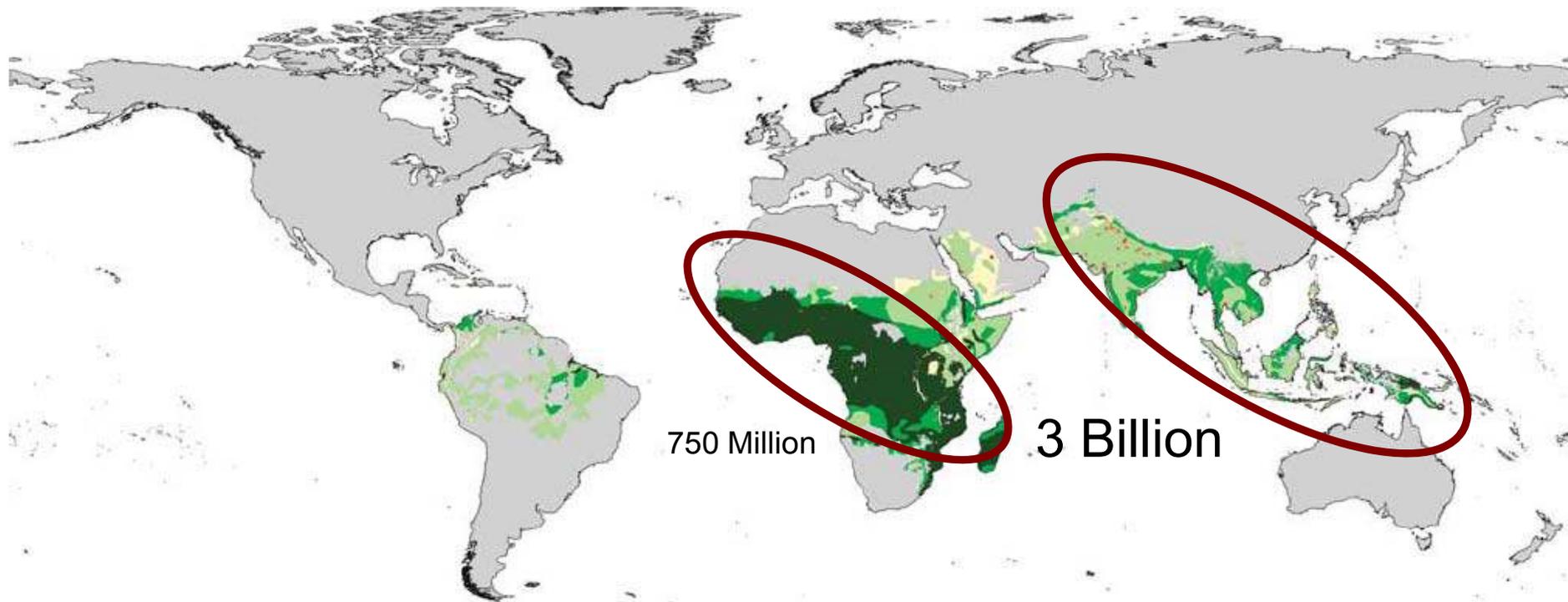


P. vivax – *P. falciparum* coinfection and antimalarial drug resistance

Ric Price

Outline

- Global Burden
- Comparative biology of Pv and Pf
- Coinfections: **Pv effect on Pf**
- Relapses and the role post treatment prophylaxis
- **Pf effects on Pv**
- Implications for resistance
- Infer implications for ACT impact



750 Million

3 Billion

Figure 2 *P. falciparum* endemicity distribution within the global limits of risk. Endemicity classes: light green, hypoendemic (areas in which childhood infection prevalence is less than 10%); medium green, mesoendemic (areas with infection prevalence between 11% and 50%); dark green, hyperendemic and holoendemic (areas with an infection prevalence of 50% or more)¹³. Unclassified areas (yellow) represent only 6% of the global

population at risk and are due to discrepancies between the 2002 delineation of risk and the endemicity risk limits developed in refs 6 and 7. Grey areas are a combined mask of areas outside of the transmission limits and areas of population density less than 1 person km⁻² (ref. 16).

