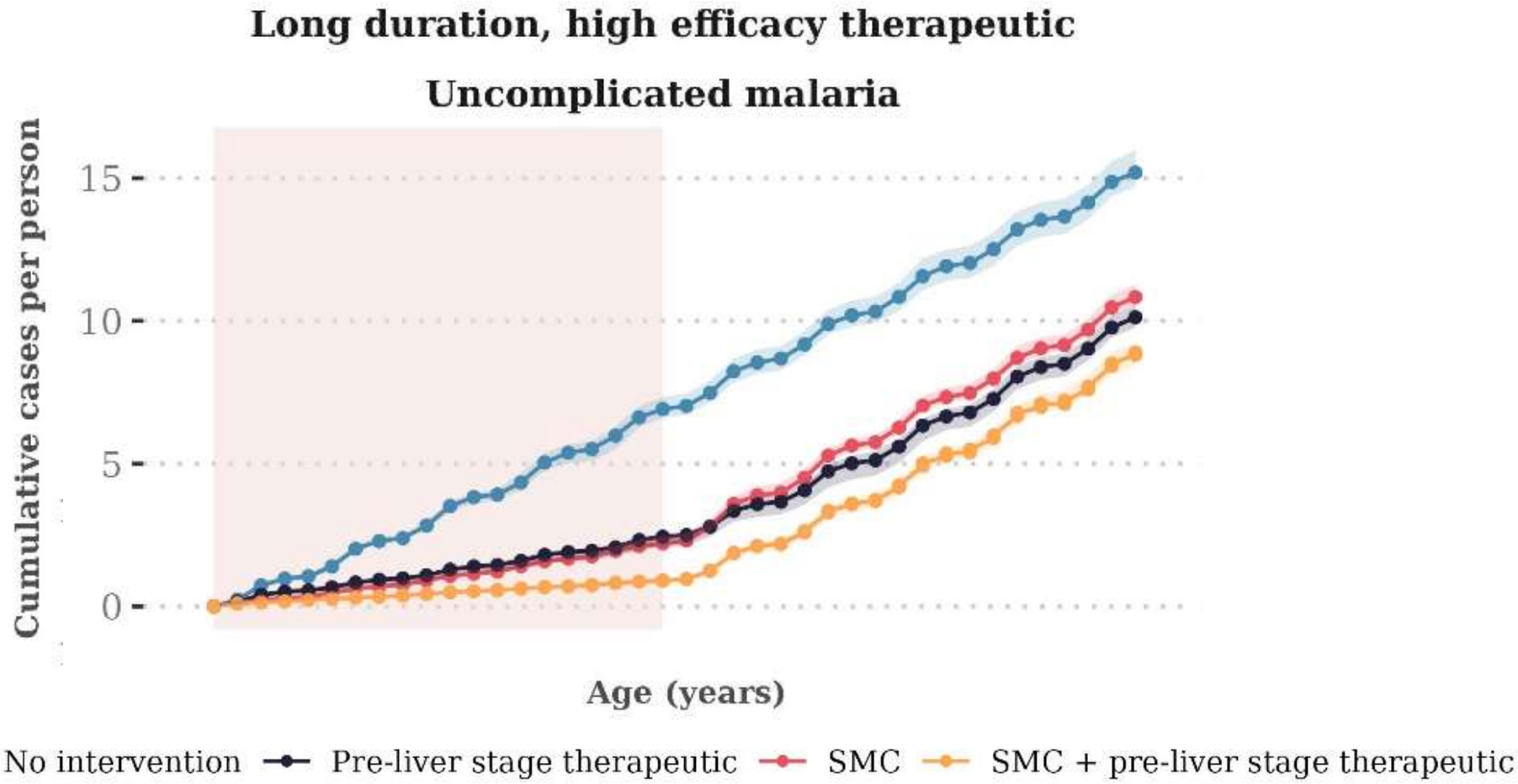


Figure includes deployment of a pre-liver stage therapeutic with a protection half-life of 354 days, 90% initial efficacy, and decay shape parameter of 1

Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

Results also confirm the public health benefits of combining pre-erythrocytic malaria therapeutics with SMC

