Using R to model the cost-effectiveness of options for the management of *Plasmodium vivax* infections

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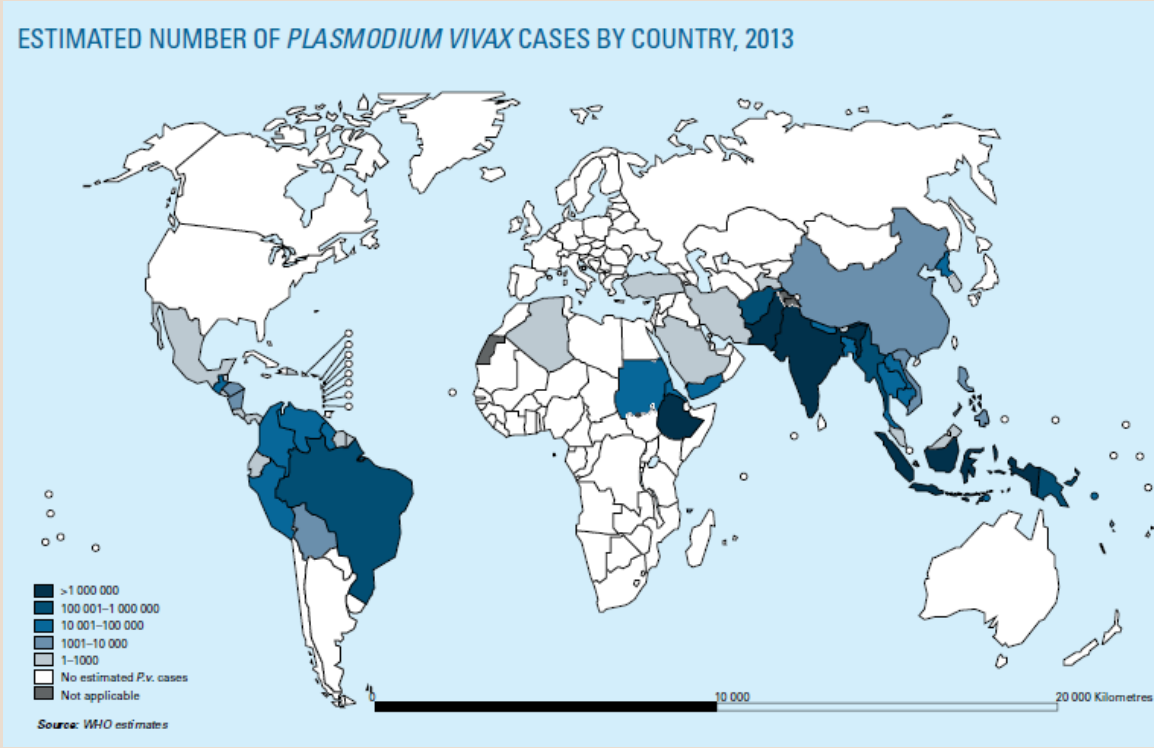
ACREME
AUSTRALIAN CENTRE OF RESEARCH EXCELLENCE IN MALARIA ELIMINATION

Plasmodium vivax malaria

- 4 types of malaria
- *P. falciparum* is the most common
  - Most cases in Africa
  - More deadly
- *P. vivax* is the most widespread: 1/3 of the world is at risk