Snow et al Nature 2005 & Hay et al Lancet ID 2004

515 (range 300-660) million episodes of clinical *P.falciparum* malaria

45% of all malaria is in SEARO (India / Indonesia) – ~ 50% due to *P. vivax*

Price et al AJTMH 2007

132 - 391 million clinical cases of *P. vivax* per year

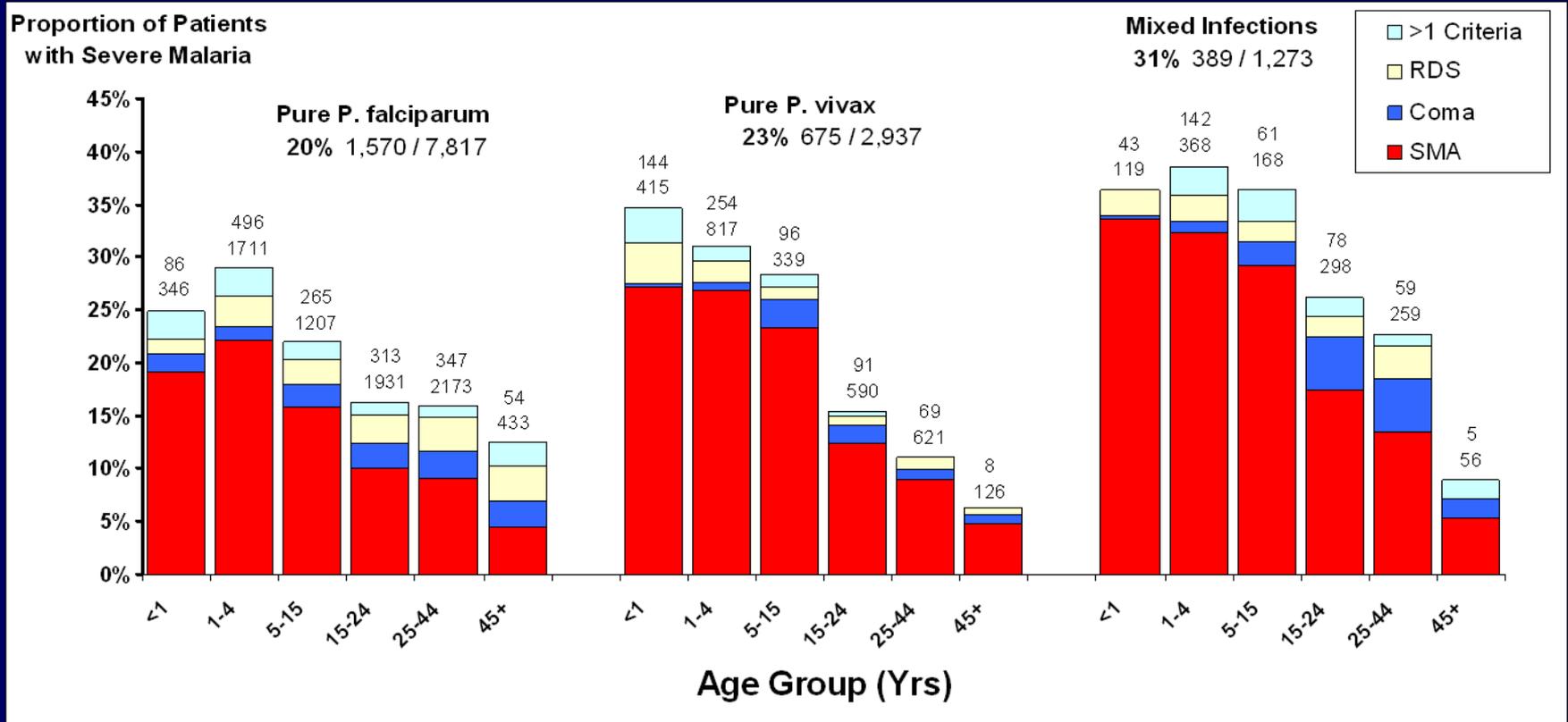
US\$ 1.4 - 4.0 billion per year

Falciparum vs Vivax

- Biology
 - Cytoadherence / Sequestration
 - Erythrocyte invasion: Duffy, young RBC, continuous culture
 - Hypnozoite “dormant” stages - Relapses
- Different epidemiology
 - Spatial limits
 - Predominance in infancy
 - Rapid acquisition of immunity
 - *Michon et al AmJTMH 76: 997-1008, 2007*
- Both cause severe and fatal disease

Vivax is Not Benign

Hospitalised Malaria in Papua, Indonesia 2004-2007



26% of malarial admissions have pure *P. vivax*

Mortality: PF 2.2%

PV 1.6%

Mix 2.2%

Falciparum vs Vivax

- Biology
- Different epidemiology
- Both cause severe and fatal disease
- Pv more toxic than Pf
 - Pyrogenic Density: Pf: 1500 μ l⁻¹ Pv: 386 μ l⁻¹
 - Hyperparasitaemia rare with Pv
- Different Transmission Dynamics

PF Gametocyte carriage

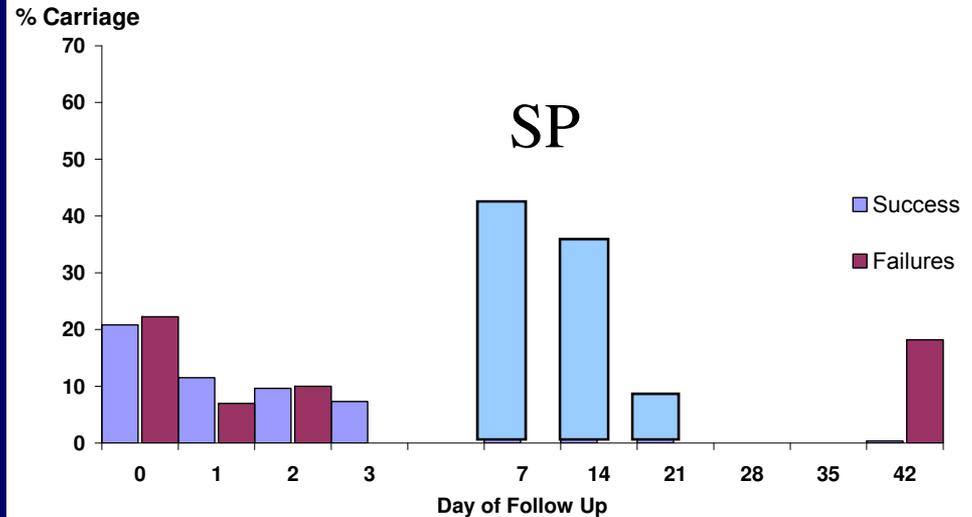
- Resistant to schizontocides
- ACT impact greatest in preventing gams in those without gams on adm
- 4-8x increase in Gam carriage if treatment failures

PV Gametocyte carriage

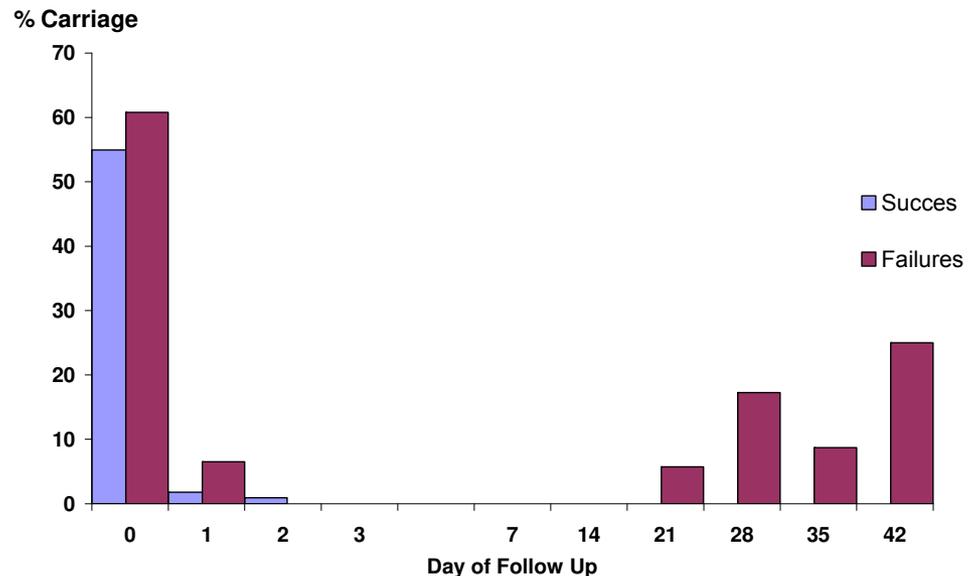
- Gams associated with asexual parasitaemia
- High prevalence on Adm
- Sensitive to schizontocides
- Late Gams mainly from relapses

Ratcliff et al Lancet: 369, 369: 757-65, 2007

PF Gametocyte Carriage Following Treatment of Pure PF



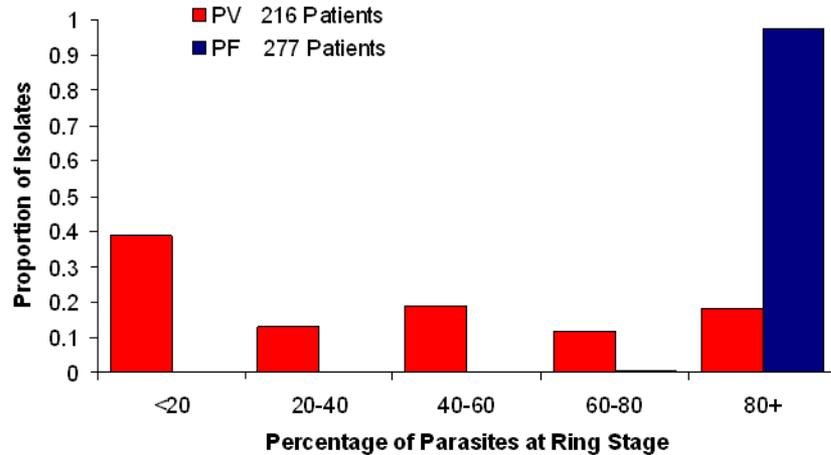
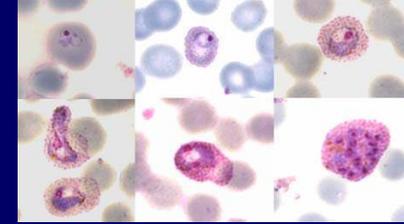
PV Gametocyte Carriage Following Treatment of Pure Pv



