Update on antimalarial drug resistance in the GMS

JITMM
13 Dec 2018

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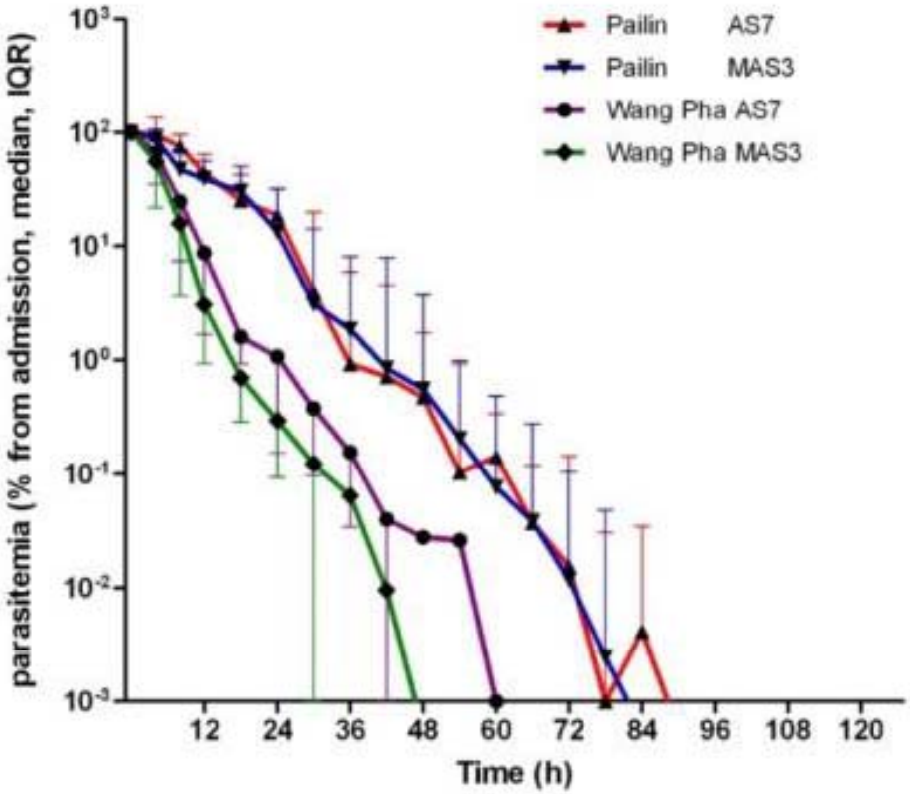
Bangkok, Thailand

Artemisinin resistance – slow clearance



Dondorp et al. N Engl J Med 2009

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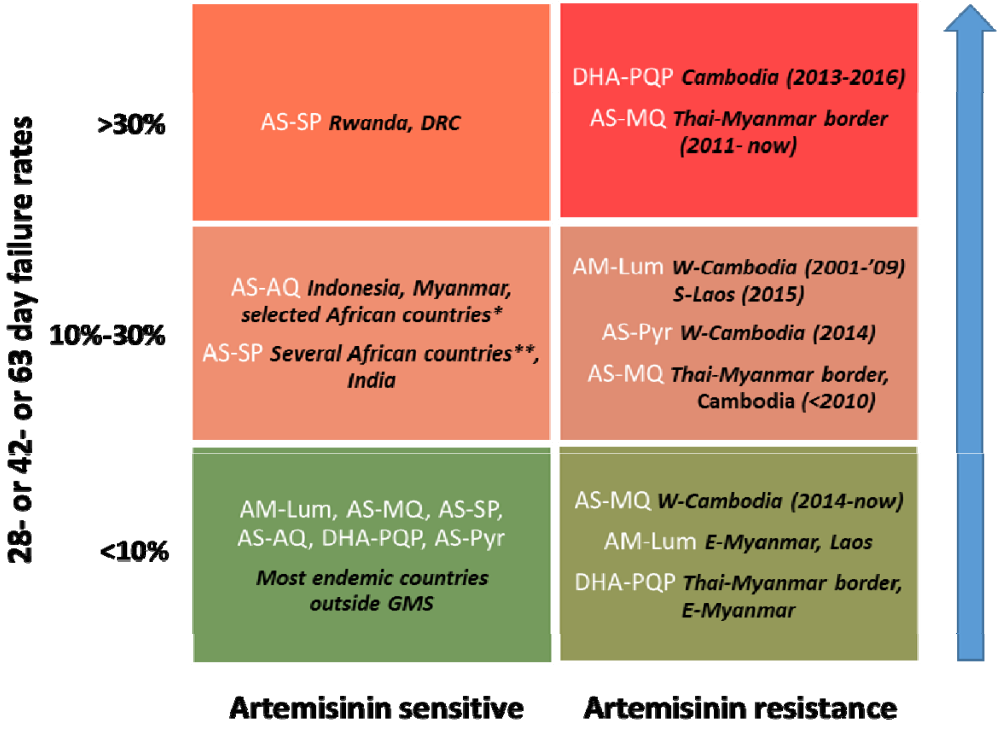
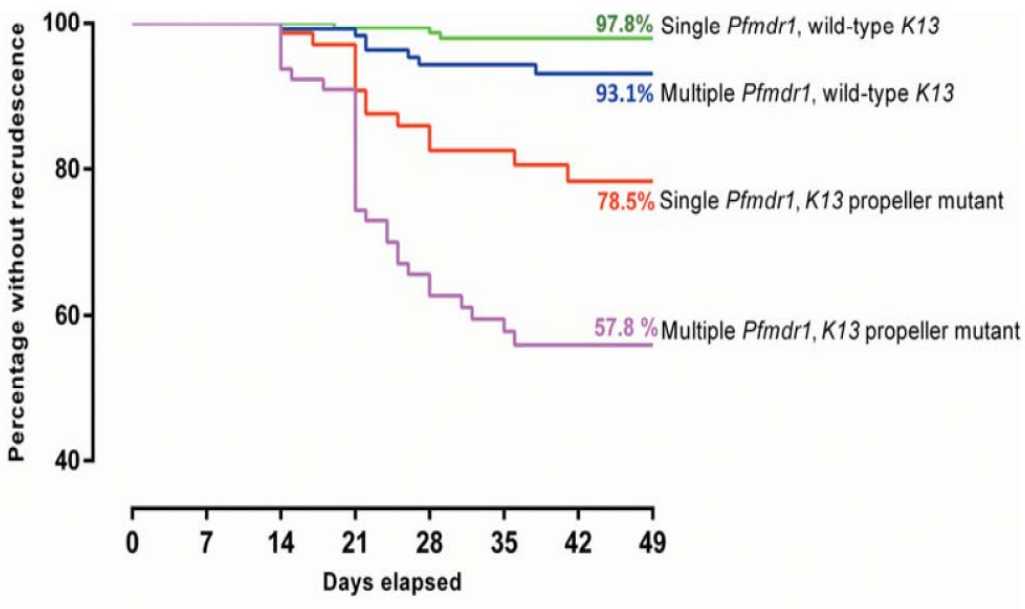
Artemisinin or partner drug resistance and ACT failure





