

Innovation Translation Impact

Safe and Effective Radical Cure of Malaria

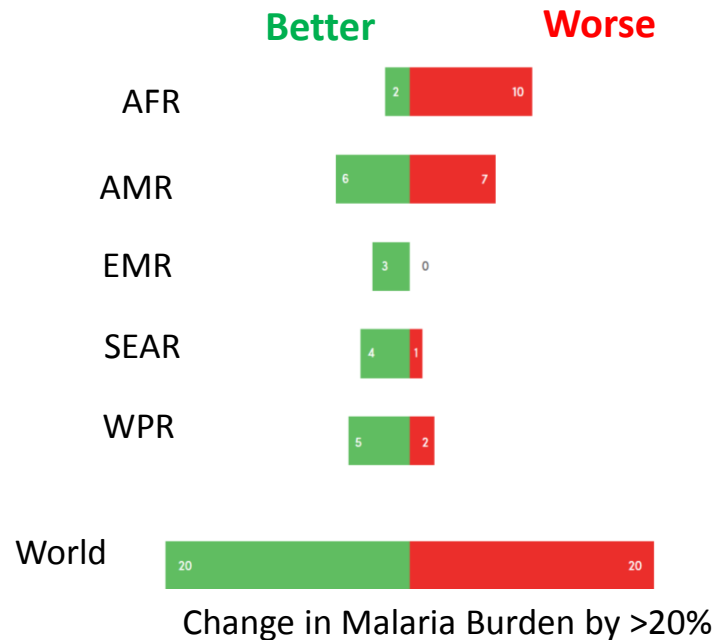
Ric Price

Malaria Elimination

Target: 90% reduction; 35 countries eliminated; Asia Pacific - Free

- Sri Lanka (2016), Paraguay (2018), Uzbekistan (2018)
- China, Bhutan, Malaysia...

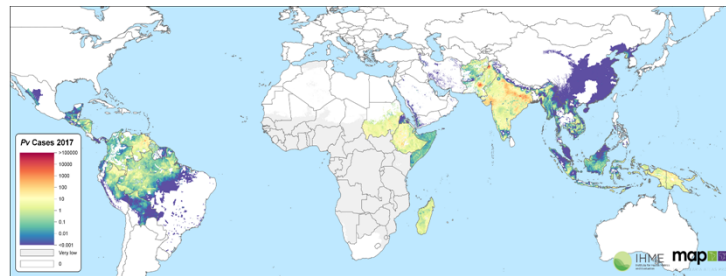
WMR	Total
2000	262 m
2013	198 m
2015	214 m
2016	217 m
2017	219 m



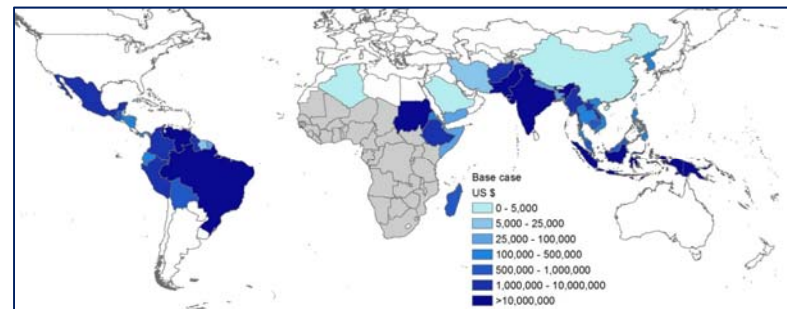
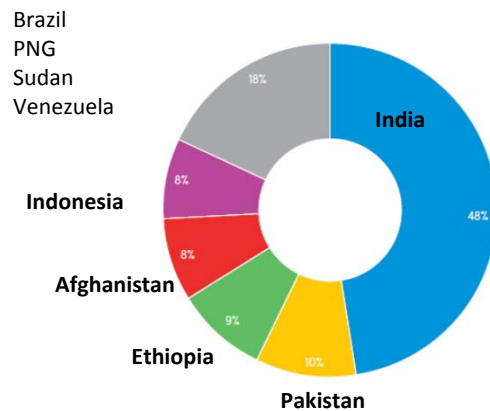
Global burden of *P. vivax*

- 2.5 billion people at risk
- 7.5-14.3 million cases

Global Burden of *P. vivax* - 2017



The Malaria Atlas Project: Battle *et al* 2018 Submitted

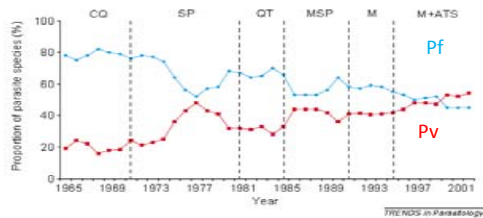


Cost **\$533 million pa**

Angela Devine *et al* 2018

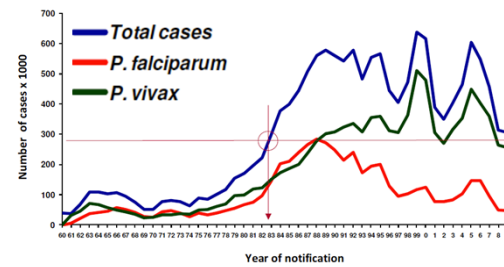
Relative rise in the burden of *P. vivax*

Thailand: 1965-2001



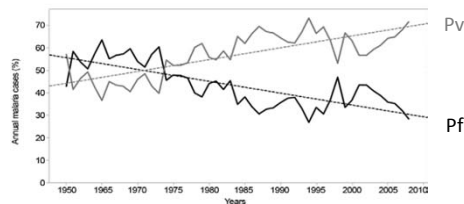
Sattabongkot et al Trends in Parasite 2004

Brazil: 1960-2009



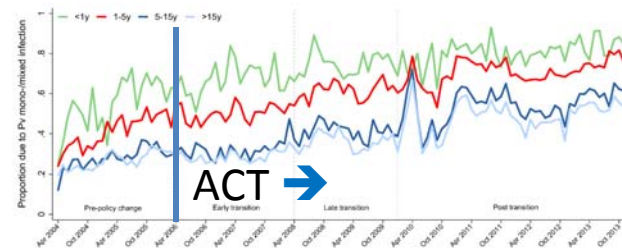
Oliveira-Ferreira et al., Malaria J 9 (1), 2010

Colombia: 1960-2008



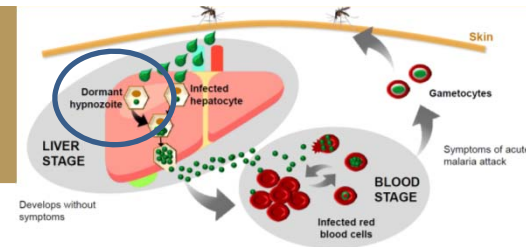
Rodriguez et al Mem Inst Oswaldo Cruz, 2011