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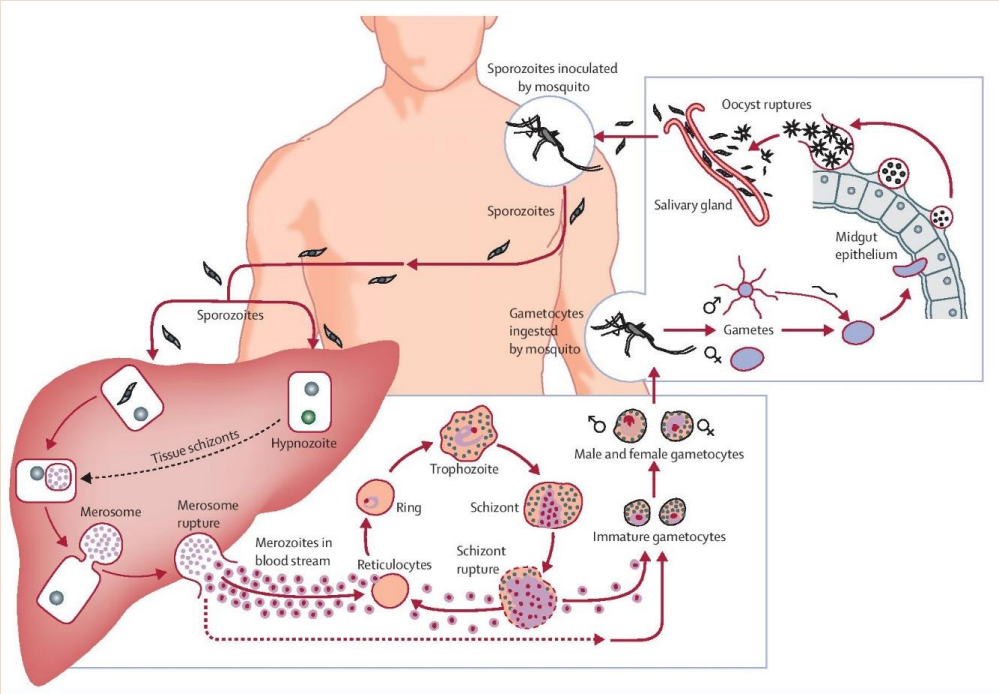
Challenges in *P. vivax* treatment

- One infection can lead to multiple relapses due to dormant parasites in the liver (hypnozoites)
- The drugs that clear these hypnozoites can cause haemolysis in individuals with G6PD deficiency



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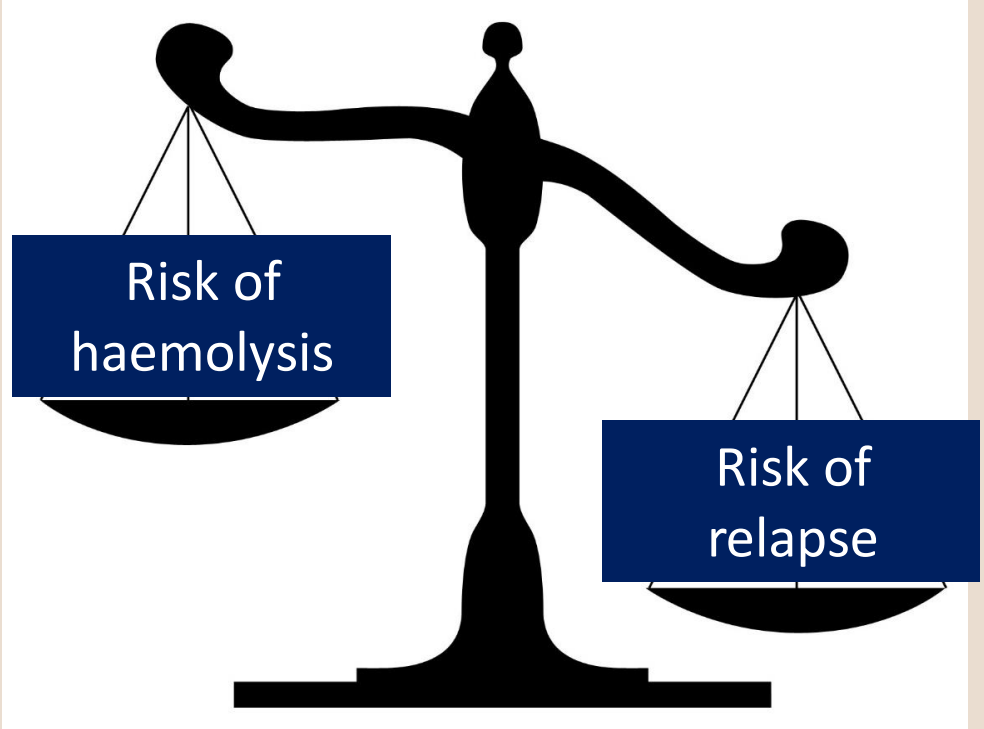
Background

