Global situation of resistance to antimalarial drugs

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Global **Malaria** Programme

World Health Organization

Treatment guidelines for falciparum malaria

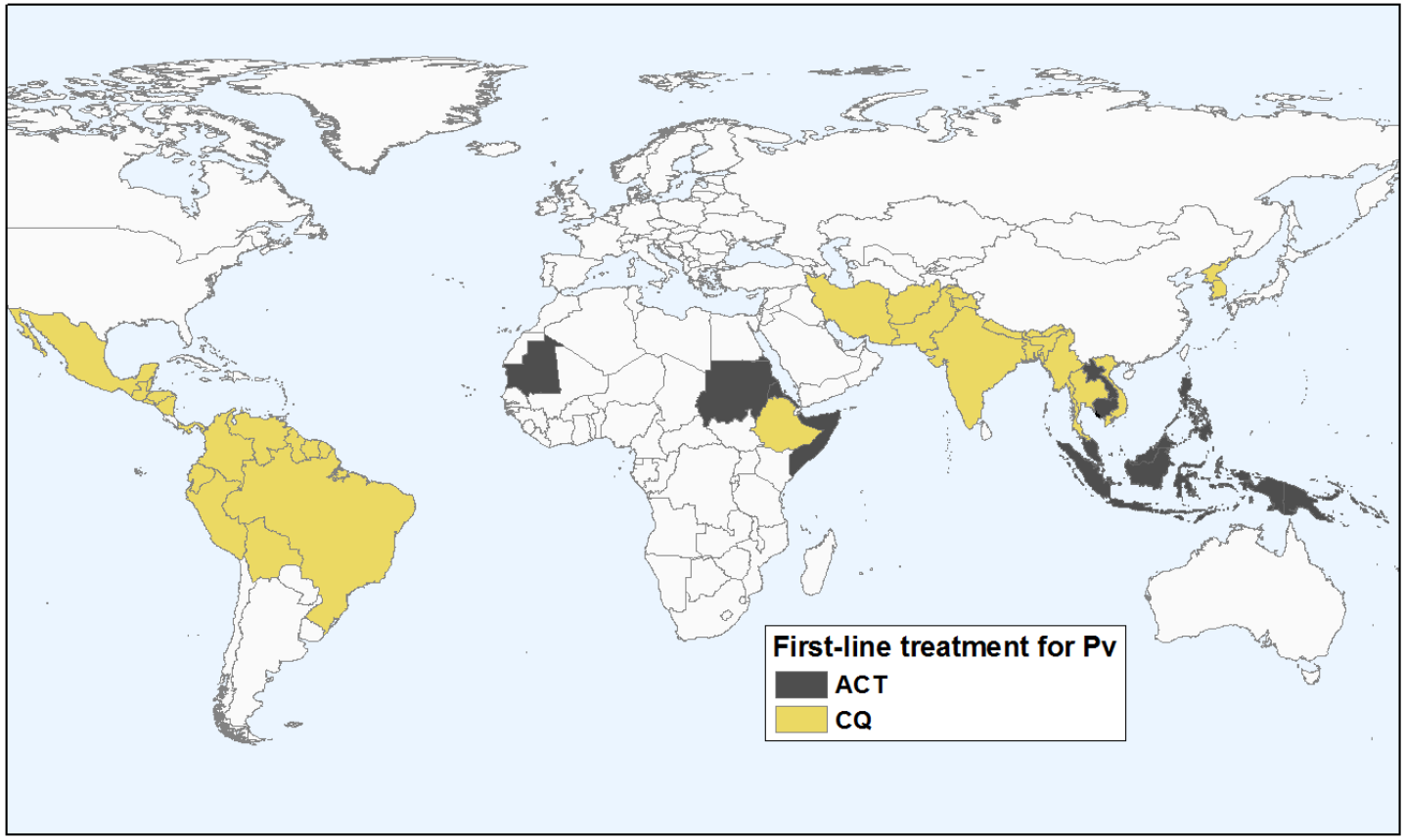
- Uncomplicated falciparum malaria

  Artemisinin-based combination therapies:
  - Artemether-lumefantrine
  - Artesunate-amodiaquine
  - Artesunate-mefloquine
  - Artesunate-SP
  - Dihydroartemisinin-piperaquine
  - Artesunate-pyronaridine (in areas where others ACTs are failing)

- Severe malaria
  - Artesunate, artemether, quinine followed by ACT

Treatment guidelines for vivax malaria

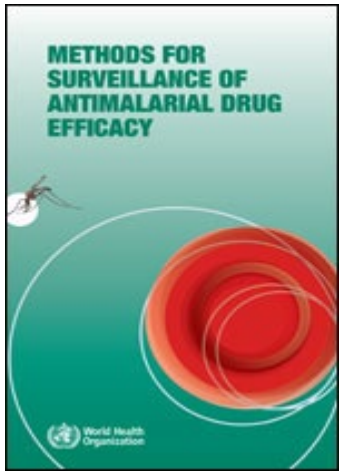
- In areas with chloroquine-susceptible infections: ACT or chloroquine (+primaquine)
- In areas with chloroquine-resistant infections: ACT (+primaquine)