Papua: 2004-2013

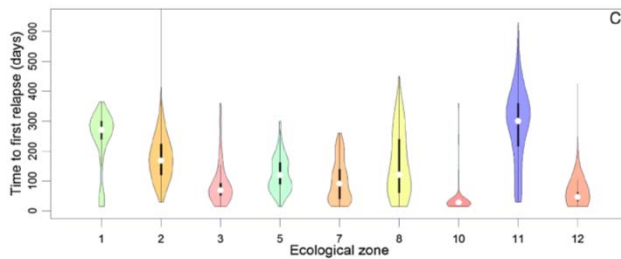
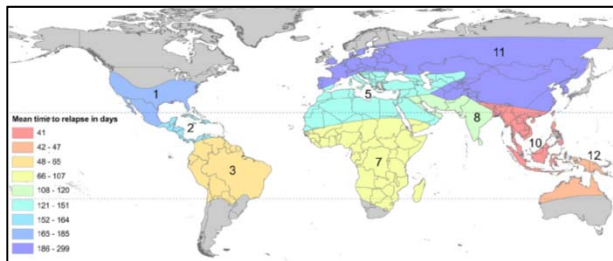


Kenangalem et al Submitted

P. vivax hypnozoites

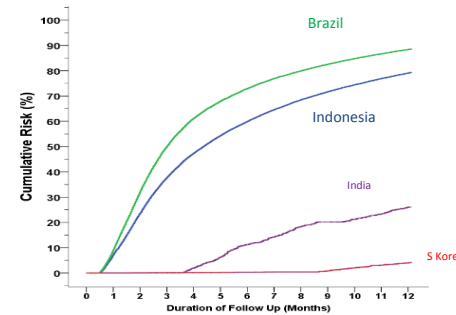


Time to relapse varies by region



Battle et al Mal J 2014

Risk of Relapse



➔ **Transmission dynamics**
 >80% of recurrences are due to relapse

➔ **Morbidity and Mortality**

The Radical Cure of *P. vivax*

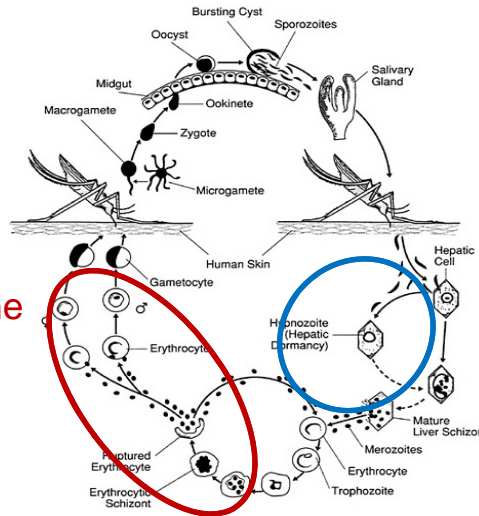
Schizontocidal Treatment

- Chloroquine
- DHA-piperaquine
- Artemether-Lumefantrine

+

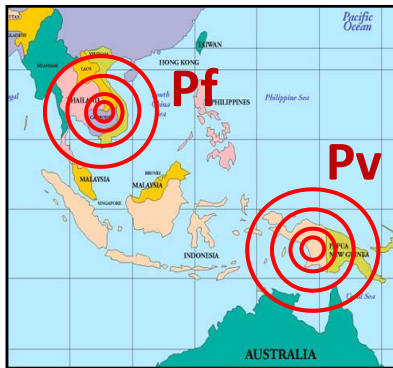
Hypnozoicidal Treatment

- Primaquine
- Tafenoquine



Blood Stage Treatment

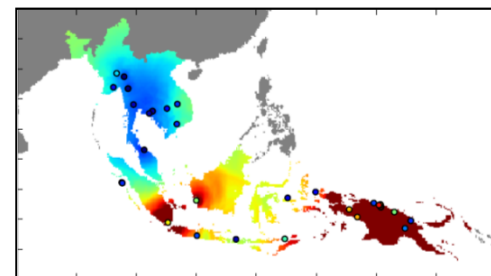
Chloroquine Resistant *P. vivax*



129 clinical Studies

CQR present in over half of the study sites

CQR	Category 1	>10% recurrence by Day 28 Lower 95%CI >5%
	Category 2	>5% recurrence by Day 28 With High Chloroquine Conc
	Category 3	>5% recurrence by Day 28 Lower 95%CI <5%
	Category 4	Case Reports
CQS		In absence of early Primaquine
Uncategorised		CQS and Early Primaquine N<5 Surveys




Price et al Lancet ID 2014

WWARN Pooled Analysis



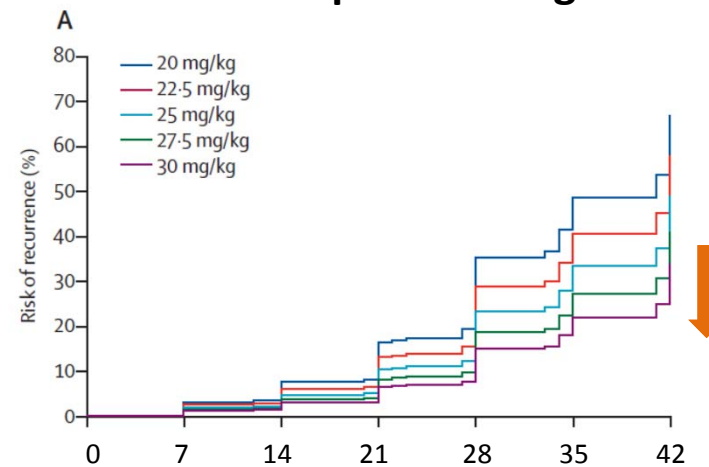
37 clinical trials:

 CQ, N=2990

 CQ + PQ, N=1790

Commons et al Lancet ID 2018

Chloroquine Dosing





For every 5 mg/kg dose increase: AHR = 0.83

In children under 5 years old increasing the dose by 5mg/kg would prevent 18% of recurrences