Results

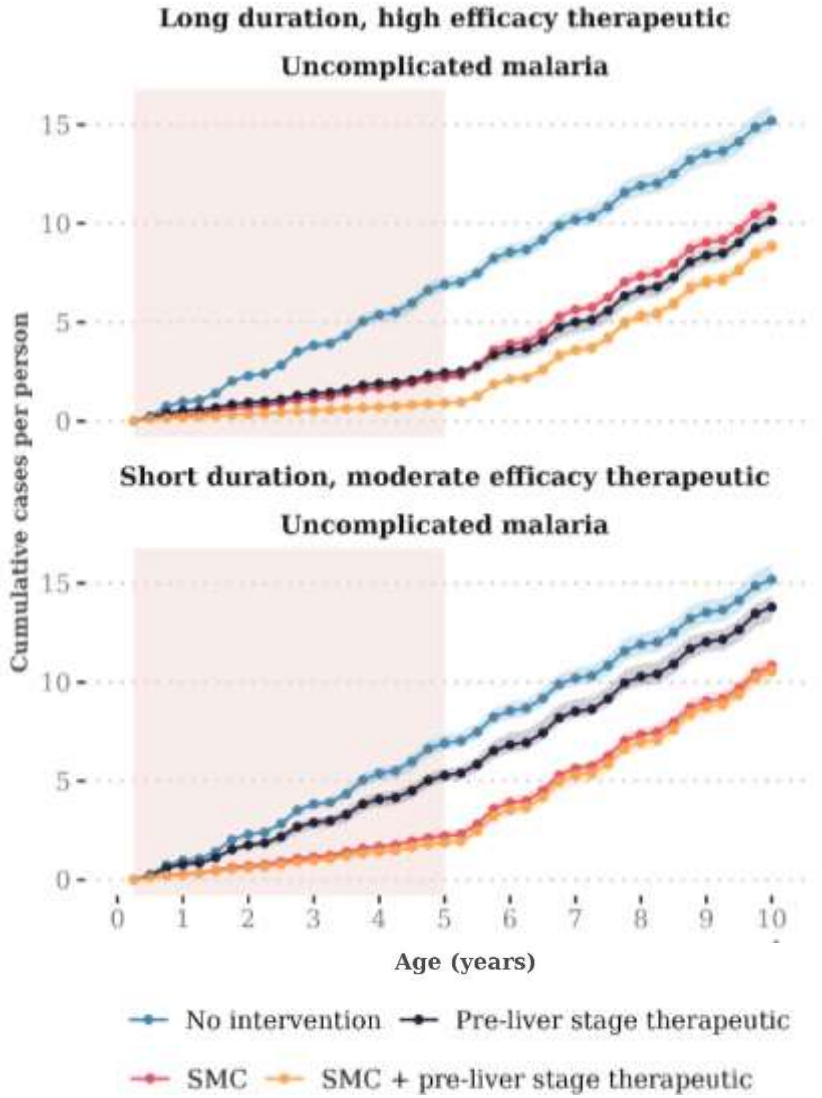
To maintain burden reductions throughout childhood, pre-liver stage therapeutics needed to have:

- **Long duration** (e.g. >230 days) and high efficacy (e.g. >50%)
- **Sustained tail of protection**, e.g. with a protective decay profile similar to RTS,S

Impact relative to SMC alone was **lower when SMC's deployment was optimised**, i.e. all children received 5 cycles of SP-AQ vs. 3 or 4 cycles

Implications

There is potential for **combining improved malaria vaccines with SMC** vs. therapeutics with rapid decay