- **Extremes in practice:** always/never prescribe radical cure to clear both blood and liver stages
- New point of care tests enable screening for G6PD deficiency before giving radical cure



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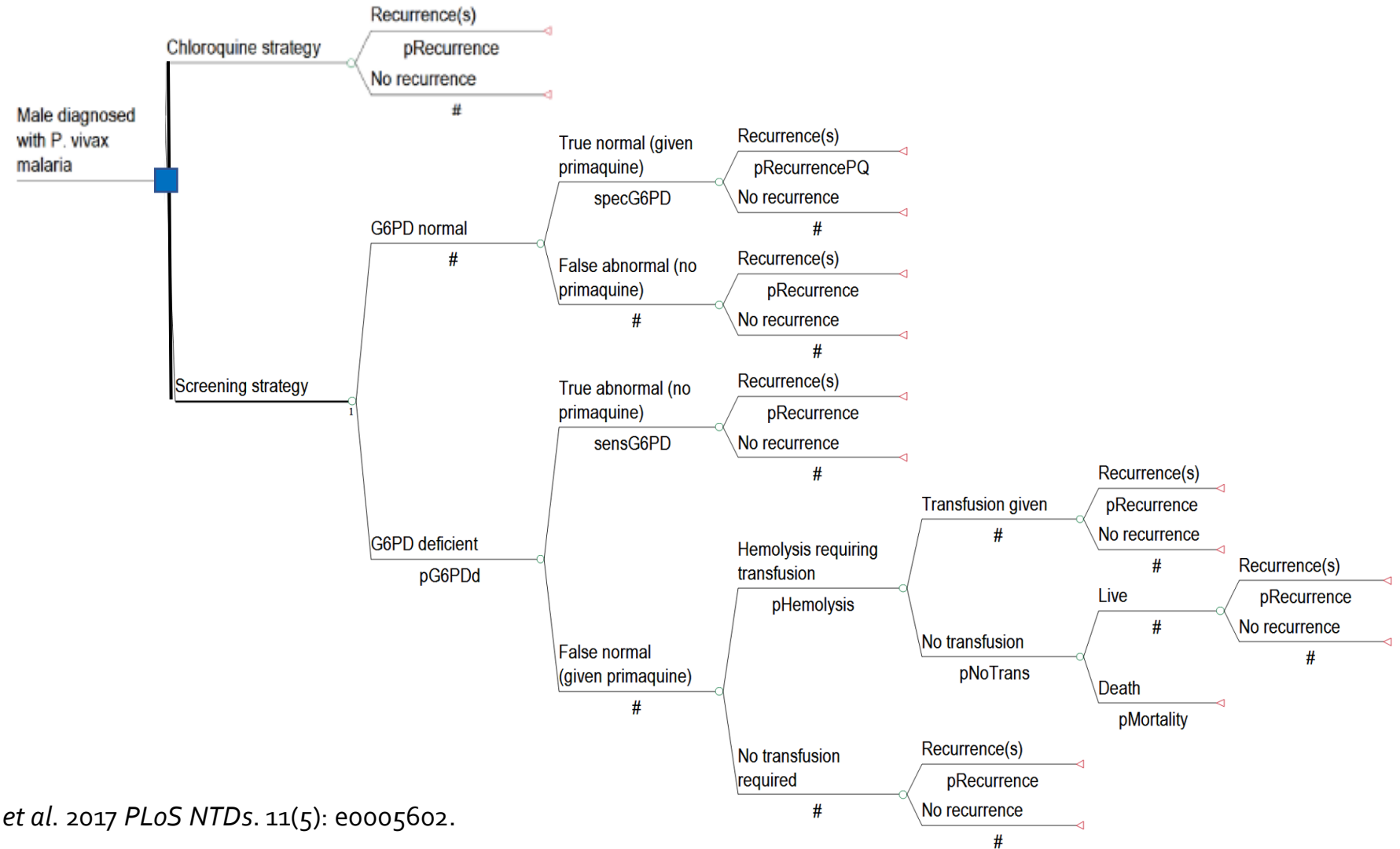
Background