AS-MQ efficacy
by PfKelch13 and PfMDR1 genotype

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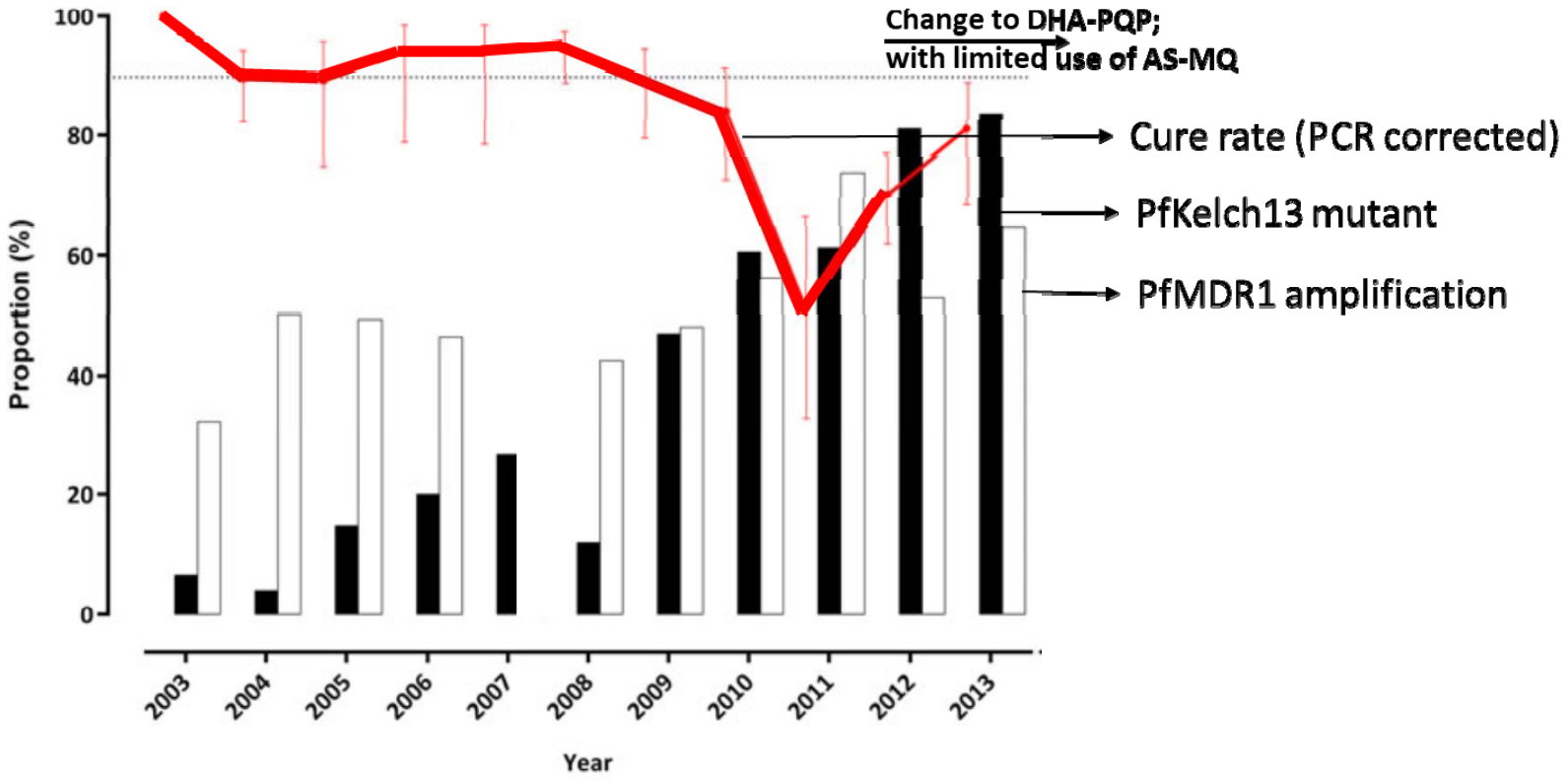
Aung Pyae Phyo et al. Clin Infect Dis 2016

Artemisinin resistance: facilitates partner drug resistance ->ACT failure

Thai-Myanmar border



Adapted from: Aung Pyae Phyo et al. Lancet 2012

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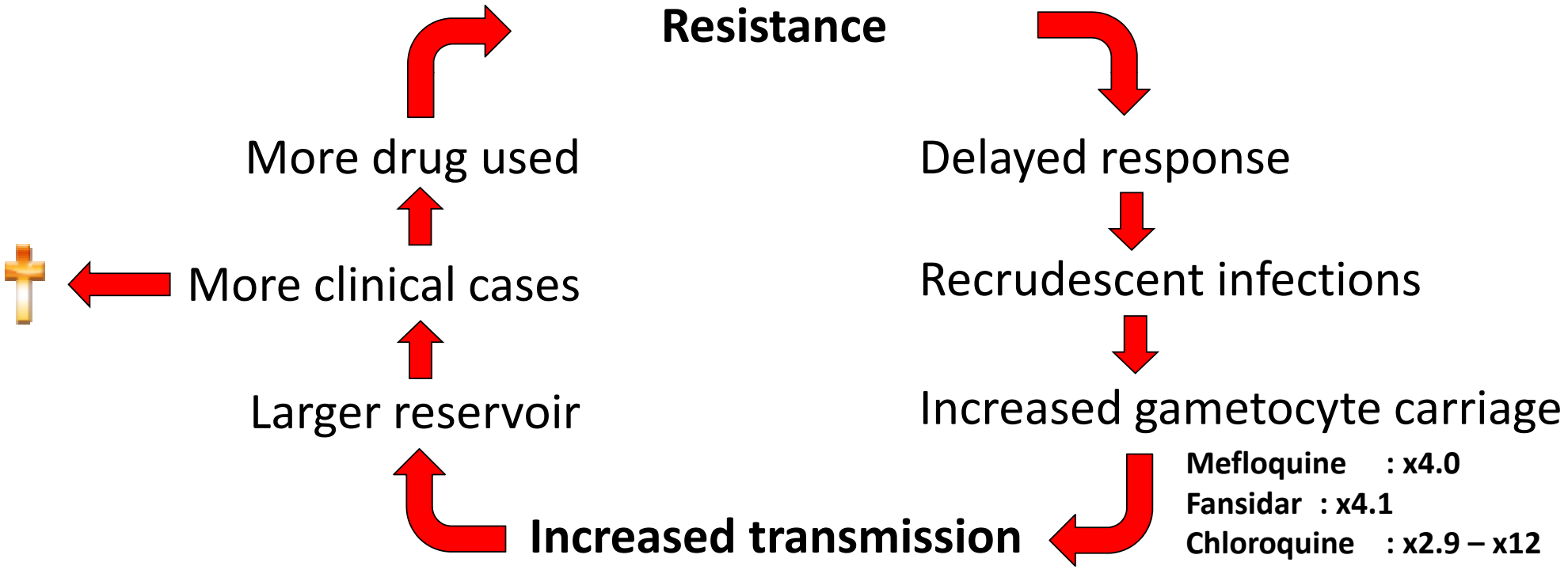
ACT failure ⇒ ↑ transmission of drug resistance