WWARN Pooled Analysis

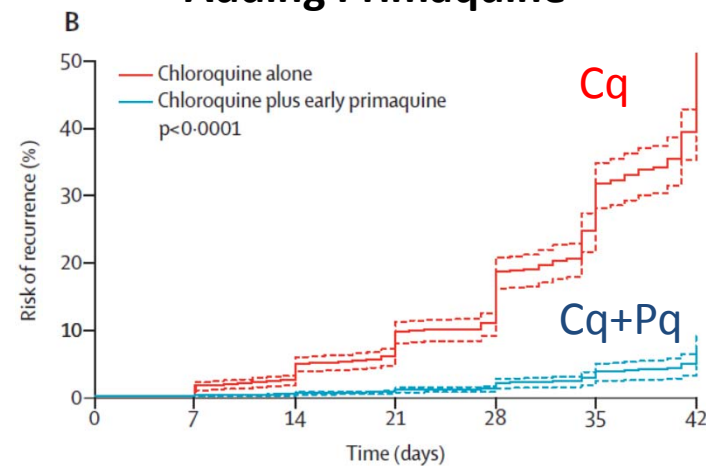


37 clinical trials:

-  CQ, N=2990
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Commons et al Lancet ID 2018

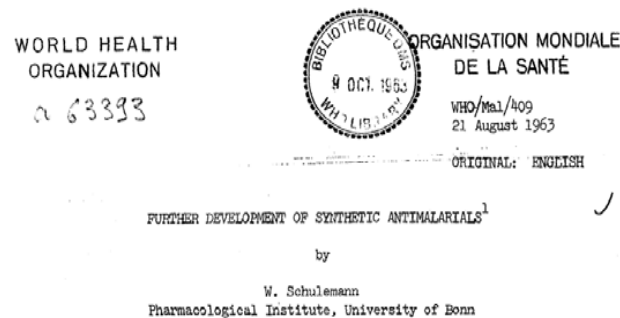
Adding Primaquine



Addition of primaquine reduces recurrences by 90%: early recrudescences and late relapses

Liver Stage Treatment

Primaquine Radical Cure



Nevertheless, the advance represented by the introduction of Primaquine is still not sufficient...

“the Group recommends that intensive research be carried out with a view to developing an anti-relapse drug free from side effects and radically curative at a single dose or at most after a three day treatment”

55 years later and...

- We still don't know the optimal dosing regimen
- Clinicians are reluctant to prescribe it
- Patients don't take a complete course

Dosing Regimens



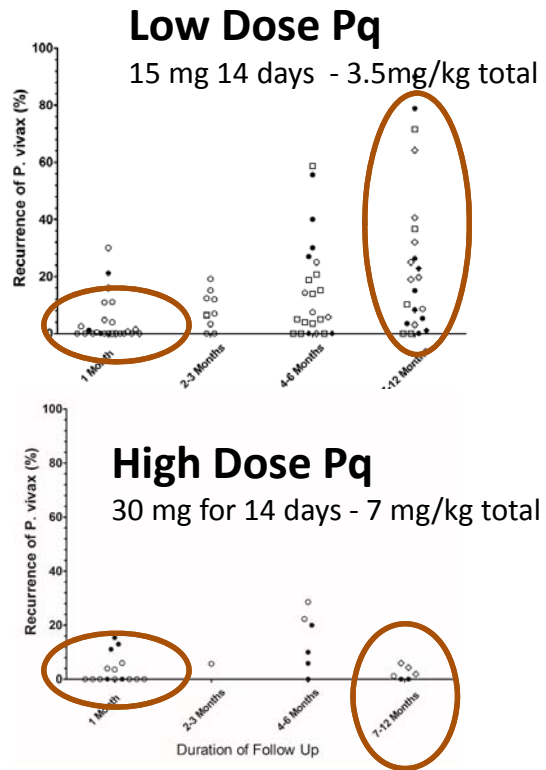
Efficacy is related to total dose given

	Total	Daily	Dose	
	mg/kg	mg/kg	mg	
Low Dose 14d	3.5	0.25	15 mg/d	Most countries
Low Dose 7d	3.5	0.5	30 mg/d	Brazil, China
High Dose 14d	7.0	0.5	30 mg/d	Papua
High Dose 7d	7.0	1.0	60 mg/d	
Weekly	6.0	0.75	45mg	

And many more options!

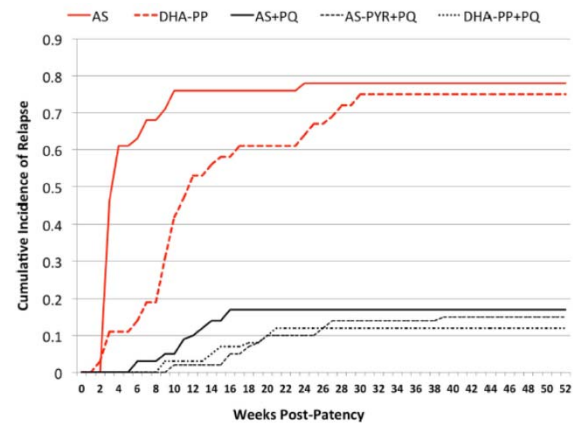
What Dose ?

The Correct Dose?



John et al MalJ 2011

Supervised High Dose Pq
+ACT Works pretty well...

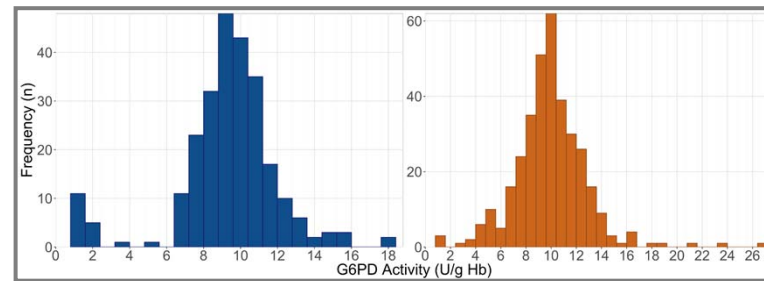
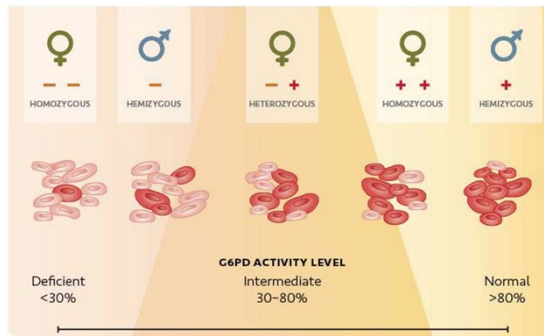


Nelwan et al AAC 2015

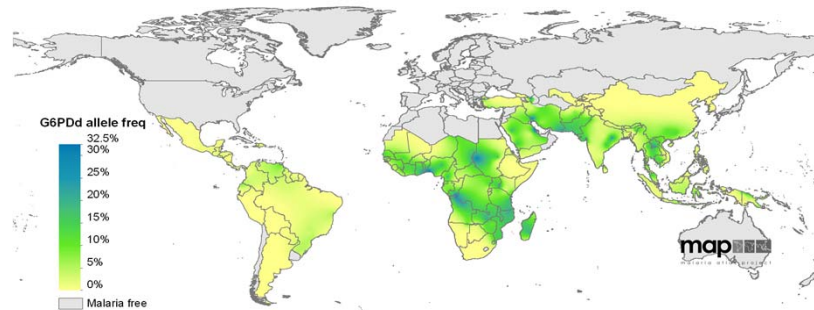
Haemolysis

Glucose 6 Phosphate Dehydrogenase deficiency

G6PD - crucial for **antioxidant defense** in red blood cells (RBC)