- Question: Is screening for G6PD deficiency before prescribing primaquine cost-effective as compared to:
  1. Not prescribing primaquine
  2. Prescribing primaquine without screening
- Part of my PhD
  - Unit moving away from paid software
  - I wanted to upskill
  - Coded base case in TreeAge first, then in R

Overview

- Analysis and results for primaquine in Thailand (published 2017 in *Plos NTDs*)
- Now adapting for a new single-dose drug (tafenoquine) as part of HTA approval process in Brazil (CONITEC)
- Experiences as a new R user, reflections & questions



Devine *et al*. 2017 *PLoS NTDs*. 11(5): e0005602.

Script 1: Model

```
### MODEL COSTS
# Chloroquine strategy
costs_CQ <- model_CQ*cMild+model_CQ*cRecur*RecurCQ
# Primaquine strategy
costs_PQ <- ((cMild+cPQ_14d+cDOTs_14d)*cohort + # all get PQ in initial visit
               cRecur_PQ*RecurPQ*p1 +           # recurrences in those who get PQ and are G6PD normal
               cRecur*RecurCQ*(p2a+p2b+p2d) +   # recurrences in G6PDd (didn't get full PQ course)
               cHaemolysis*p2b                  # cost of haemolysis in G6PDd who got PQ & received tra
)
# Screening strategy
costs_screen <- (cohort*(cMild+cG6PDtest) +         # all get a G6PD test
                   (cPQ_14d+cDOTs_14d)*(prop1+prop4) +     # 14d PQ given to those who test normal
                   (cPQ_8w+cDOTs_8w)*(prop2+prop3) +       # 8w PQ given to those who test deficient
                   cRecur_screen*RecurPQ*(prop1) +         # Recurrences in those who got 14d PQ
                   cRecur_def*RecurPQ*(prop2+prop3) +      # Recurrences in those who got 8w PQ
                   cRecur_def*RecurCQ*(prop4a+prop4b+prop4d) +  # Recurrences in those who don't get PQ
                   cHaemolysis*prop4b                      # cost of haemolysis in FN who got PQ & trea
)
# Incremental costs
IncrCosts_CQ <- (costs_screen - costs_CQ)
IncrCosts_PQ <- (costs_screen - costs_PQ)
```

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Script 2: parameters + analysis script

```
# COSTS
cG6PDtest <- 1.50 + 0.25    # Ley 2015 for RDT cost + non-RDT costs from Lubell 2007
cHaemolysis <- 320.71       # 1 week hospitalization + 1 unit blood
cPQ <- 0.06                 # per pill: Intl Drug Price Indicator Guide 2014 (for 60kg person)
cDOTs <- 1.67              # per observation: Kyaw 2016 half day of work *13 days of DOTs (overestimate)
cMild <- 7.86               # cost of an outpatient visit at a health centre in Thailand (WHO CHOICE)
cSevere <- 196.22           # cost of IP Pf malaria in Mae Sot treated with artesunate (Kyaw 2014)
```

```
source ("Pv model (M).R")
model_PQ                                    # check that
model_screen                                # check that
## Record results in vectors
# Base case costs
base_costs_CQ <- costs_CQ
base_costs_PQ <- costs_PQ
base_costs_screen <- costs_screen
# Base case DALYs
base_DALYs_CQ <- DALYs_CQ
base_DALYs_PQ <- DALYs_PQ
base_DALYs_screen <- DALYs_screen
# Base case incrementals for cohort
base_IncrCosts_CQ <- IncrCosts_CQ
base_DALYavert_CQ <- DALYavert_CQ
base_IncrCosts_PQ <- IncrCosts_PQ
base_DALYavert_PQ <- DALYavert_PQ
base_ICER_CQ <- base_IncrCosts_CQ / base_DALYavert_CQ
base_ICER_PQ <- base_IncrCosts_PQ / base_DALYavert_PQ
```