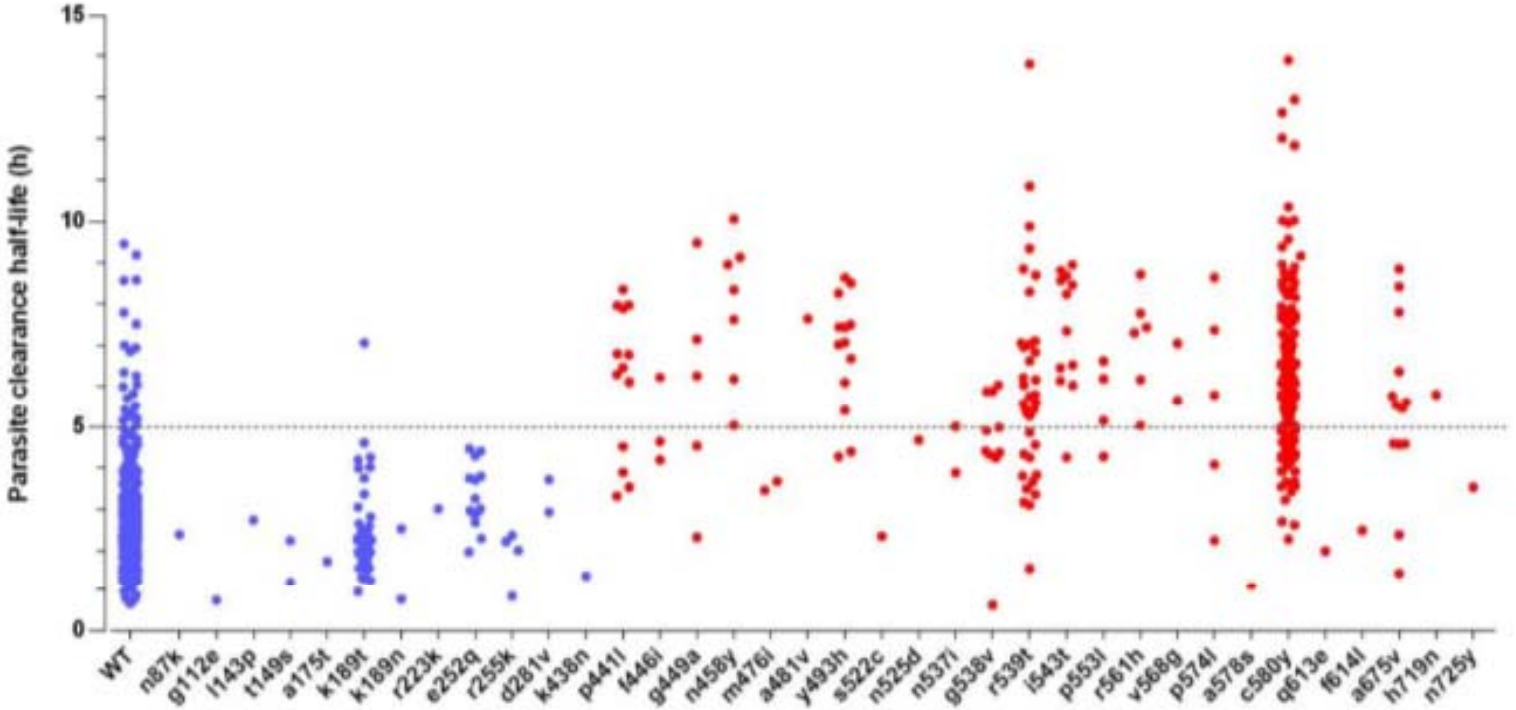


Drakely et al. 2004;
Barnes & White 2005

Price et al. 1996;
Bousema et al 2003

≥ 75 mutations in the propeller region of Kelch 13

Association with slow clearance not uniform



K13 mutation	Classification
E252Q	Not associated
P441L	Associated
F446I	Associated
G449A	Associated
N458Y	Associated
Y493H	Confirmed
R539T	Confirmed
I543T	Confirmed
P553L	Associated
R561H	Confirmed
V568G	Associated
P574L	Associated
A578S	Not associated
C580Y	Confirmed
A675V	Associated

WHO update on resistance 2016

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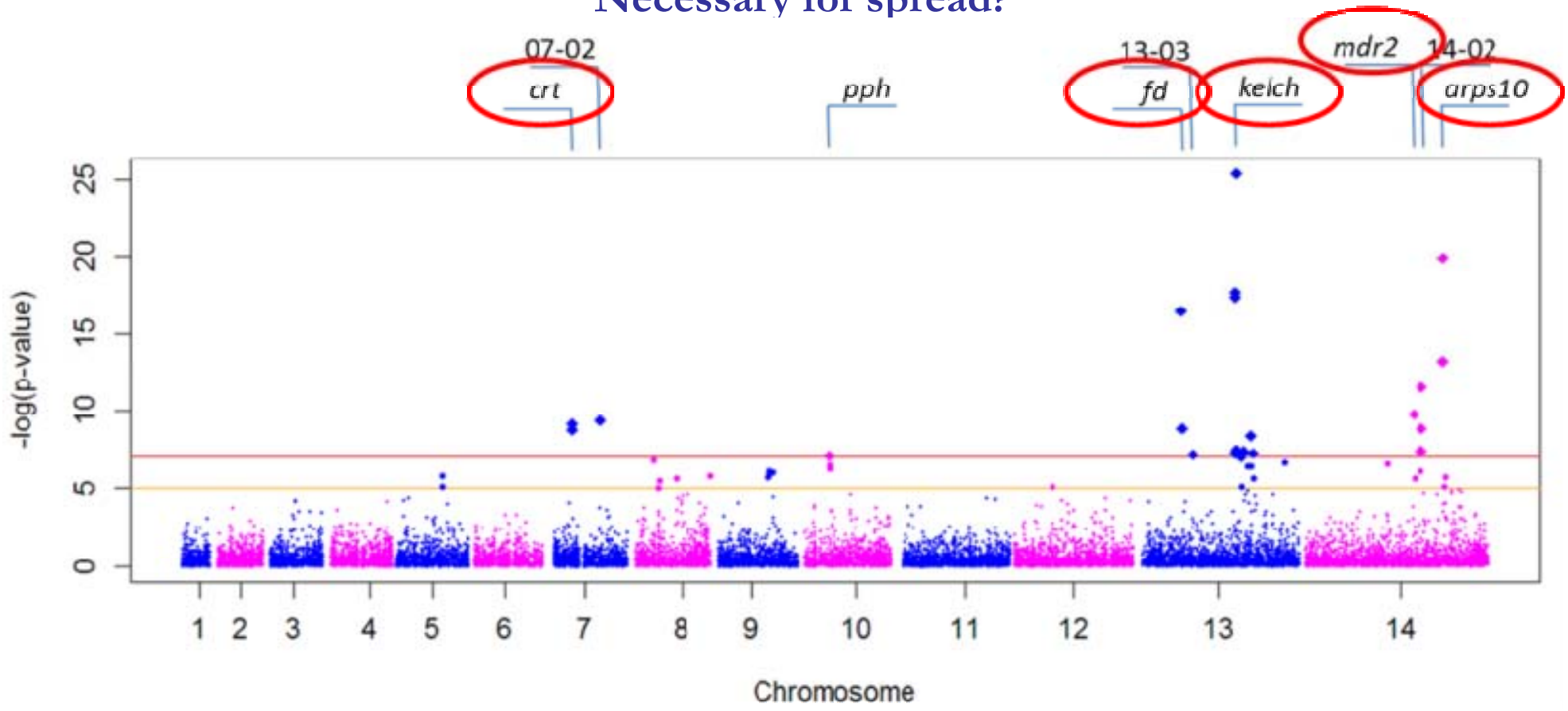
Ashley et al.
N Engl J Med 2014

Permissive or compensatory backbone mutations

Necessary for spread?