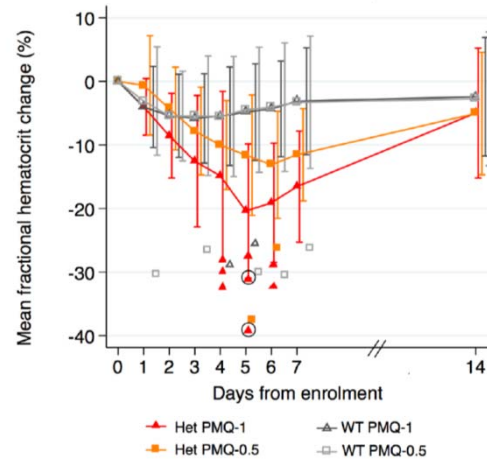
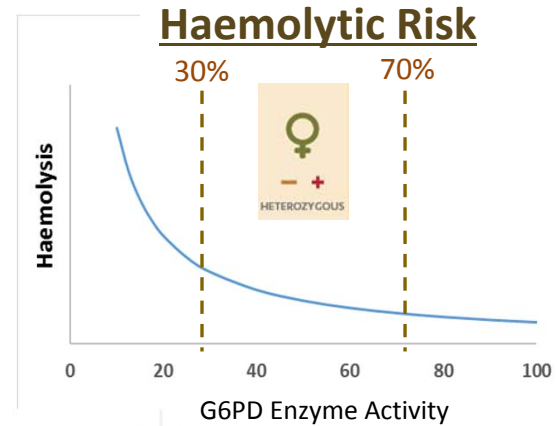
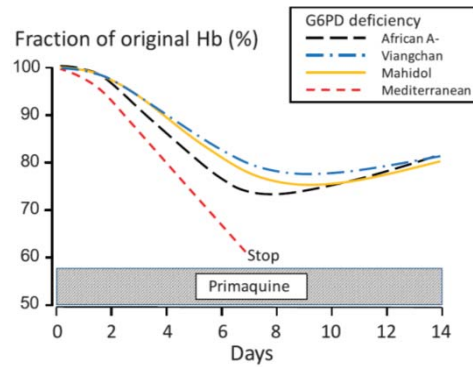
G6PDd distribution



Howes et al. 2012. *PLoS Med.*

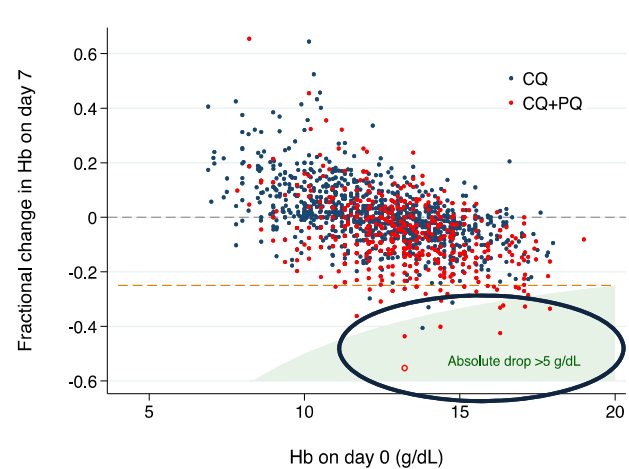
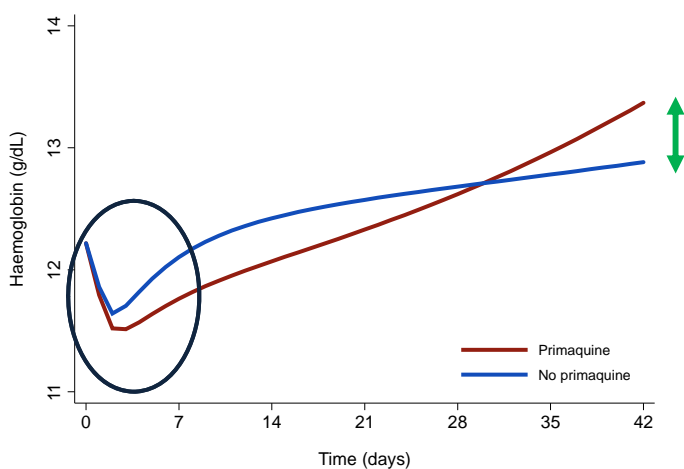
Haemolytic Risk

Variant Specific



Chu et al PlosMed 2017

Primaquine: Good and Bad

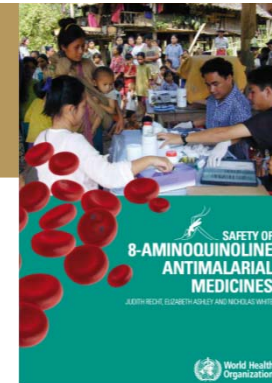


3,421 patients (29 studies) included in the analysis
1,975 with chloroquine alone prior to day 42
1,446 with chloroquine and primaquine on day 0

Commons et al Submitted

Primaquine Safety

- Primaquine exposure in > 36 million individuals^{1,2}
 - 219 SAEs - mostly severe hemolysis¹ (none if G6PD normal)



		Population	SAEs	Risk
MDA	15-30mg daily	9 million	16 severe haemolysis 2 methaemoglobinaemia 1 severe urticaria	1.8 per million
Patients	15-30mg daily		24 severe haemolysis 1 neuropsychiatric ³	