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One-way SA

```
# G6PDd
pG6PDd <- c(0.069, 0.206)
pG6PDn <- 1 - pG6PDd
source ("Pv model (M).R")
IncrCosts_pG6PDd_CQ <- IncrCosts_CQ
DALYavert_pG6PDd_CQ <- DALYavert_CQ
IncrCosts_pG6PDd_PQ <- IncrCosts_PQ
DALYavert_pG6PDd_PQ <- DALYavert_PQ
pG6PDd <- 0.137
pG6PDn <- 1 - pG6PDd

# RDT sensitivity
pTP <- c(0.9, 1)
pFN <- 1 - pTP
source ("Pv model (M).R")
IncrCosts_pTP_CQ <- IncrCosts_CQ
DALYavert_pTP_CQ <- DALYavert_CQ
IncrCosts_pTP_PQ <- IncrCosts_PQ
DALYavert_pTP_PQ <- DALYavert_PQ
pTP <- 0.99
pFN <- 1 - pTP          # 1 - sensitivity
```

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New scripts

```r
params <- list(
  "pvpts" = c(200, 37, 1169),      # Throug
  "drate" = c(0.05, 0, 0.1),       # discou
  "biolife" = c(3, 1, 5),          # Lifeti
  "pAdhere" = c(0.837, 0.2, 1.0),  # perce
  "propR" = c(0.77, 0.4, 0.85),    # propor
  "rr" = c(0.547, 0.386, 0.775),   # RR of
  "nRecurCQ" = c(2, 1, 3),         #*ASSUMP
  "nRecurRC" = c(1, 1, 2),         #*ASSUMP
  "pG6PDd" = c(0.048, 0.036, 0.065), # % w
  "pTP" = c(0.98, 0.90, 1.00),       # sen
  "pTN" = c(0.97, 0.90, 1.00),     # speci
  "pTPq" = c(1.00, 0.95, 1.00),    # sensi
  "pTNq" = c(0.96, 0.90, 0.98),    # speci
  "pHaem" = c(0.1, 0.05, 0.15),    # haemol
  "pTrans" = c(0.36, 0.18, 0.55),  # % rec
  "pMortH" =  c(0.08, 0.04, 0.13),   # Dea
  "Pv_severe" = c(0.03, 0.015, 0.045),  #
  "Pv_death" = c(0.0003, 0, 0.00045),   #
  "cHaem" = c(368.3, 184.15, 552.45),   #
  "cPQ" = c(0.14, 0.07, 0.21),     # Peixo
  "cTQ" = c(1.4, 1.4, 2.1),        # cost
  "cDOTs"= c(51, 25, 76),          # Sampa
```

```r
base.model <- function(params){
  cohort <- 1000                  # to tabulate numbers
  pG6PDn <- 1 - params$pG6PDd     # 1 - propororion G6PDd
  pFN <- 1 - params$pTP           # 1 - sensitivity (Qual test)
  pFP <- 1 - params$pTN           # 1 - specificity (Qual test)
  pFNq <- 1 - params$pTPq         # 1 - sensitivity  (Quant test)
  pFPq <- 1 - params$pTNq         # 1 - specificity (Quant test)
  Pv_mild <- 1 - params$Pv_severe - params$Pv_death
  rate <- (1-(1+params$drate)^(-1*params$biolife))/params$drate # An


  # Total recurrences
  RecurCQ <- params$propR * params$nRecurCQ                    # in all
  RecurRC <- params$propR * params$rr* params$nRecurRC     # in all w
  Recur_noDOTs <- RecurCQ*(1-params$pAdhere) + RecurRC*params$pAdher

  # Quantitative test cost per patient
  cQuant <- params$cStrip +
    params$cMachine/rate/params$pvpts +
    params$cQA +
```

```r
# Get lower limit case
lower.output <- matrix(NA, nrow = length(params), ncol=10)
for (i in 1:length(params)){
  tmp.params <- sapply(params, "[[",1)
  tmp.params[i] <- sapply(params, "[[", 2)[i]
  tmp.params <- as.data.frame(t(tmp.params))
  lower.output[i,] <- unlist(base.model(tmp.params))
}
```