Falciparum vs Vivax

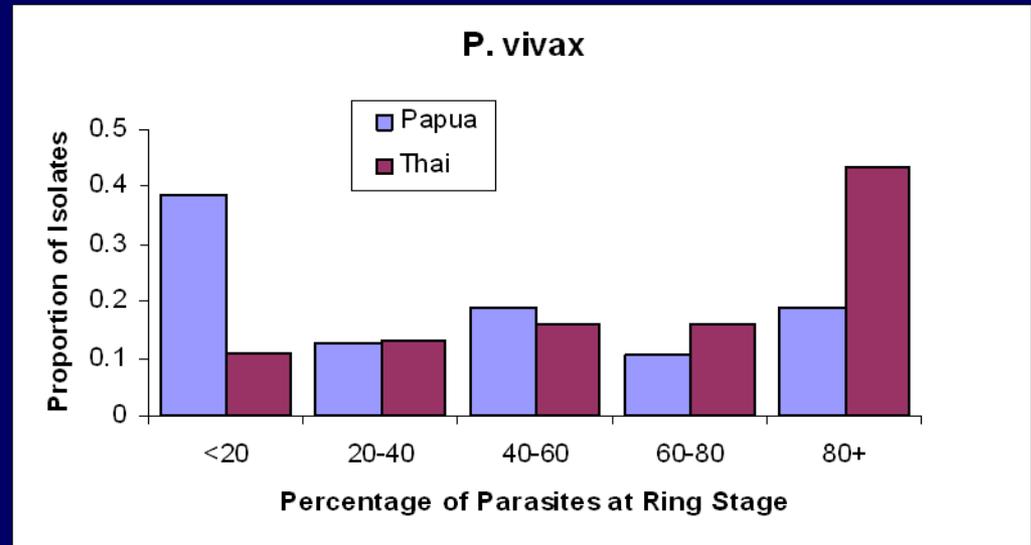
- Biology
- Different epidemiology
- Both cause severe and fatal disease
- Pv more toxic than Pf
- Different Transmission Potential
- All stages in periperipheral blood

Initial Stage of Parasite



Relevance for:

- In vitro susceptibility
- ? Clinical efficacy



Pf and Pv Coinfections

- Outside of Africa Pf invariably coexists with Pv
- Mixed Infections are common but often missed
 - Poor differentiation at early stages
 - Microscopists stop at first parasite
 - Thick and Thin
 - Clinical / Presumptive diagnosis 80-90%
- *Mayxay et al TIP 2004:*
 - Mixed infections rarely reported (<2%)
 - In clinical studies 10 - 30%
 - 20 - 50% rates with PCR methods
 - ? >50% with occult hypnozoite infection

Coinfections in Clinical Trials

Compared to Pure Pf, Mixed Infections...

- **Severe malaria: 4.2x lower risk**
Luxemburger et al TRSTMH 91: 256-262, 1997
- **Treatment Failure: 1.8x lower risk**
Price et al TRSTMH 91: 574-577, 1997
- **Gametocyte Carriage: 3.5x lower risk**
Price et al AmJTMH 60: 1019-1023, 1999
- **Anaemia: 1.8x lower risk of anaemia**
1.3x faster recovery
Price et al AmJTMH 65: 614-622, 2001
- **Reciprocal Seasonality**
Maitland TransRSTMH 90: 614-629, 1996

Why ?

Reduced Biomass

Dyserythropoiesis

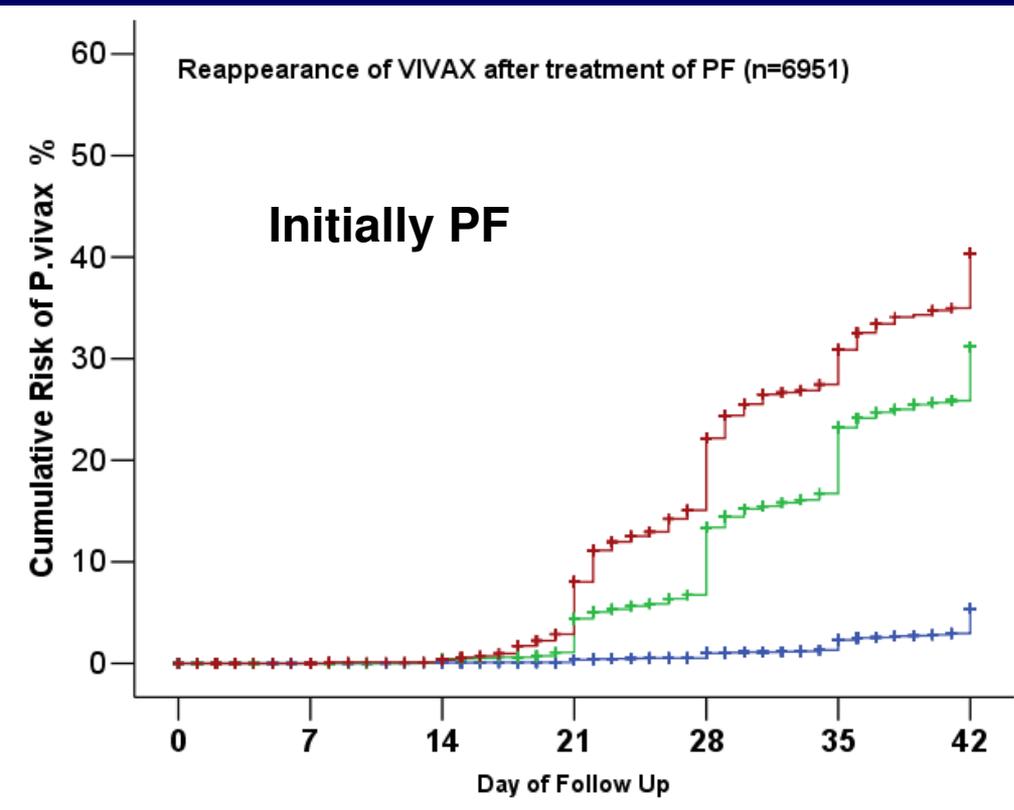
Earlier Presentation

Cross sp immunity

Vivax Relapses

- Frequent
 - 30-80% within 2 months
- Time of relapse is strain dependent: *21 days to months*
- Confound clinical efficacy trials
 - Poor differentiation: Recrudescence, Reinfection and Relapse
 - *Chen et al JID 195, p934-41, 2007*
 - *Imwong et al JID 195, p927-33, 2007*
- Frustrate control programmes
- No “reasonable” terminal prophylaxis