- 14 deaths: 12 haemolysis, 1 hepatic necrosis, 1 unknown

→ Mortality Risk = 1 in 621,428

¹ WHO Safety of 8 aminoquinolines 2014; ² Ashley MaJ 2014

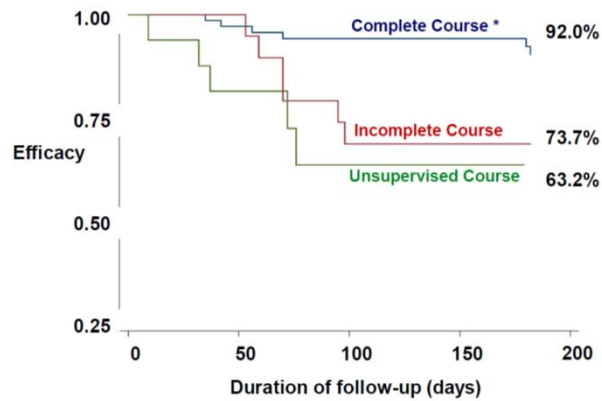
Adherence

Patients Don't Complete a 14 Day Regimen for an Acute Febrile Illness

Primaquine efficacy is related to total mg/kg dose ingested

Clinical Trial

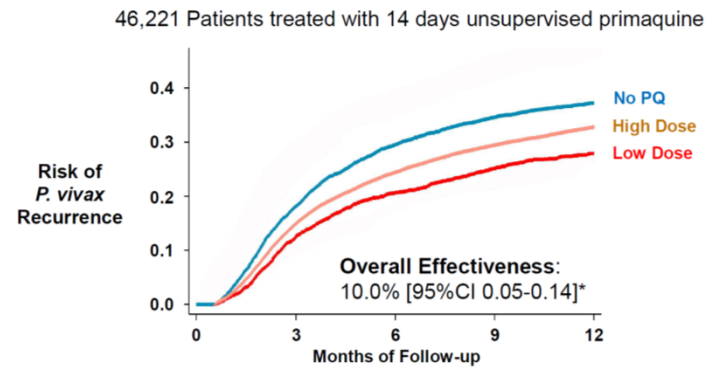
Ethiopia



Abreha et al Plos Med 2017

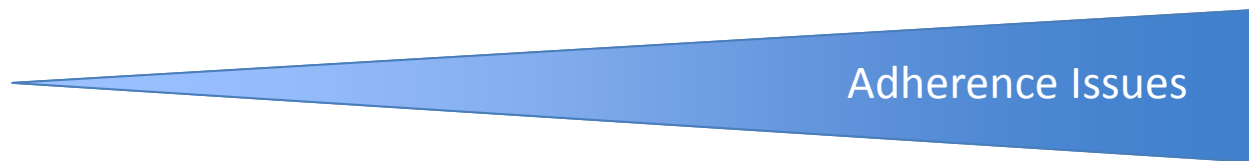
Clinical Practice

Papua Indonesia

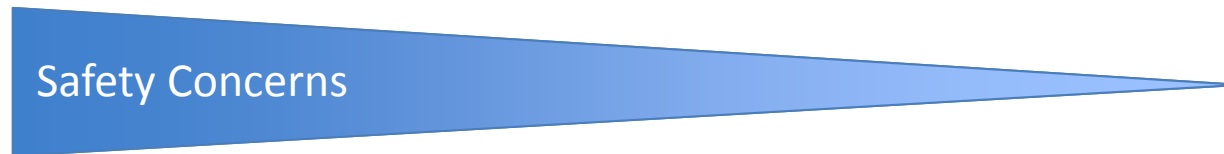


Douglas et al Plos Med 2017

The Long And The Short Of It....



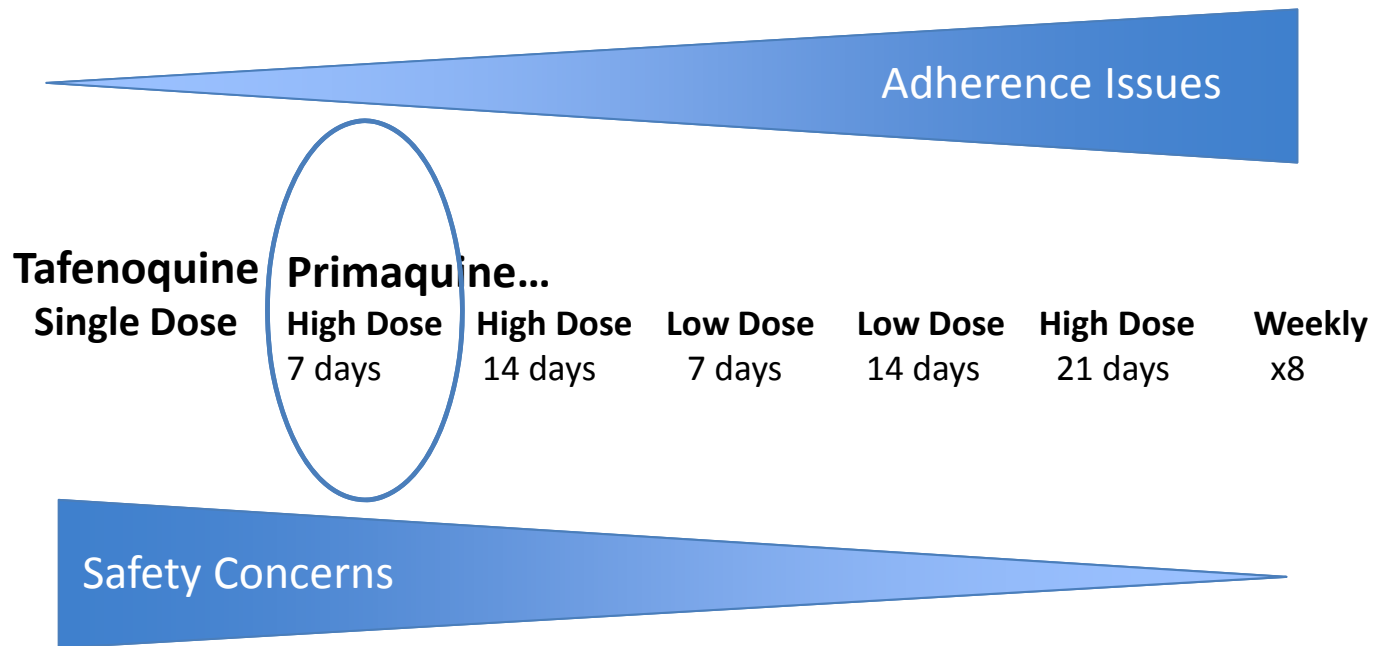
Tafenoquine	Primaquine...					
Single Dose	High Dose	High Dose	Low Dose	Low Dose	High Dose	Weekly
	7 days	14 days	7 days	14 days	21 days	x8



Innovation:

Short Course Treatments

The Long And The Short Of It....