Definitions

- ***Antimalarial resistance*** is defined as the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within tolerance of the subject;
- ***Artemisinin resistance*** is defined as delayed parasite clearance following treatment with an artesunate monotherapy or with an ACT – partial resistance would be more appropriate wording;
- ***Multidrug resistance* (MDR)** is resistance to more than 2 antimalarial compounds of different chemical classes. This term usually refers to *P. falciparum* resistance to chloroquine, sulfadoxine-pyrimethamine, and a third antimalarial compound;
- ***Treatment failure (≠ resistance)*** is the inability to clear parasites from a patient's blood or to prevent their recrudescence after the administration of an antimalarial. Many factors can contribute to treatment failure, including incorrect dosage, poor patient compliance, poor drug quality, and drug interactions and resistance. Most of these factors are addressed by therapeutic efficacy studies.

Monitoring efficacy and resistance



- Therapeutic efficacy studies (TES)
  - Prospective evaluations of patients' clinical and parasitological responses to treatment for uncomplicated malaria.
  - Considered the gold standard for assessing antimalarial drug efficacy. The resulting data are used to inform national malaria treatment policy in malaria endemic countries.
  - Studies conducted according to the WHO protocol, repeatedly at the same sites and at regular intervals, allow early detection of changes in treatment efficacy and comparison of results within and across regions over time.
- Molecular markers
  - Drug resistance is one of the causes of treatment failure. Once genetic changes associated with resistance are identified (molecular markers), drug resistance can be confirmed and monitored with molecular techniques.

Molecular markers of drug resistance for falciparum

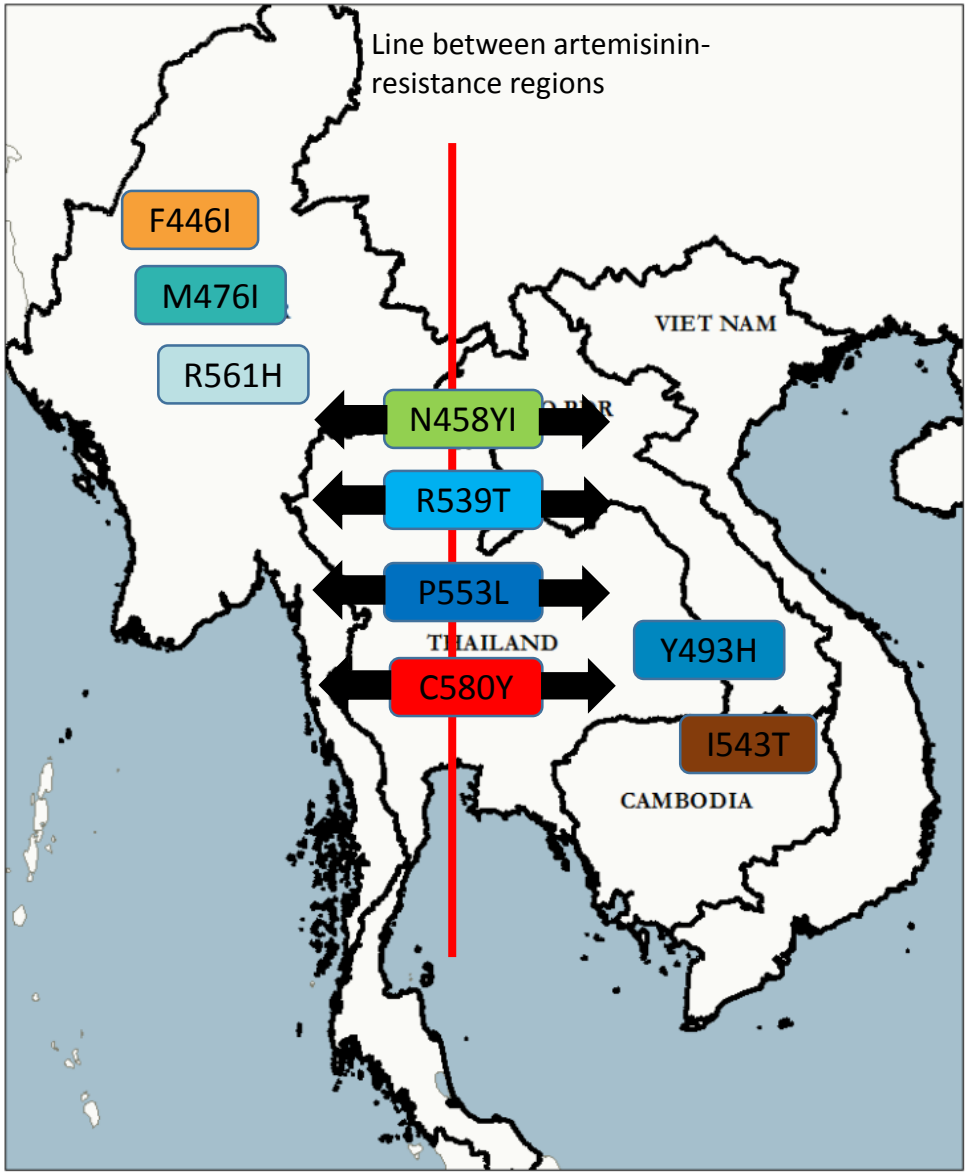
Chemical family	Drug	Molecular marker
4-Aminoquinolines	Chloroquine	*Pfcrt* SNP*
	Amodiaquine	Molecular marker yet to be validated. Studies show that amodiaquine select for *Pfmdr1* (86Y)
	Piperaquine	*Pfpm2-3* copy number
Antifolates	Pyrimethamine	*Pfdhfr* SNP*
	Sulfadoxine	*Pfdhps* SNP*
Amino-alcohols	Mefloquine	*Pfmdr1* copy number
	Lumefantrine	Molecular marker yet to be validated. Studies show that lumefantrine select for *Pfmdr1* (N86). Recent data do not confirm *Pfmdr1* copy number as a marker of lumefantrine resistance.
Sesquiterpene lactones	Artemisinin and artemisinin derivates	*PfK13* SNP*
Naphthoquinone	Atovaquone	*Pfcytb* SNP*