P. Vivax Recurrences



Artes / Quinine 40% [36-45]

Hal / AL 31% [28-34]

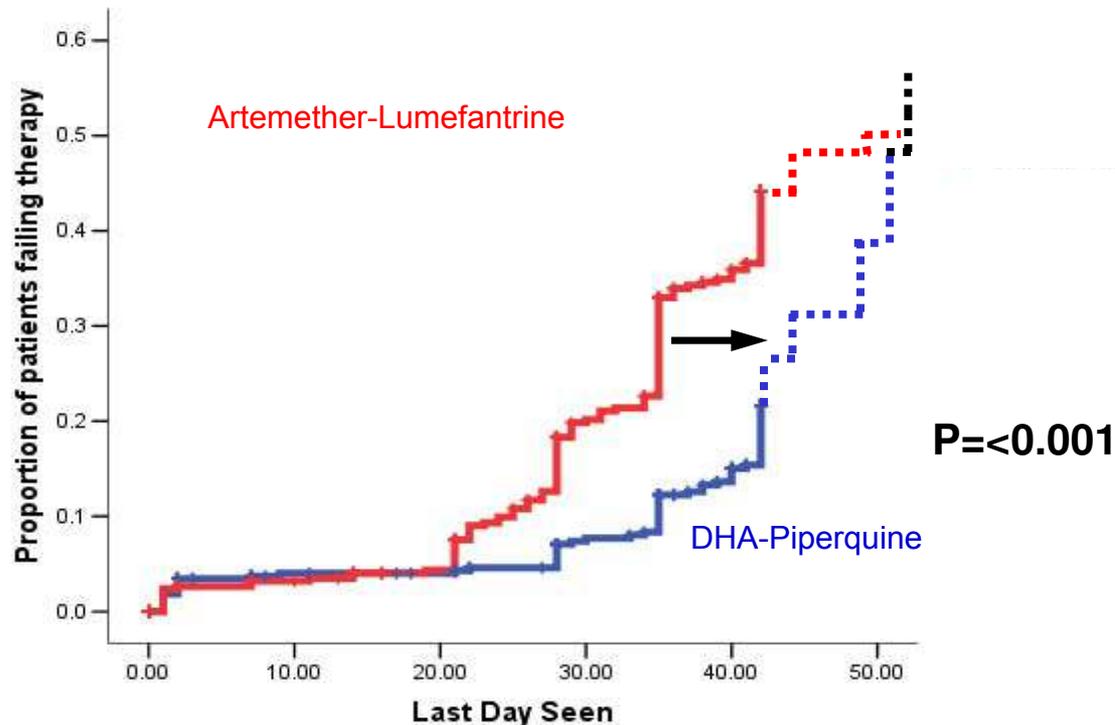
Mfq / Mfq+Art 5.4% [4.4-6.4]

$P < 0.001$



Post Treatment Prophylaxis of ACT against multidrug resistant Pf and Pv Papua, Indonesia

Recurrence of any parasitaemia



DHP:

Fewer Gametocytes

Rate Ratio 6.6 [2.8-16]

Less Anaemia

RR 2.0 [1.2-3.6]

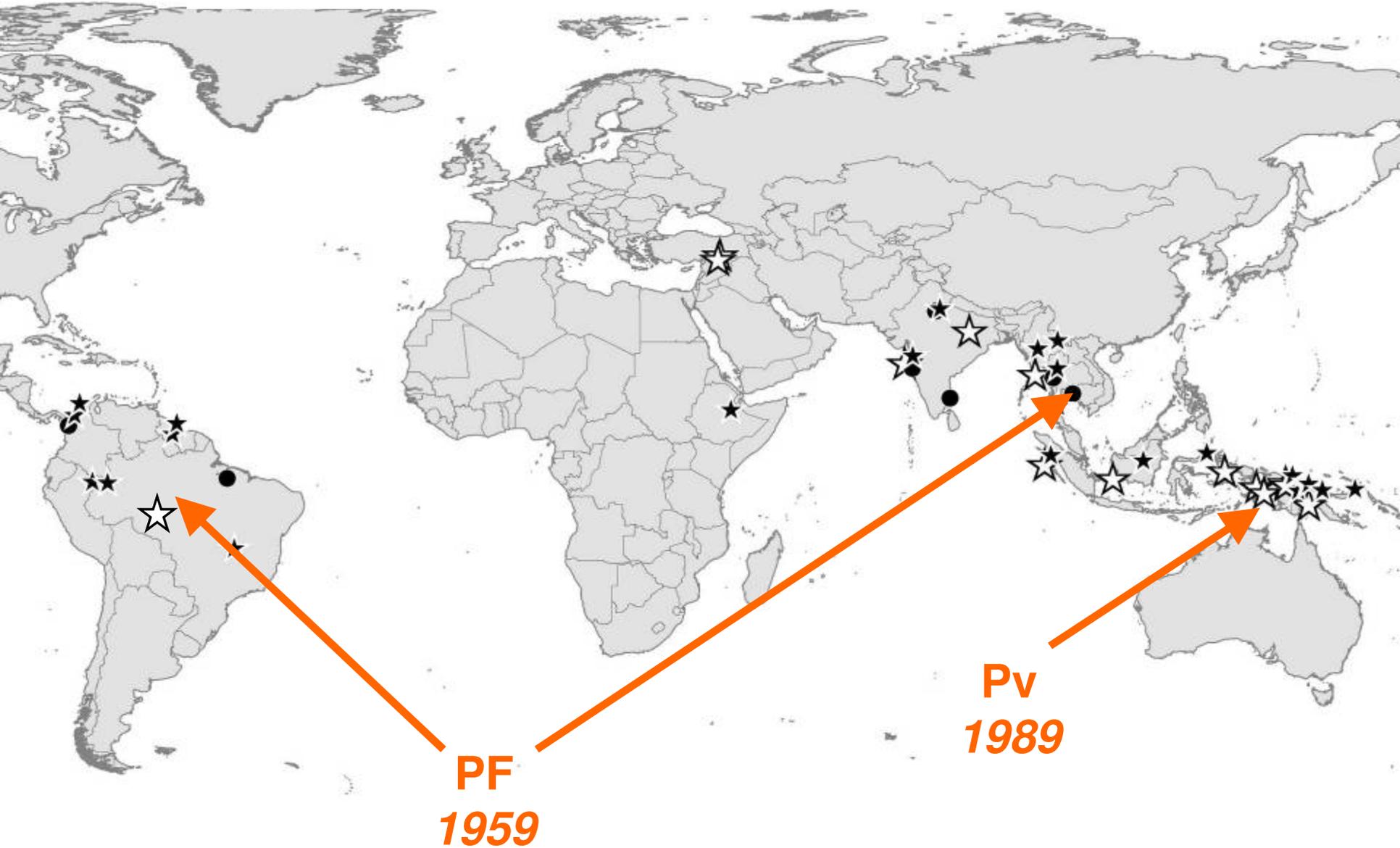
Less visits to clinic

Happier Patient

*Effect on drug
resistant P. vivax...*

Emerging Chloroquine Resistant *P. vivax*

N=72 Articles



PF
1959

Pv
1989

Speed of CQR

Pf vs Pv

30 year gap in the emergence of CQR...