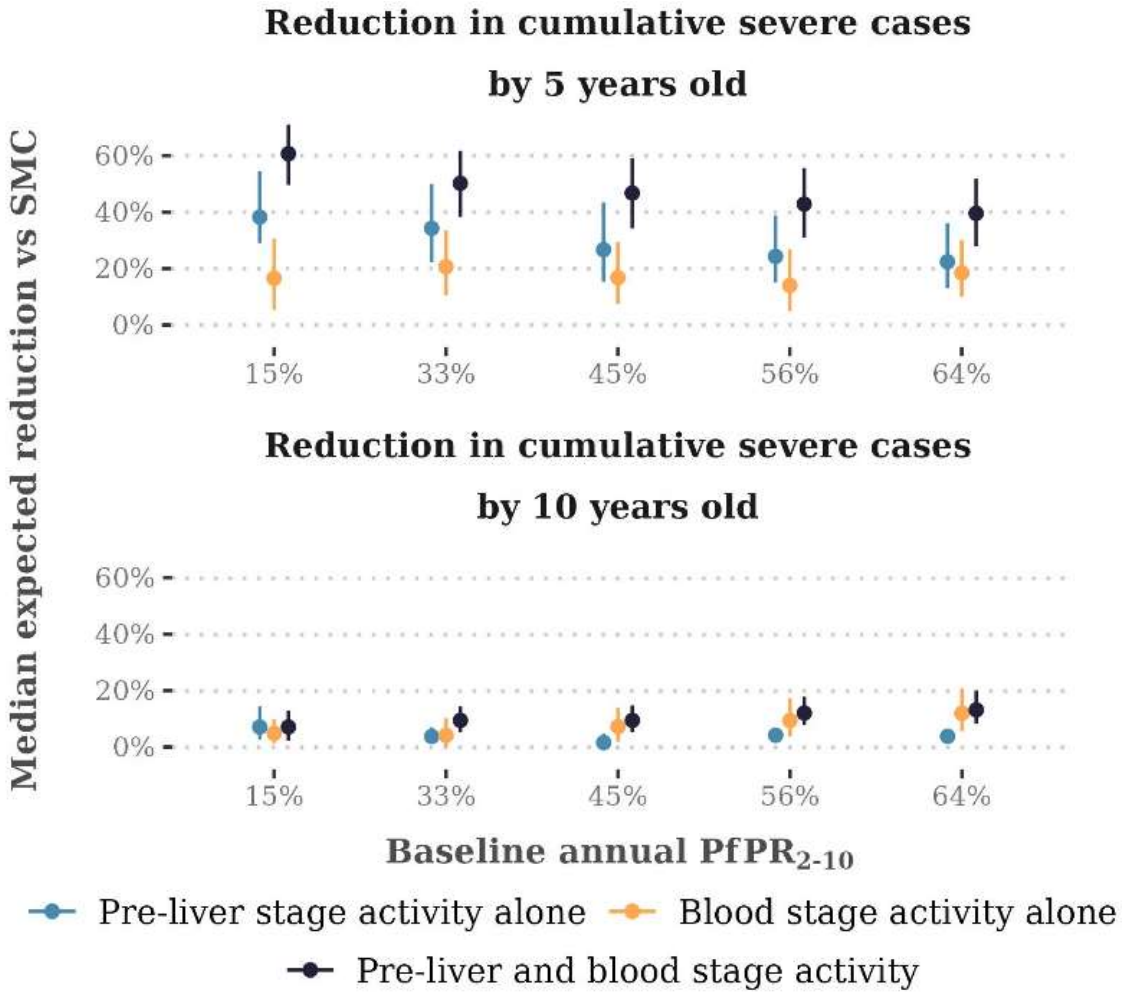
Results highlight a public health need for therapeutics with multi-stage activity for impact on severe disease

Results

- Multi-stage therapeutics with **blood stage activity** may be preferred for interventions that aim to reduce the burden of **severe malaria** in children
- Combining a **multi-stage therapeutic** with SMC led to **greater reductions in cumulative severe cases** throughout childhood than therapeutics with single

Implications

There is a public health need for a malaria therapeutic with **both pre-liver stage and blood stage activity**



Work in draft, contact lydia.braunack-mayer@swisstph.ch and melissa.penny@thekids.org.au with questions

Outlook

1 Our results indicate an opportunity to **increase the effectiveness of seasonal malaria chemoprevention** by combining it with seasonal deployment of a **multi-stage therapeutic**

2 This represents our first target product profile modelling for **novel, multi-stage malaria therapeutics**, and provides a **proof-of-concept** for future multi-stage modelling

3 **Future opportunities** include:

- Modelling the benefit of multi-stage therapeutics with different use-cases (e.g. perennial settings, non-seasonal deployment, all-age targeting)
- Validating models for clinical trial outcomes from combination vaccines and monoclonal antibodies
- Exploring the potential public health impact of long-acting injectable drugs

Thank you

Lydia Braunack-Mayer
Dr Sherrie Kelly
Dr Thiery Masserey
Dr Narimane Nekkab

Prof Melissa Penny
Dr Josephine Malinga

Dr Jean-Luc Bodmer

PD Jörg Möhrle

Contact us

lydia.braunack-mayer@swisstph.ch

melissa.penny@thekids.org.au