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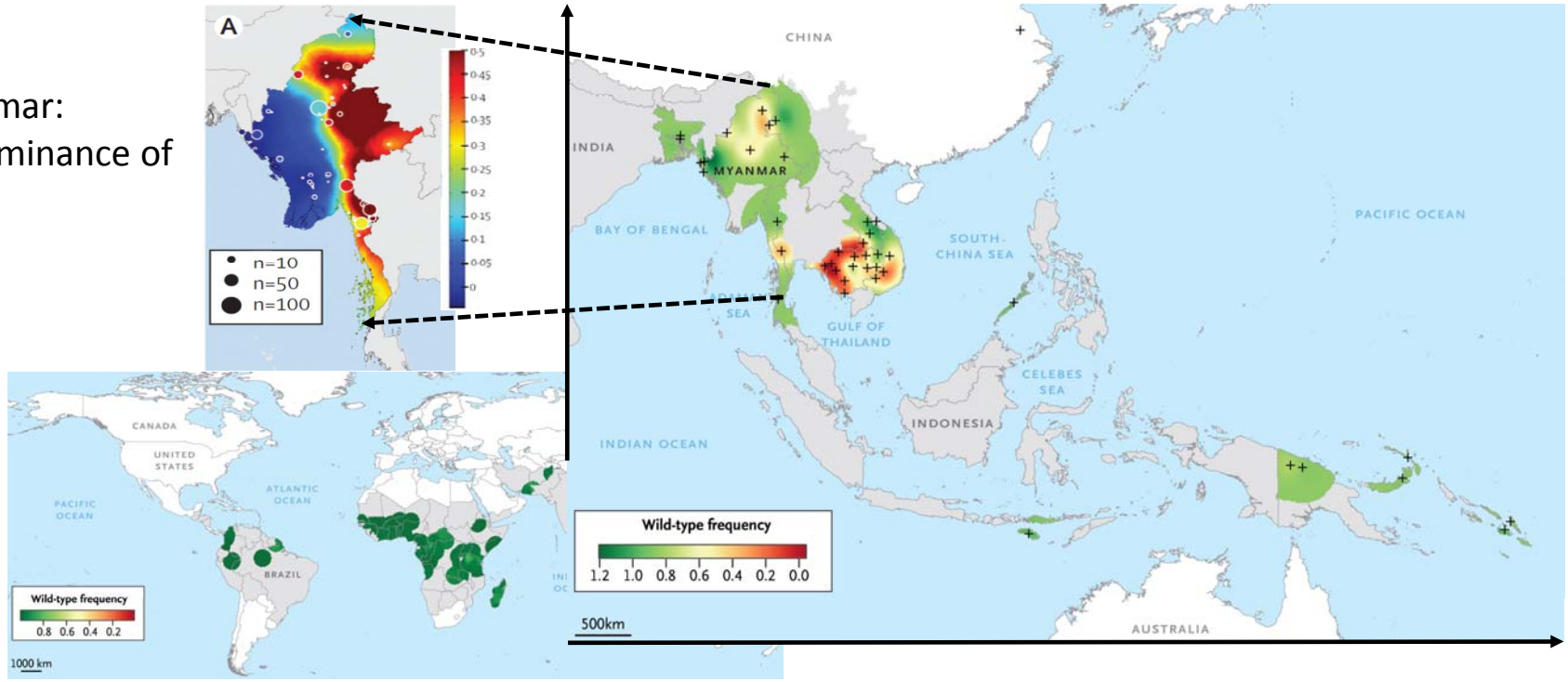
Miotto et al; Nature Gen 2015

Current GMS *PfKelch13* map

Myanmar: predominance of F446I



Menard et al. N Engl J Med 2016

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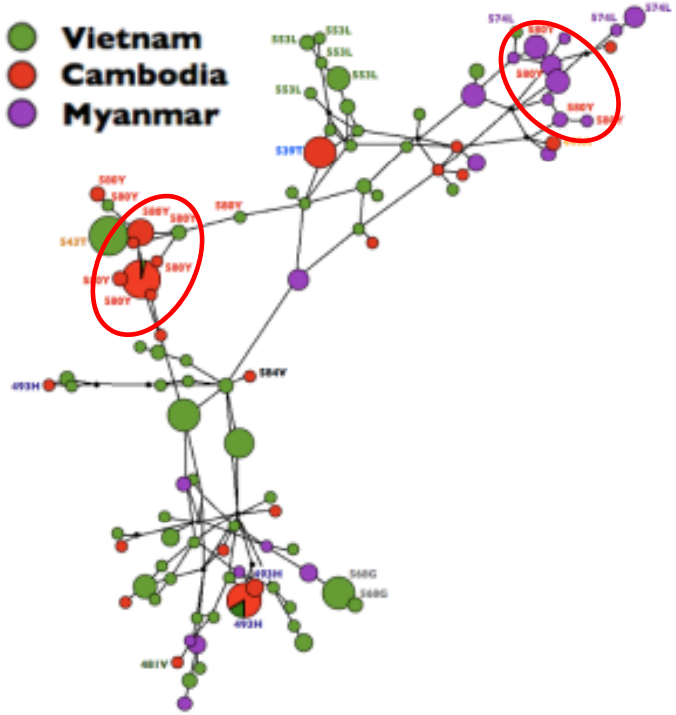
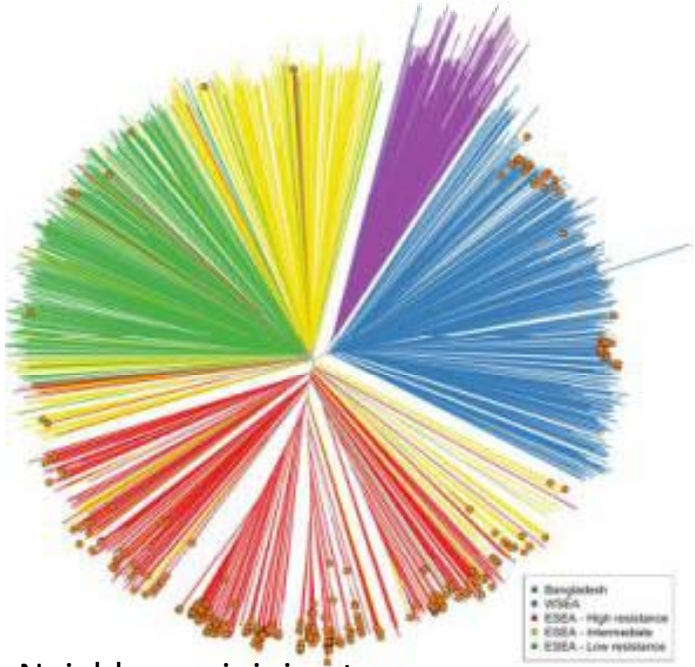
Tun et al. Lancet Infect Dis 2016

Multiple occasions of PfKelch Δ emergence



Median Joining Haplotype Network of
K13 Mutations and SNPs
within Linkage Disequilibrium
of the K13 Propeller Protein



Neighbour –joining tree
of samples carrying K13 SNPs

K580Y mutant found in Myanmar did not spread from Cambodia
-it arose independently in Myanmar