- Difficult diagnosis
- Early resistance overlooked
- Global annual biomass 20 fold lower
 - 5×10^{18} for PF vs 2×10^{17} for Pv
- Transmission dynamics
- Resistance mechanism
- Differential drug policy
- ...

Molecular Markers of Antimalarial Drug Resistance

Pf Molecular Markers

Pfcrt

PfDHFR

PfDPHS

Pfmdr1 SNP

CN

PfOther

Cq

Pyr

Sulf

Cq, Aq

Mfq, Lum, Hal, As

??

Pv Molecular Markers

Pvcrt

PvDHFR

PvDPHS

Pvmdr1 SNP

CN

PvOther

Chloroquine Resistance



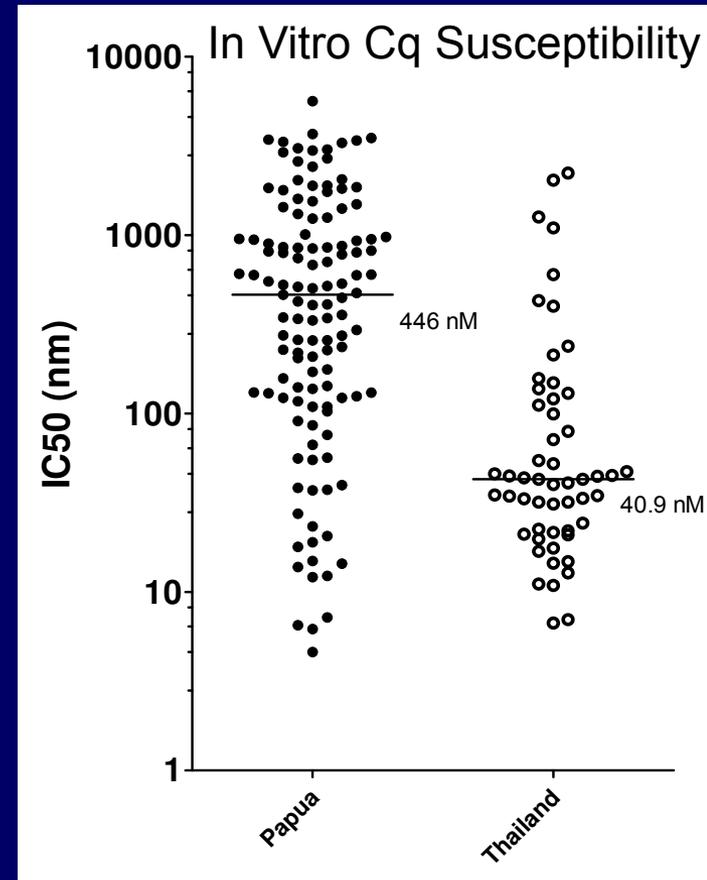
Papua CQR:

Ratcliff et al TRSTMH: 101, 351-359, 2007

- Day 28 risk of failure
65% [95% CI 49-81]
- Early Treatment Failure
16% (6/37)

Thailand CQS:

Luxemburger et al TRSTMH: 256-62, 1997



Chloroquine IC50 and *Pvmdr1* Y976F

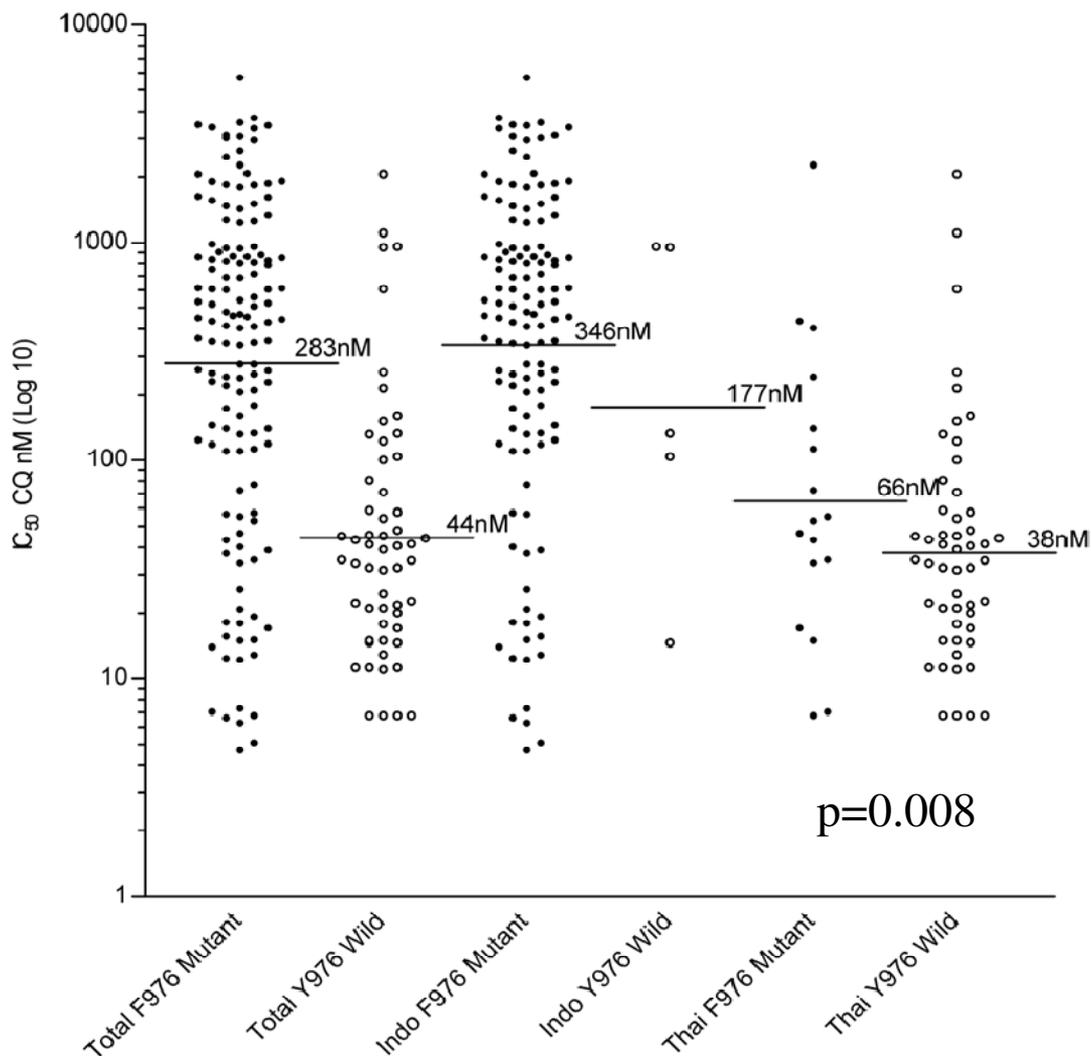
Pvmdr1 Y976F

Papua 96% (123/128)