Thailand Results

- Screening strategy averted DALYs
- Screening strategy saved costs when compared to giving primaquine without screening
- Screening modestly increased costs when compared to not giving primaquine
  - ICER = $6 for males
  - ICER = $12 for females

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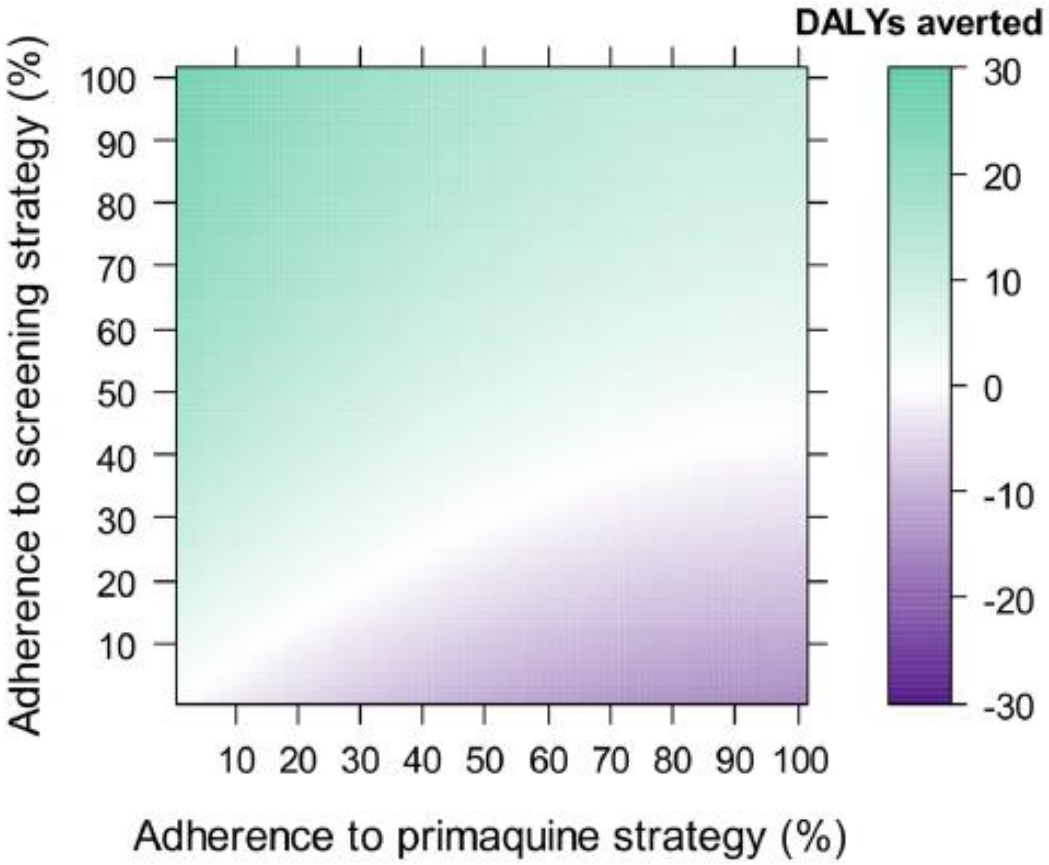
Two-way SA

- Green favours screening strategy
- Purple favours primaquine strategy



R-Shiny app

- LOTS of variation between settings (epidemiology & costs)
- Can use google analytics to track
- Pushing for policy change
- Should the online model include a disclaimer?