IMPROV Study

IMproving Primaquine Radical cure Of Vivax

A multicentre study double blind placebo controlled trial:

- Indonesia, Vietnam, Afghanistan, Ethiopia

Chloroquine or DHA-Piperaquine Plus:

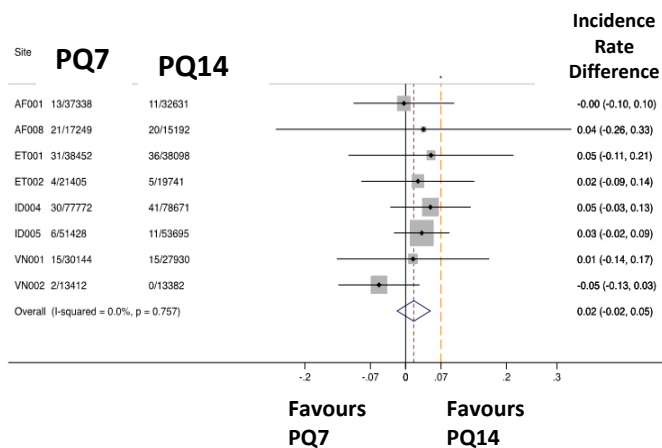
1. Placebo
2. Primaquine 1mg/kg/day for 7 days
3. Primaquine 0.5mg/kg/day for 14 days

2,388 patients, followed for 12 months
Repeat dosing

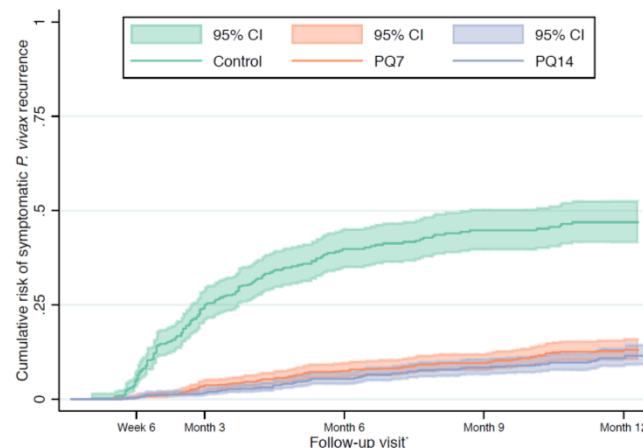


7 days PQ is non inferior to 14 days PQ

Symptomatic *P. vivax* Recurrence 12m



Incidence Rate Difference:
IR = 0.02 (95% CI -0.02 to 0.05)



Incidence Risk: PQ7 vs Control:
HR = 0.18 (95% CI 0.13 to 0.26)

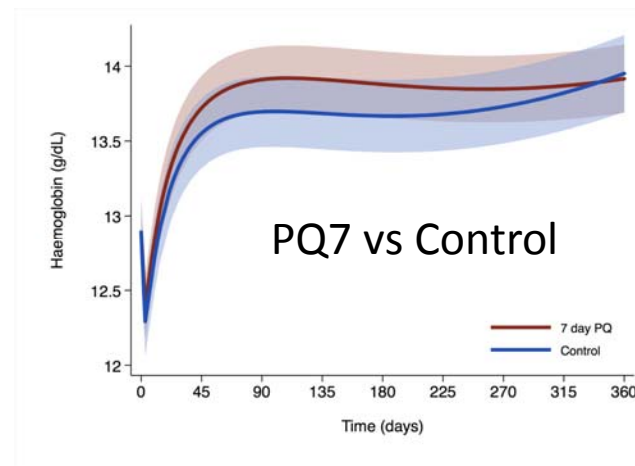
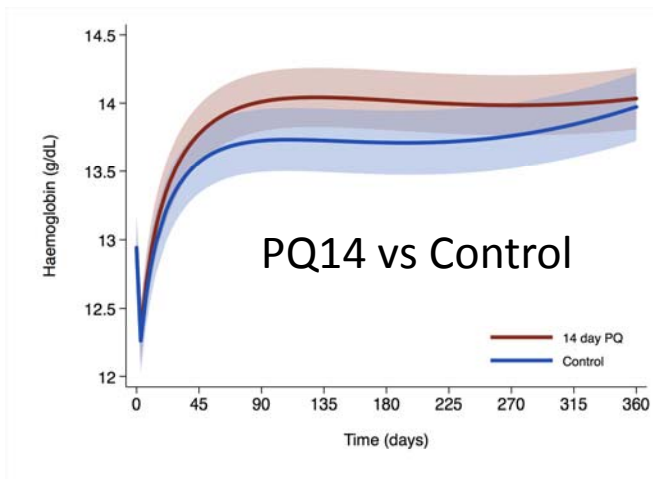
IMPROV Study

High Dose Pq Tolerability

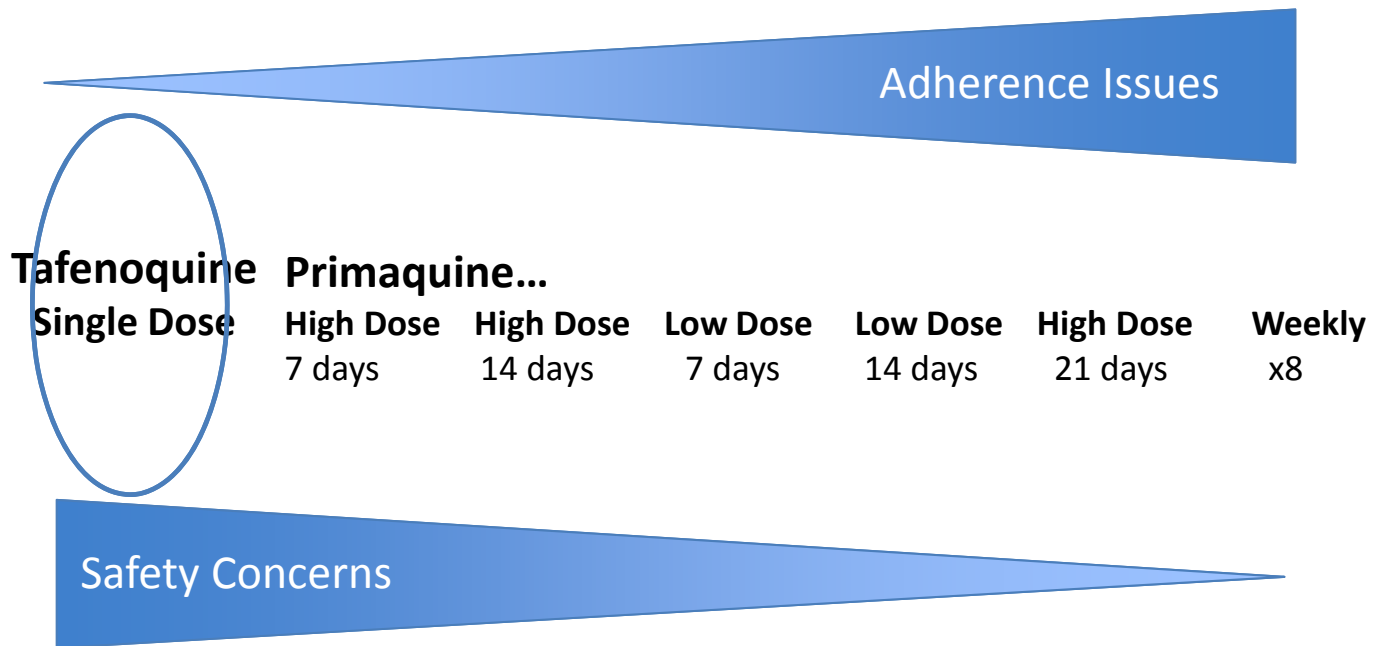
Time Point	Outcome measure	Control	PQ7	PQ14
		N=464	N=935	N=937
1 hour	Vomiting	11 (2.4%)	21 (2.2%)	20 (2.1%)
42 days	SAE PQ related	0 (0.0%)	9 (1.0%)	1 (0.1%)
	AE All severities	1 (0.2%)	13 (1.4%)	2 (0.2%)