Shannon Takala-Harrison et al
J Infect Dis 2014

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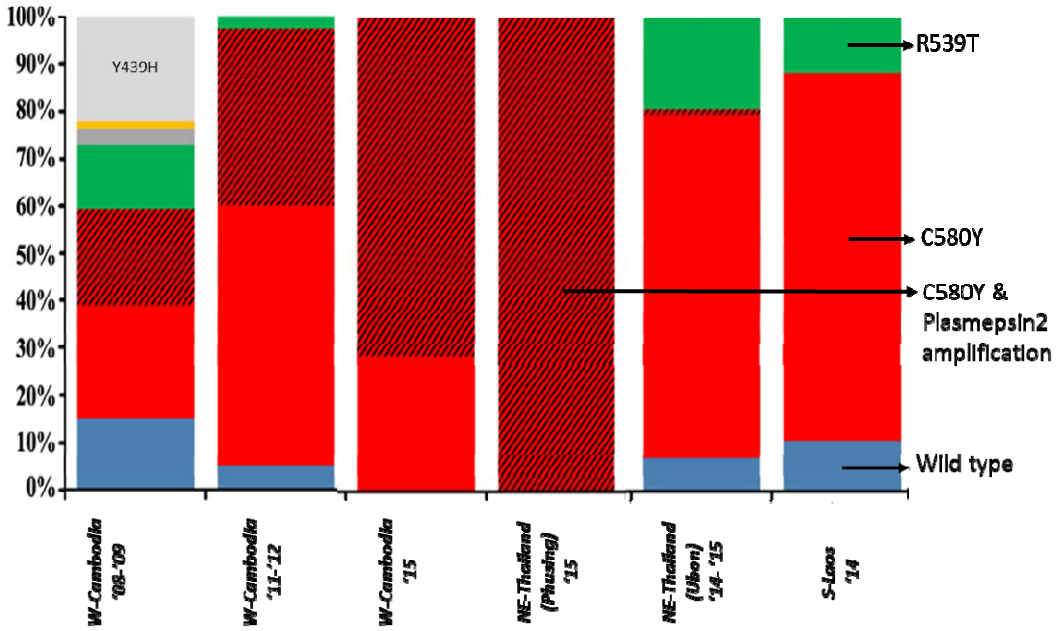
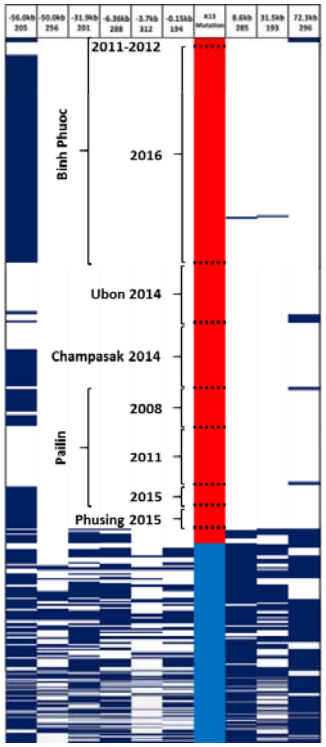
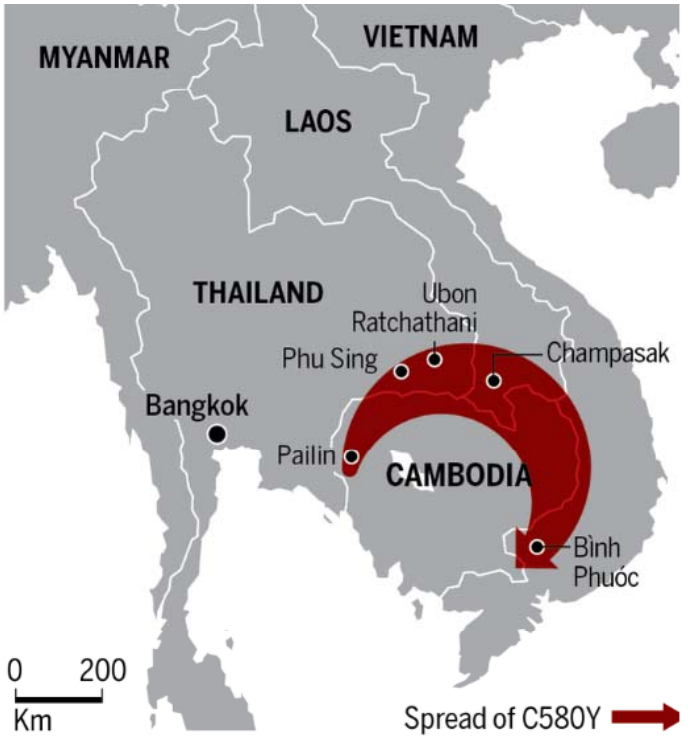
Miotto et al. Nature Gen 2015

Over time: single long haplotype of C580Y spreads







Imwong et al.
Lancet Infect Dis 2017

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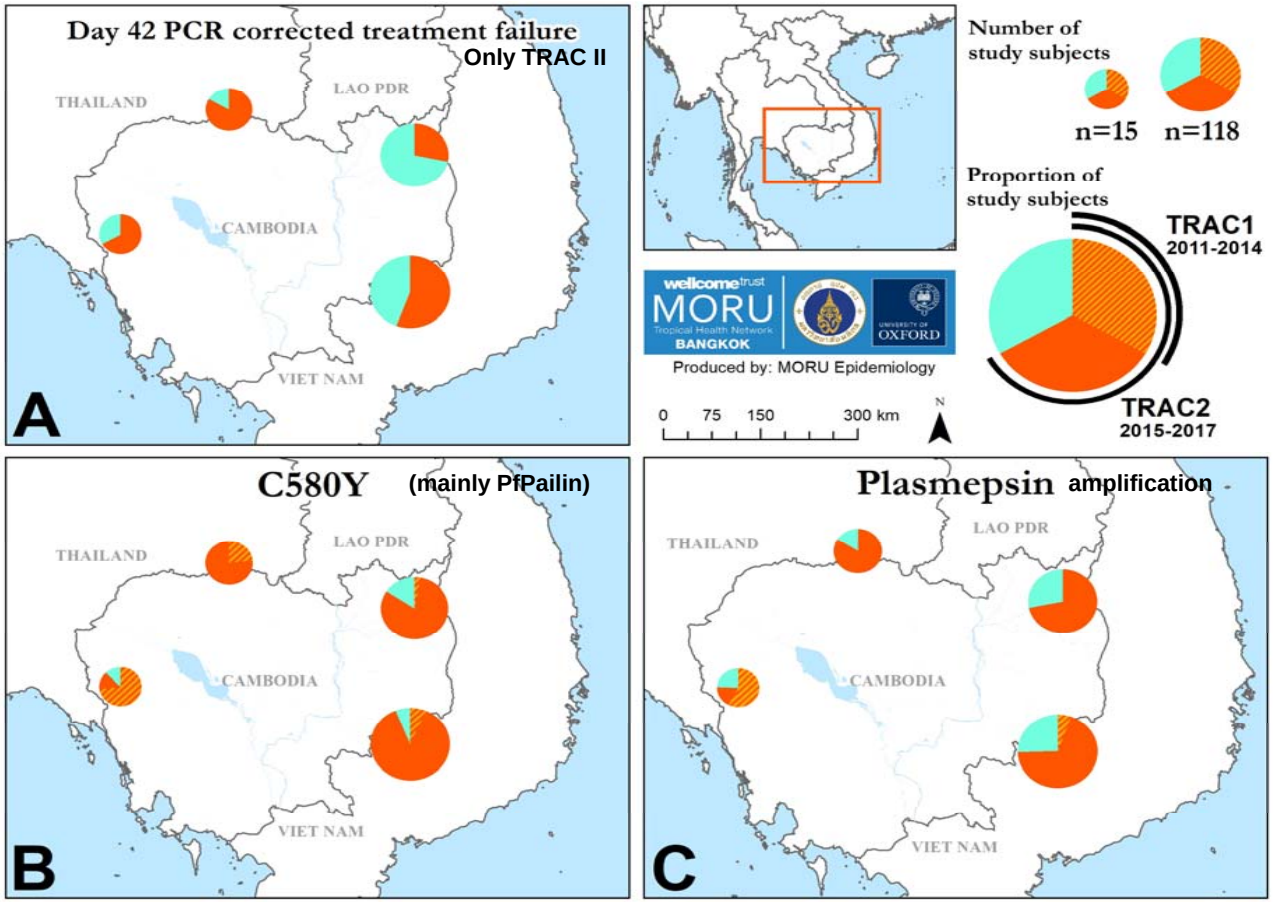
And takes over