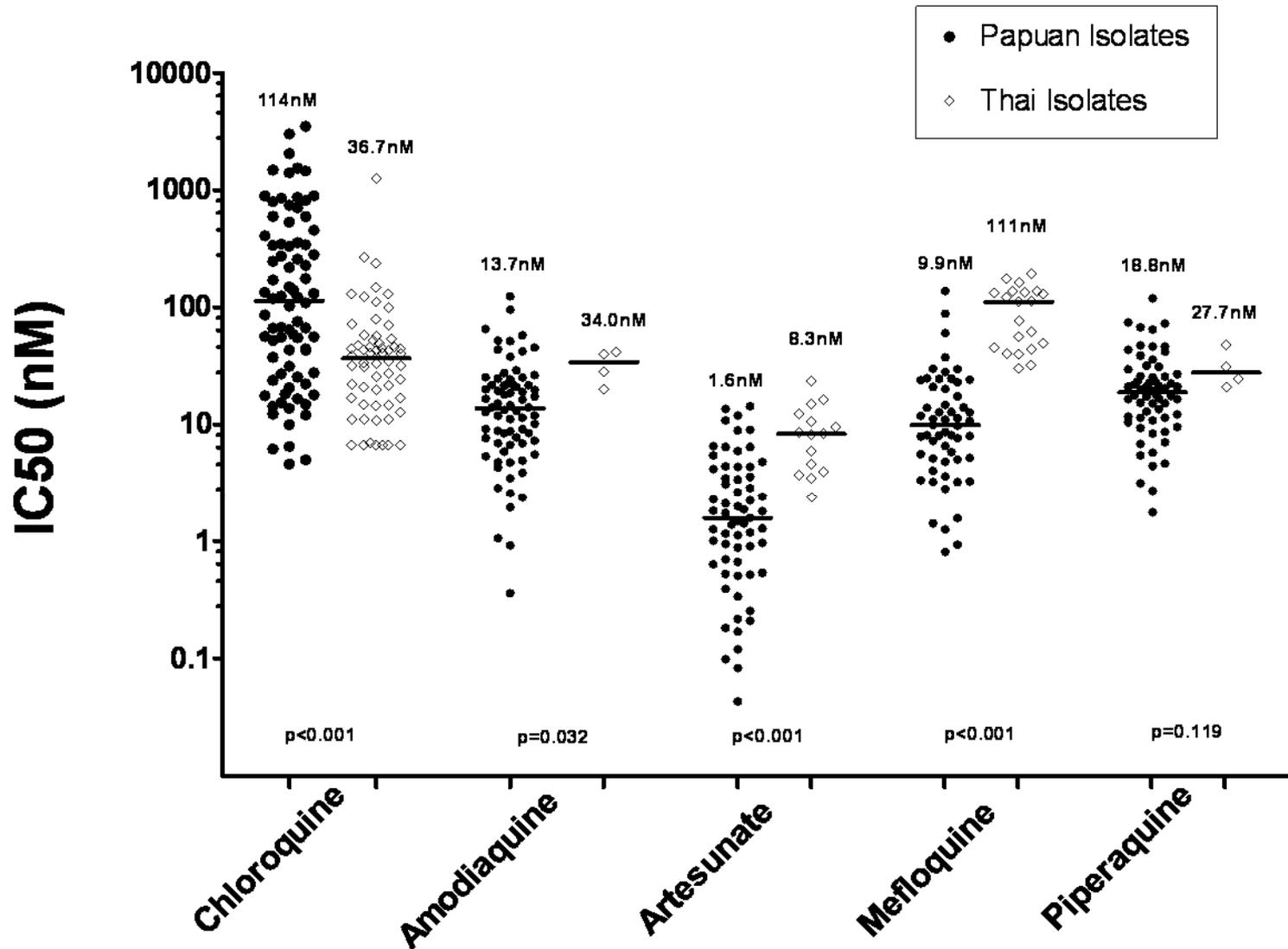
VS

Thai 25% (17/69)

$p < 0.001$



Papua vs Thailand



Pvmdr1 Amplification

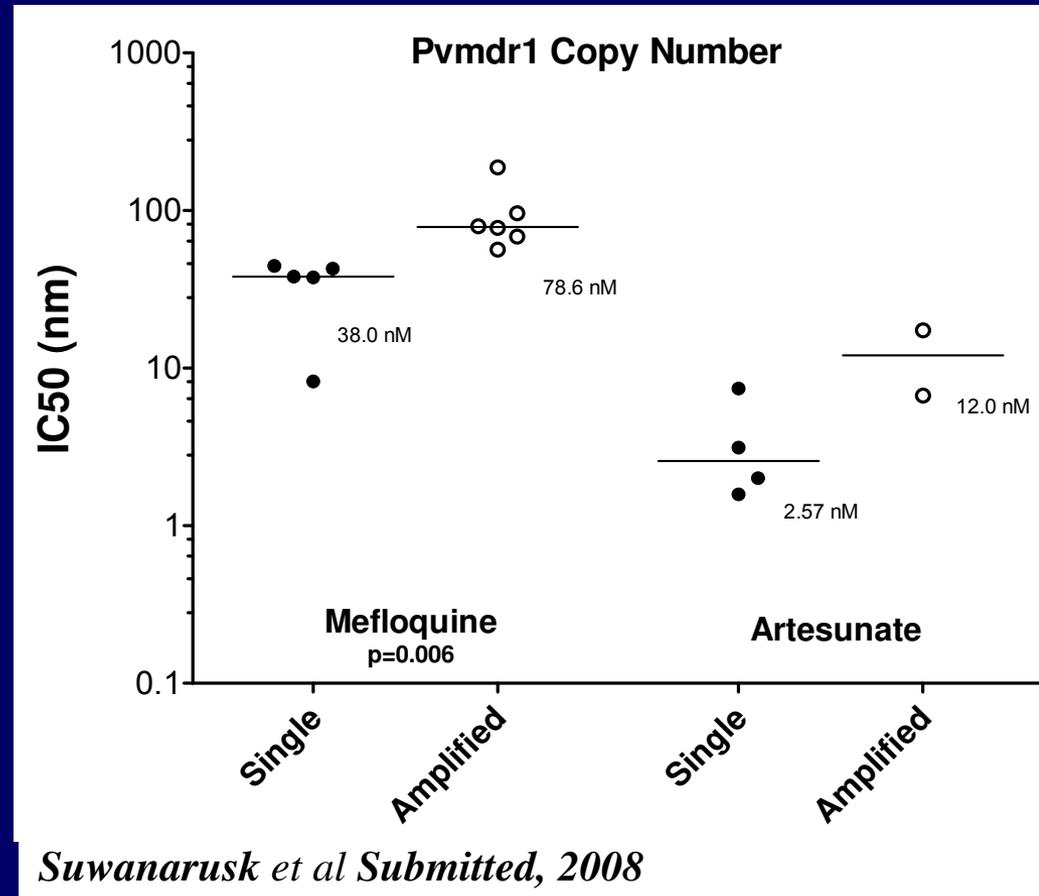
rtPCR Assay

Increased CN:

Thai: **21%** (15/71)

Papua: **0%** (0/114)

All amplifications Wild type 976Y



Cq for Pv

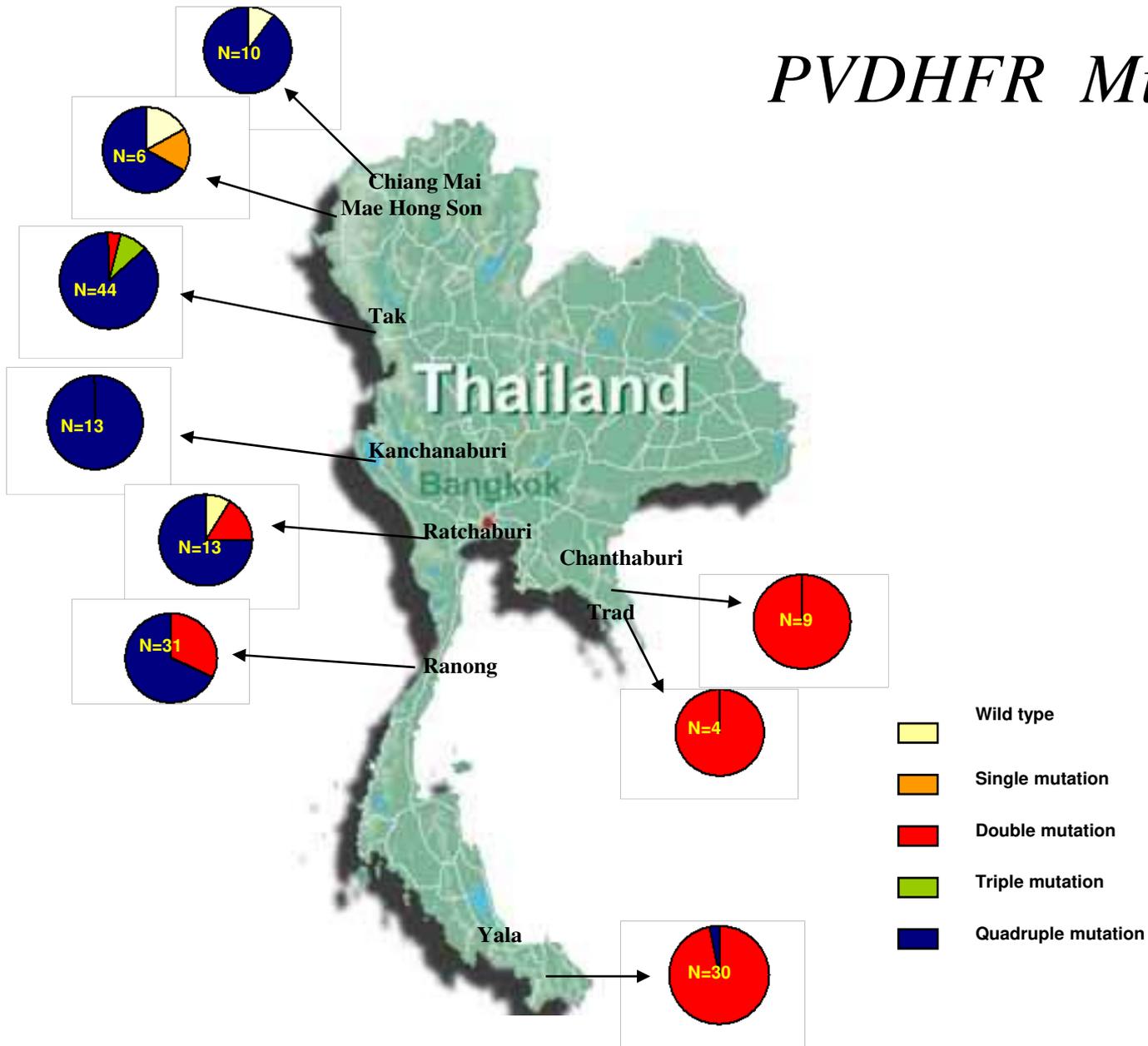
→ Pvmdr1 976F

Mfq (+As) for Pf

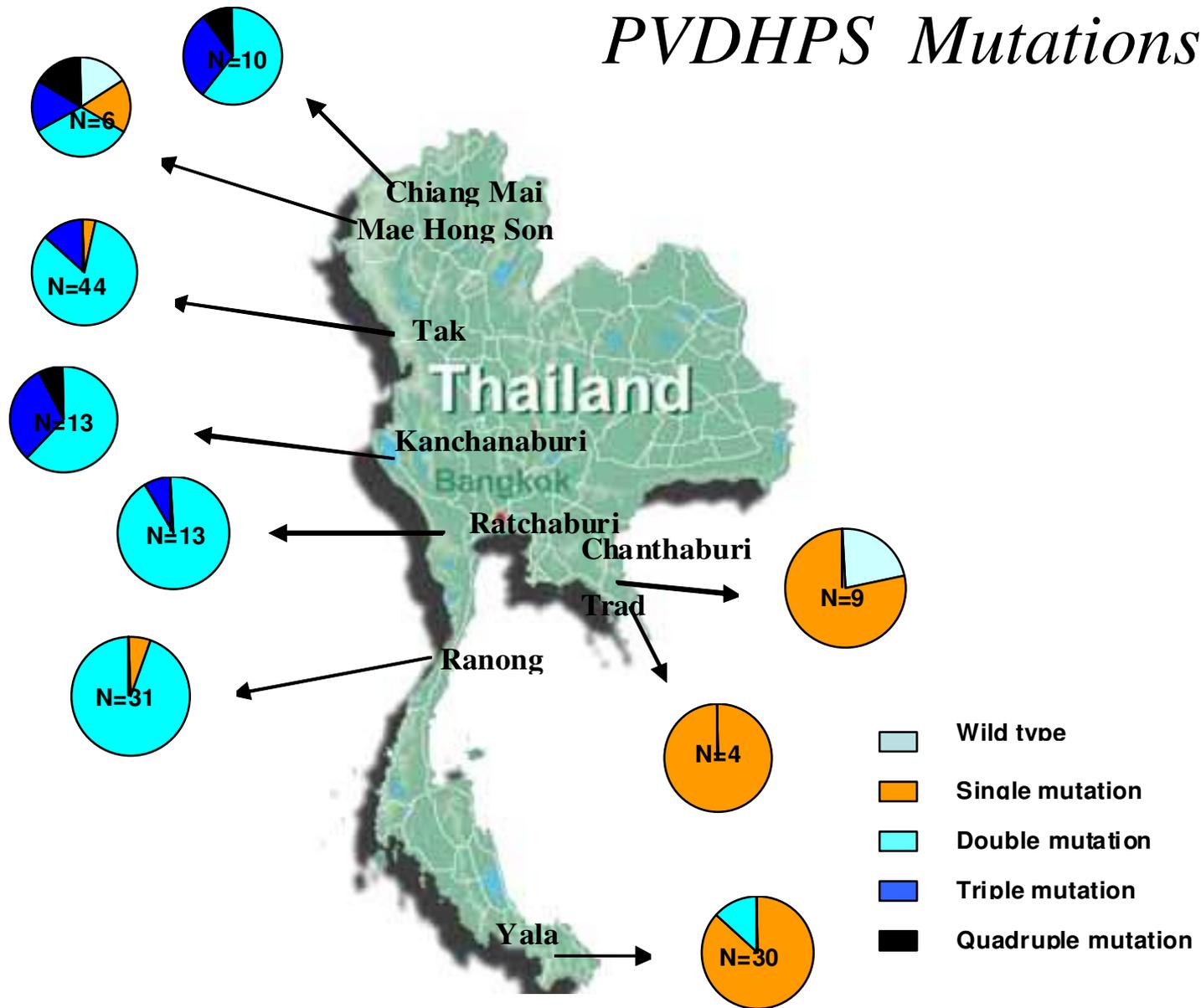
→ Pvmdr1 976Y CN

*Is Thai Pf policy
retarding CQRPv?*

PVDHFR Mutations



PVDHPS Mutations



Conclusions

- The morbidity and mortality of vivax is often ignored - NOT benign
- Vivax creates huge challenges for control programmes
- Similarities in resistance mechanisms – pvmdr1 SNPs and CN

- Coinfections are ubiquitous outside of Africa
- Pv → Pf - Implications for efficacy and transmission dynamics
- Pf → Pv - Policy driving cross species resistance

- Ongoing appreciation for the dynamic epidemiology and drug policy for both species

Outside of Africa, modeling the impact of ACT and emergence of resistance of Pf without incorporating Pv is of “limited utility”...