High Dose PQ

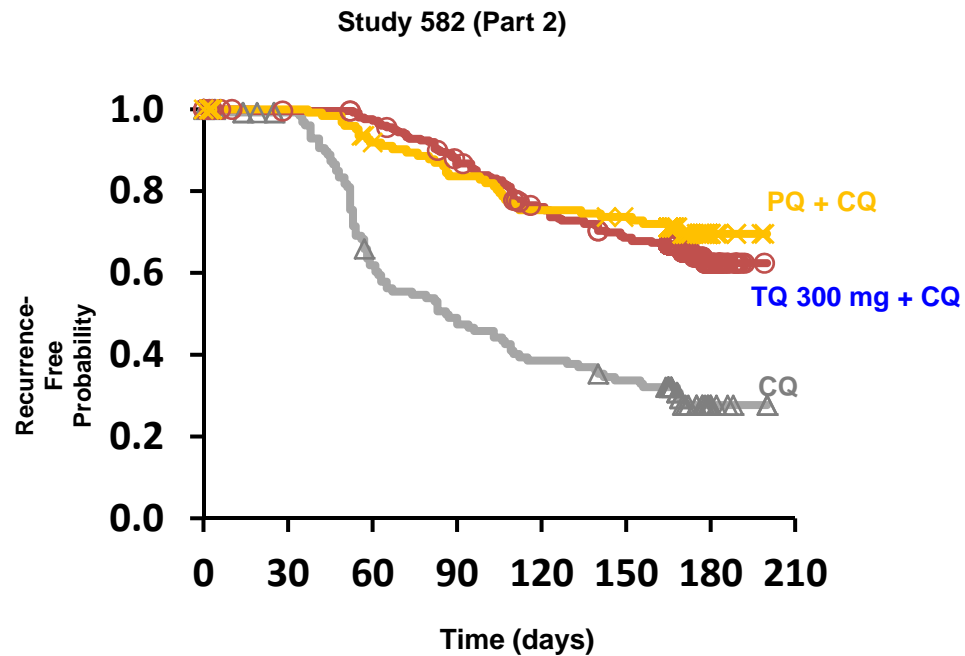
High dose primaquine is associated with higher mean Hb



The Long And The Short Of It....



Single Dose Radical Cure - Tafenoquine



- Trialled against low dose Pq
- Plus Chloroquine
 - Pts >16 yrs
 - G6PD >70%

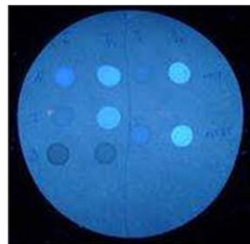
FDA Approval in USA – July 2018
TGA approval in Australia – August 2018



Innovation:

Point of Care G6PD Diagnostics

Qualitative G6PD testing

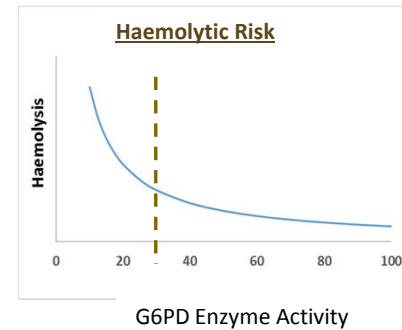


- Standard test
- Waterbath
- UV-light
- Refrigerator
- Long time to result
- Difficult to read
- Short shelf life
- Approx. 50c to \$11 per test



- Result in 20 minutes
- Same performance as FST
- Approx. 1.5 US Dollar / test

30% G6PD activity



Quantitative G6PD testing

Spectrophotometry

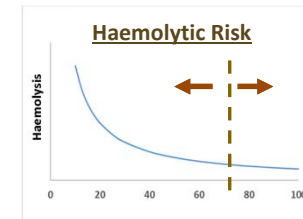


- Reference method
- Lab infrastructure
- Complicated
- Very expensive
- Long time to result

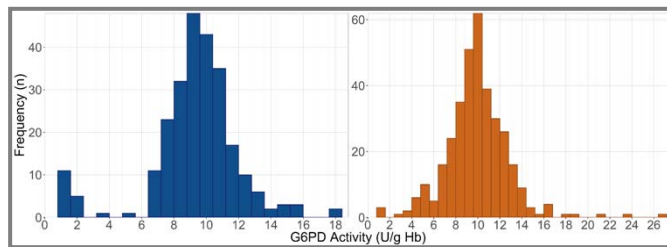
Biosensors



- Handheld
- Temp dependent
- Result in few minutes
- Result in IU/dL or U/gHb
- Machine approx. 200-700 USD
- Strips approx. 1.5-2.5 USD



G6PD Enzyme Activity



U/gHb → % Activity

Alam et al PLoS One 2018



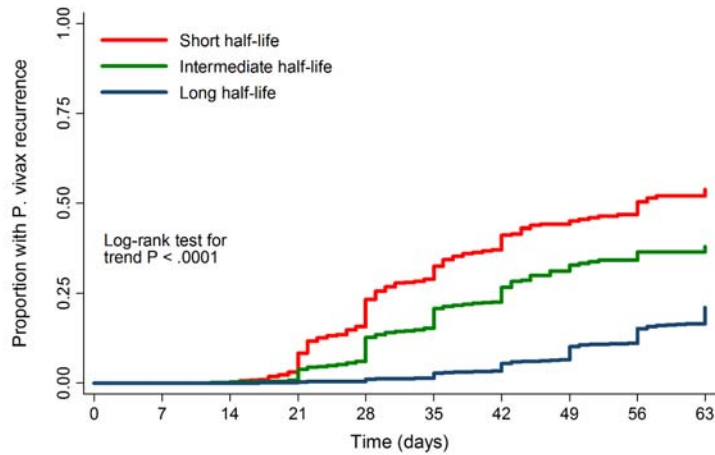
Innovation:

Broadening the indication

High Risk of Pv after Pf

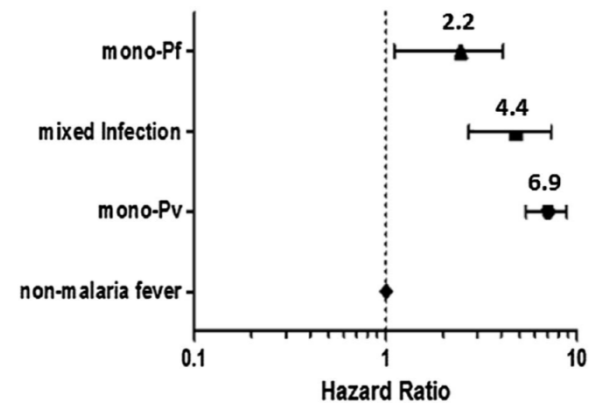
Thailand

43% risk of Pv recurrence in patients with Pf treated with AL



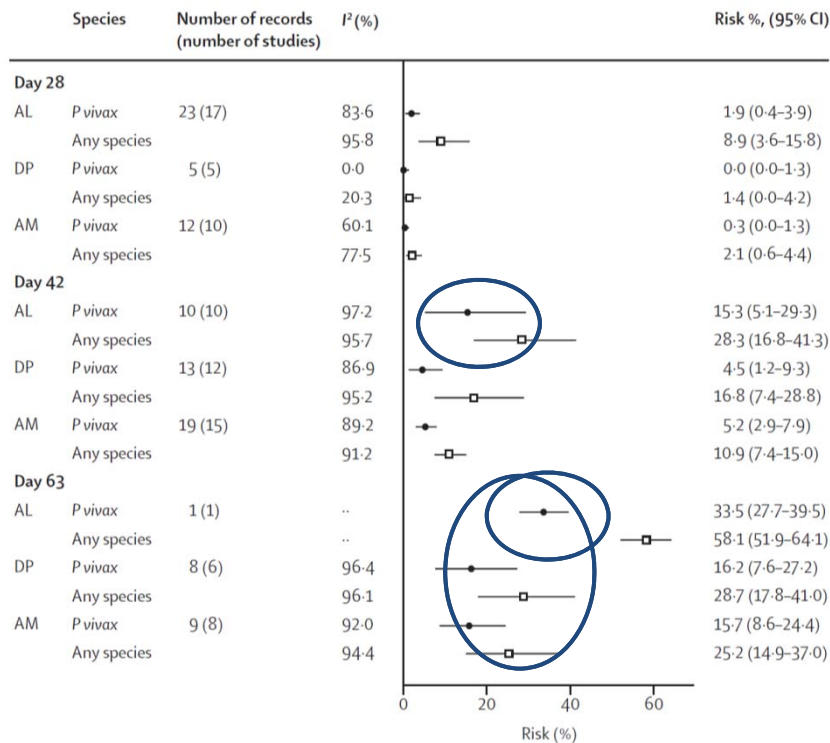
Douglas et al CID 2011

Brazil



Vito-Silva et al MalJ 2016

Risk of Pv after Pf



After ACT...

The greatest risk of
recurrent parasitaemia
and transmission is from
P. vivax not *P. falciparum*

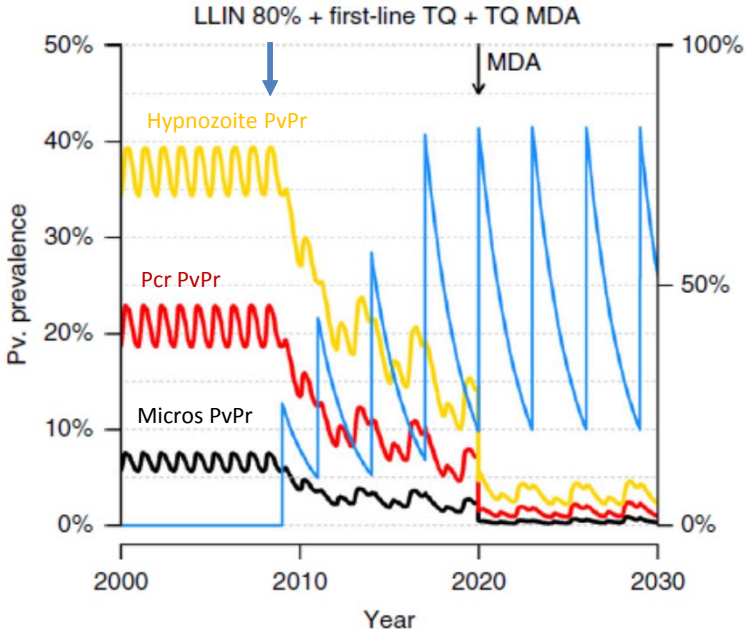
153 studies, 31,262 patients, 323 site-specific

Commons et al Lancet ID, In Press

Impact

Mass Drug Administration

Papua
New
Guinea



White et al Nature Communications 2018

Cost Effectiveness

G6PD Screening and Primaquine

Thailand

Costs: Treatment, Diagnosis, Recurrence, Pq Adverse events

Cq alone

vs



Cq/Pq
G6PD Screening

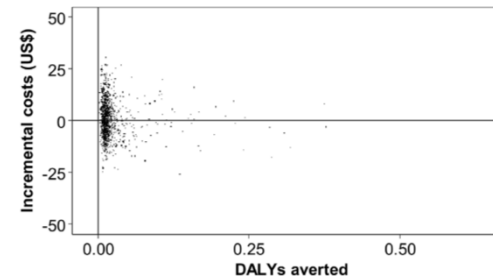
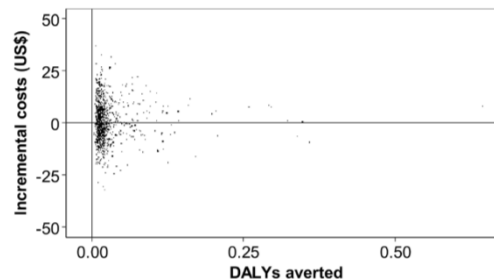
vs



Cq/Pq
No G6PD Screening

Similar Costs
+ Averting DALYs

Screening: modest cost saving
+ Averting DALYs



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

Devine et al PLoS NTD 2017

Translation



- **Radical Cure**
 - is crucial for timely control and elimination
 - has potential to save lives
 - can be cost effective
- **We have the tools to hand**
 - G6PD diagnostics
 - Short course Pq / Tfq
- **So what is the problem ?**

INNOVATE but prioritise the Basics

- Passive → Active case detection
- Prevention

TRANSLATION: Evidence and Action, ? Consensus

IMPACT: Accountable - to patients, funders, the public

IMPROV



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