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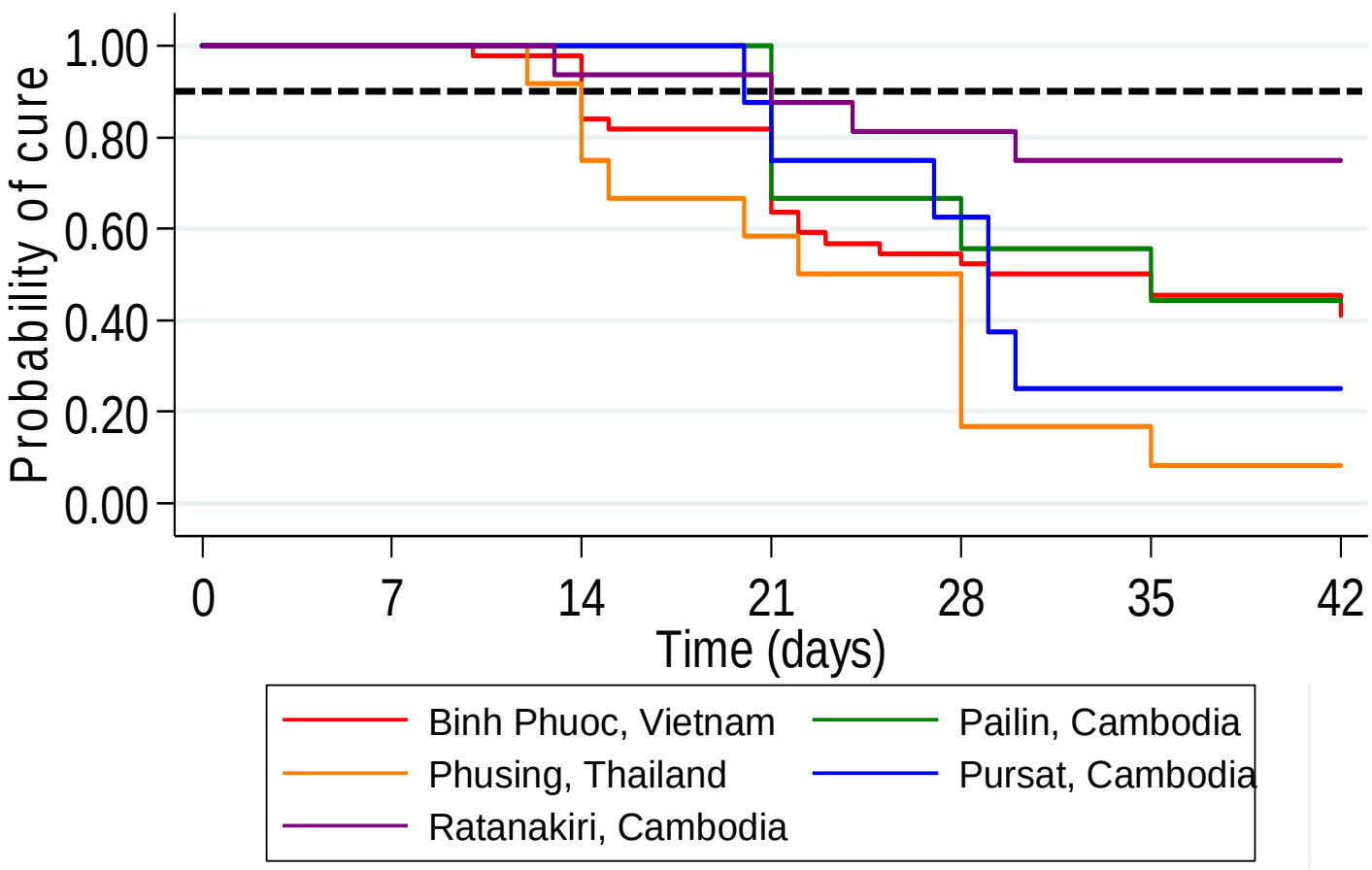
Van der Pluijm; in preparation

Increasing failure of DHA-piperaquine (east of BKK)



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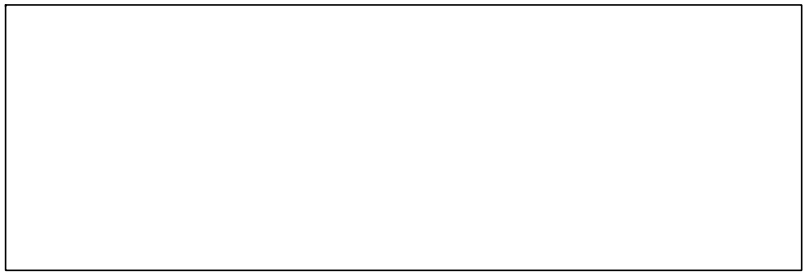
Van der Pluijm; in preparation

PfCRT mutations p



Time (days)

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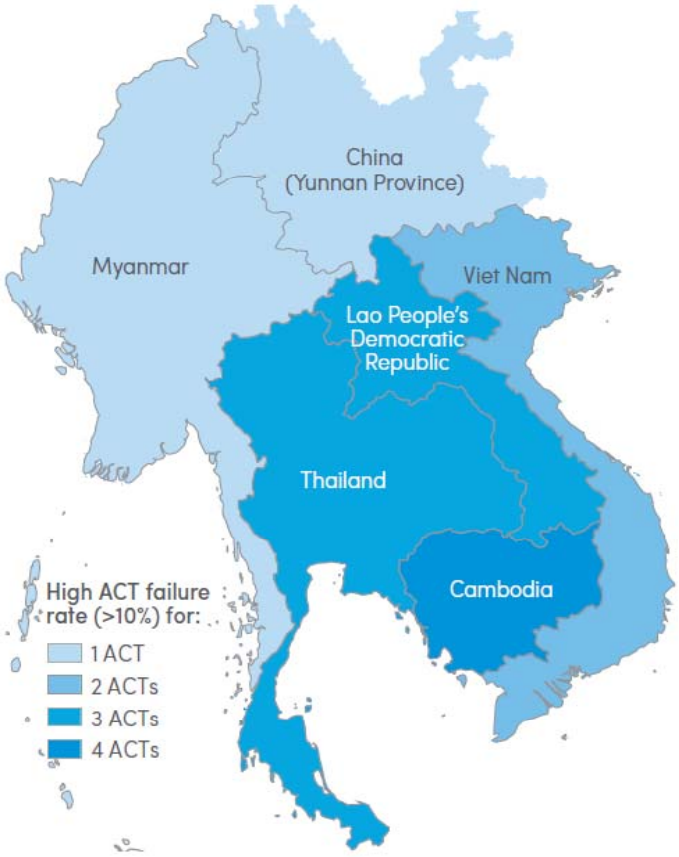
Van der Pluijm; in preparation