Website: https://malaria.shinyapps.io/g6pd_screening/

Cost effectiveness of G6PD screening

Model Overview

A single infection with *Plasmodium vivax* malaria can cause multiple episodes of illness due to dormant liver parasites called hypnozoites. Primaquine is the only drug available to treat hypnozoites but is under-used because it can cause life-threatening hemolysis in people who have an inherited condition called glucose-6-phosphate dehydrogenase (G6PD) deficiency. In our model, this is the chloroquine strategy. In other locations, primaquine is given without testing for G6PD deficiency (the primaquine strategy), putting patients at unnecessary risk of hemolysis. New rapid diagnostic tests provide the opportunity to screen for G6PD deficiency prior to primaquine treatment. In our model, this is the screening strategy, which includes 8 weekly doses of primaquine for those who test G6PD deficient. Our study describes a cost-effectiveness analysis that we did for a Thailand-Myanmar border setting. A full description of our model is here: [link to journal website].

Here we provide our interactive model for adaptation to other locations. Change the parameters below to see how they change the results on the right. The model assumes observed primaquine therapy.

Recurrences | G6PD | RDT | Costs | DALYs

Model Parameters

These parameters result in an average of 2.6 recurrences when treated with chloroquine only and an average of 0.2 recurrences when treated with chloroquine plus primaquine (14 day or 8 weekly).

Percent treated with chloroquine only who have at least 1 recurrence

0 — 0.73 — 1

Relative risk of having at least 1 recurrence if given 14 day primaquine

0 — 0.22 — 1

Mean number of recurrences over 1 year if given chloroquine

3.54

Mean number of recurrences over 1 year if given chloroquine with primaquine

1.16

Percent of women who are pregnant so cannot take primaquine

0 — 0.11 — 1

Percent of women who need to take a pregnancy test

0 — 0.5 — 1

Assumes that all women of childbearing age who do not know they are pregnant receive a pregnancy test.

Males | Females

Results

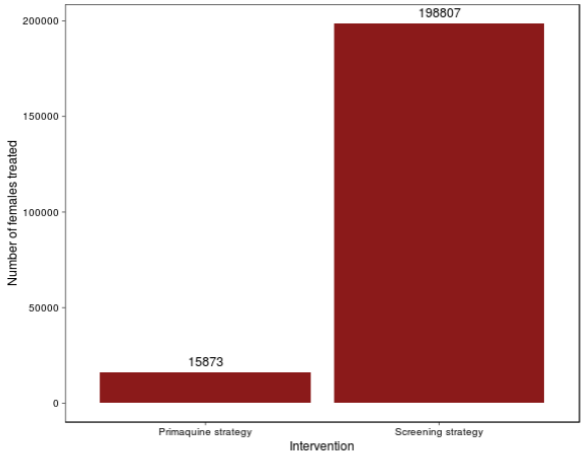
Compared to the chloroquine strategy

For females, the screening strategy cost US$ 0.4 more than the chloroquine strategy with 0.0238 averted DALYs.

Compared to the primaquine strategy (no G6PD screening)

For females, the screening strategy cost US$ 2.2 less than the primaquine strategy with 0.0041 averted DALYs.

Number of females that you would need to treat before seeing one death due to primaquine-induced hemolysis



Future work and discussion questions

- Consensus on model parameters for Brazil
- 5 comparators for Brazil – how do you automate code to pick which are cost-effective (PSA)?
- How do you draw decision tree diagrams?
- Is there a package or way to graph tornado diagrams?
- Have other people built shiny apps for their models?
- How do you maintain your R language skills?

Thank you!

MMV
Medicines for Malaria Venture

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Benedikt Ley

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