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Ferryanto Chalfein
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...

NIHRD

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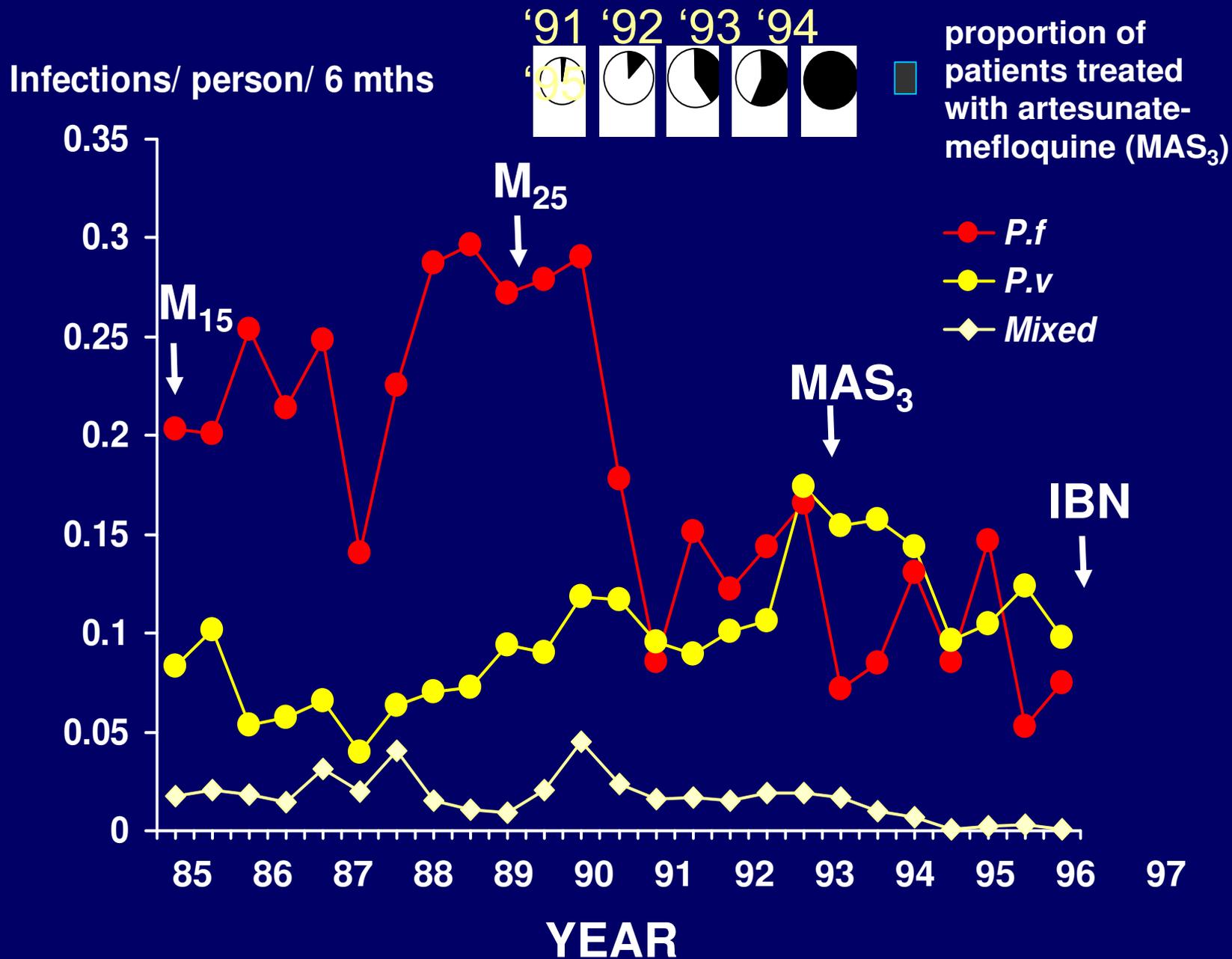
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The End

Global Burden of *P. vivax*

- Population at Risk:
 - Guerra et al *Trends Parasitol* 2005 **2,596** million
- Number of Infections with *P. vivax* each year:
 - Mendis et al *AJTMH* 2001 **71-80** million
 - Hay et al *Lancet ID* 2004 **132 - 391** million
- Economic burden:
 - Conservatively US\$ 1.4 - 4.0 billion per year



DHP in Timika, Papua Indonesia

Policy Change in March 2006...

Population of 160,000

95,820 patients treated

687,569 tablets distributed (free)

27Kg of DHA and 220kg of Pip

DHP in Timika, Papua Indonesia