ACT failure in the GMS



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Dr Pascal Ringwald,
World Malaria Report 2018, WHO

Spread of resistance: chloroquine & pyrimethamine

Dondorp et al
Nat Rev Microbiol. 2010

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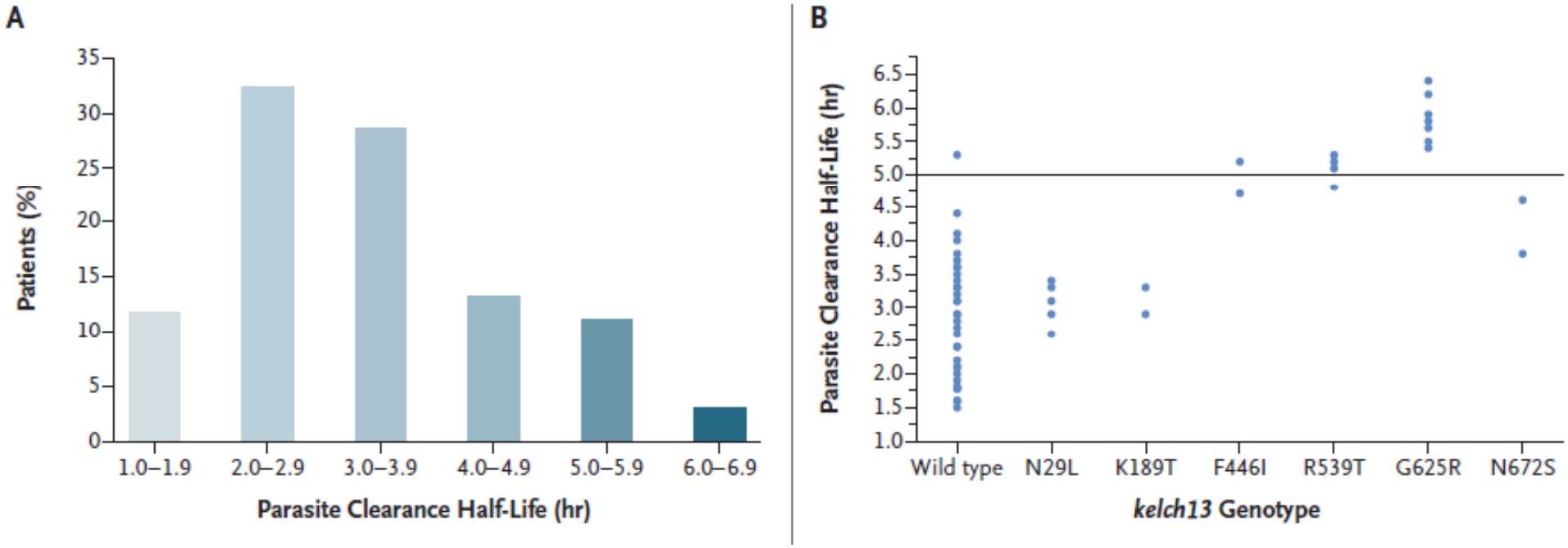
Adapted from Chris Plowe

Spread to India (West-Bengal)….?

2013-2014



Das et al
N Engl J Med 2018

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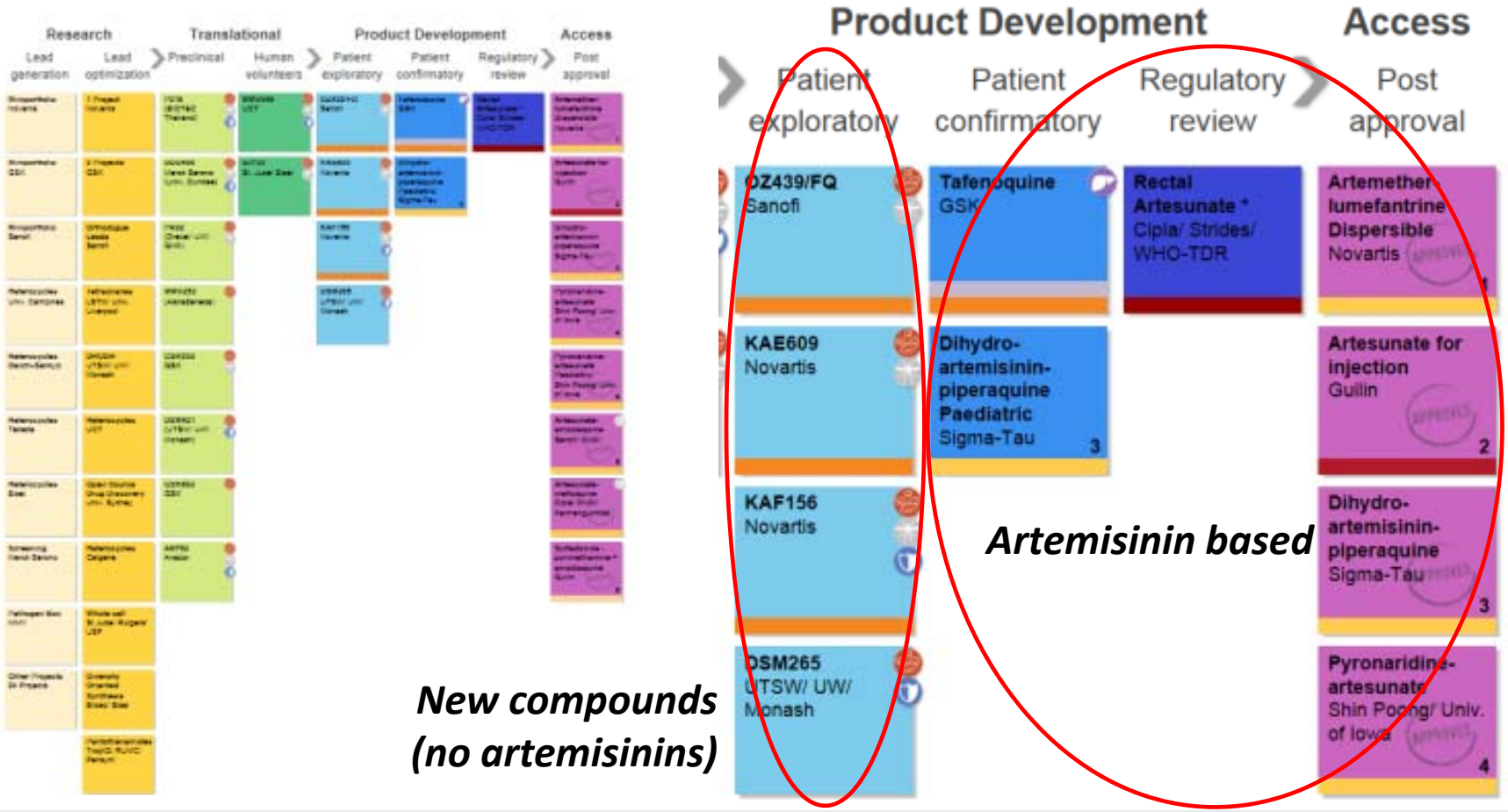
Conclusion

Ever increasing artemisinin and partner drug resistance in the Greater Mekong Subregion
This threatens malaria control in the GMS and can spread

We have to eliminate (falciparum) malaria from the GMS before it becomes untreatable and before it spreads further (India…..)

This requires: a sense of urgency, a common spirit, good governance, good coordination, regionally adapted integrated strategies, impact evaluation and good surveillance, collaboration between public and private sector, targeting difficult to reach populations, targeting the asymptomatic reservoir, adequate funding, and persistence till the end goal is reached!

Drug development pipeline



Source: MMV website

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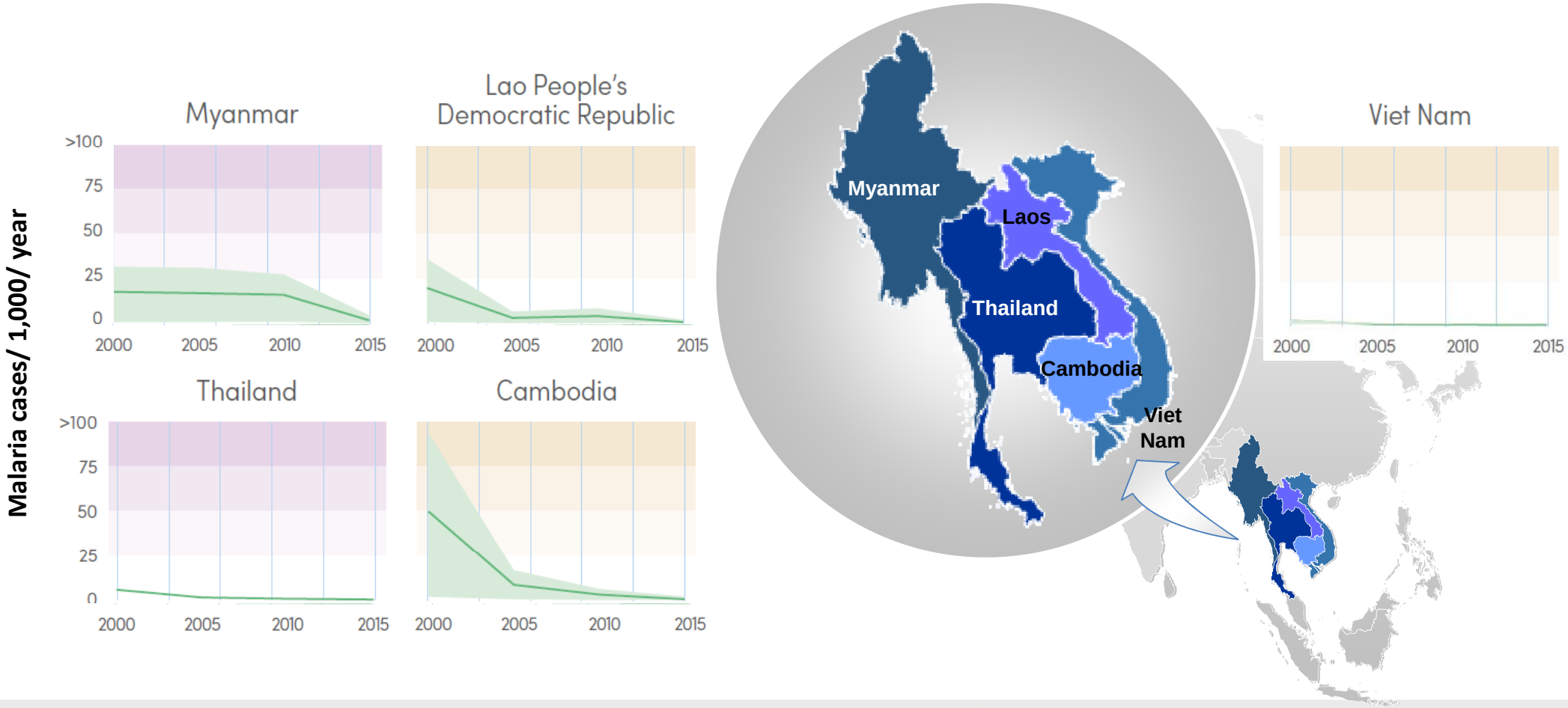
Transmission is going down in the GMS



World Malaria Report, WHO

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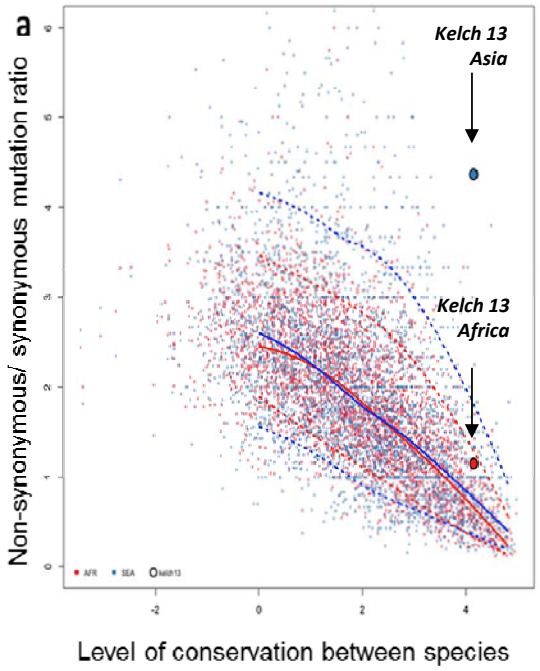
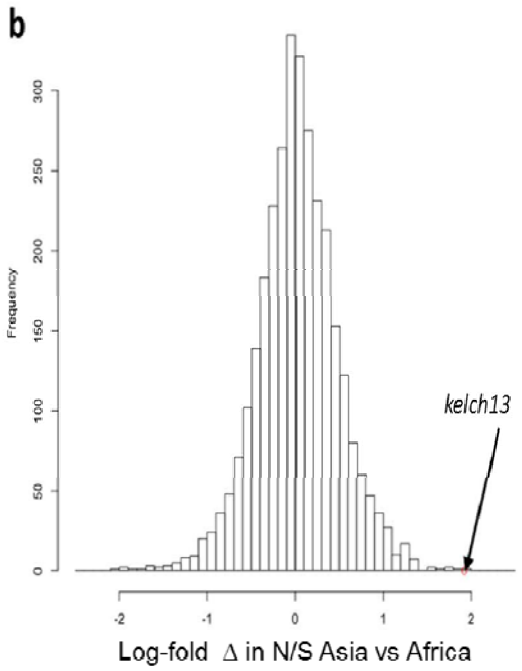
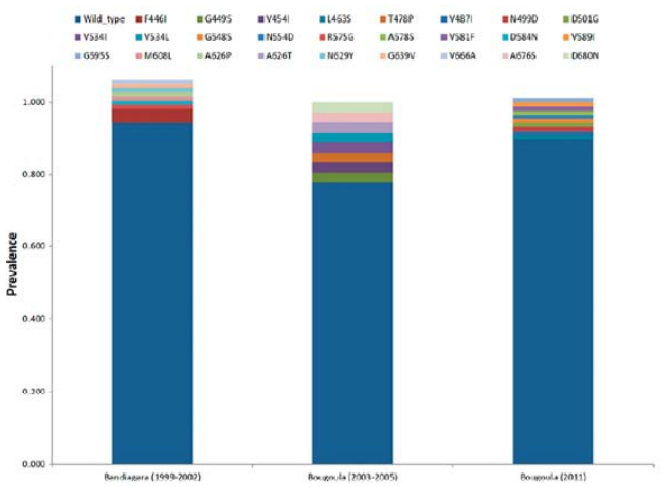
PfKelch13 Δ in Africa: no evidence for selection





Bougoula-Hameau and Bandiagara



Miotto et al. Nat Gen 2015

Ouattara et al. Am J Trop Med Hyg 2015