* SNP: Single nucleotide polymorphisms

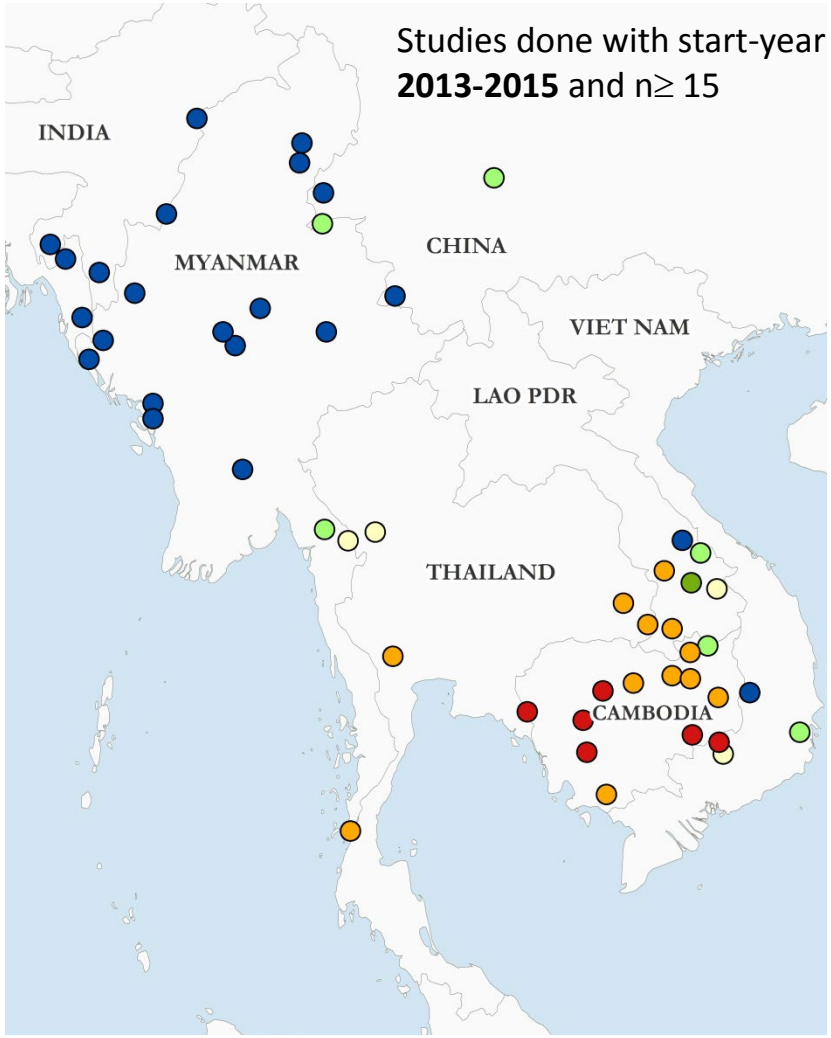
Monitoring artemisinin resistance

- In vivo artemisinin resistance is defined as delayed parasite clearance. In TES seen as increased proportion of patients positive on day 3.
- Artemisinin resistance is also monitored via different validated K13 mutations.

Distribution of K13 mutants in the GMS



Percentage of samples with C580Y mutation



Percentage of parasites with C580Y

- 0
- 0.01 - 5
- 5.01 - 20

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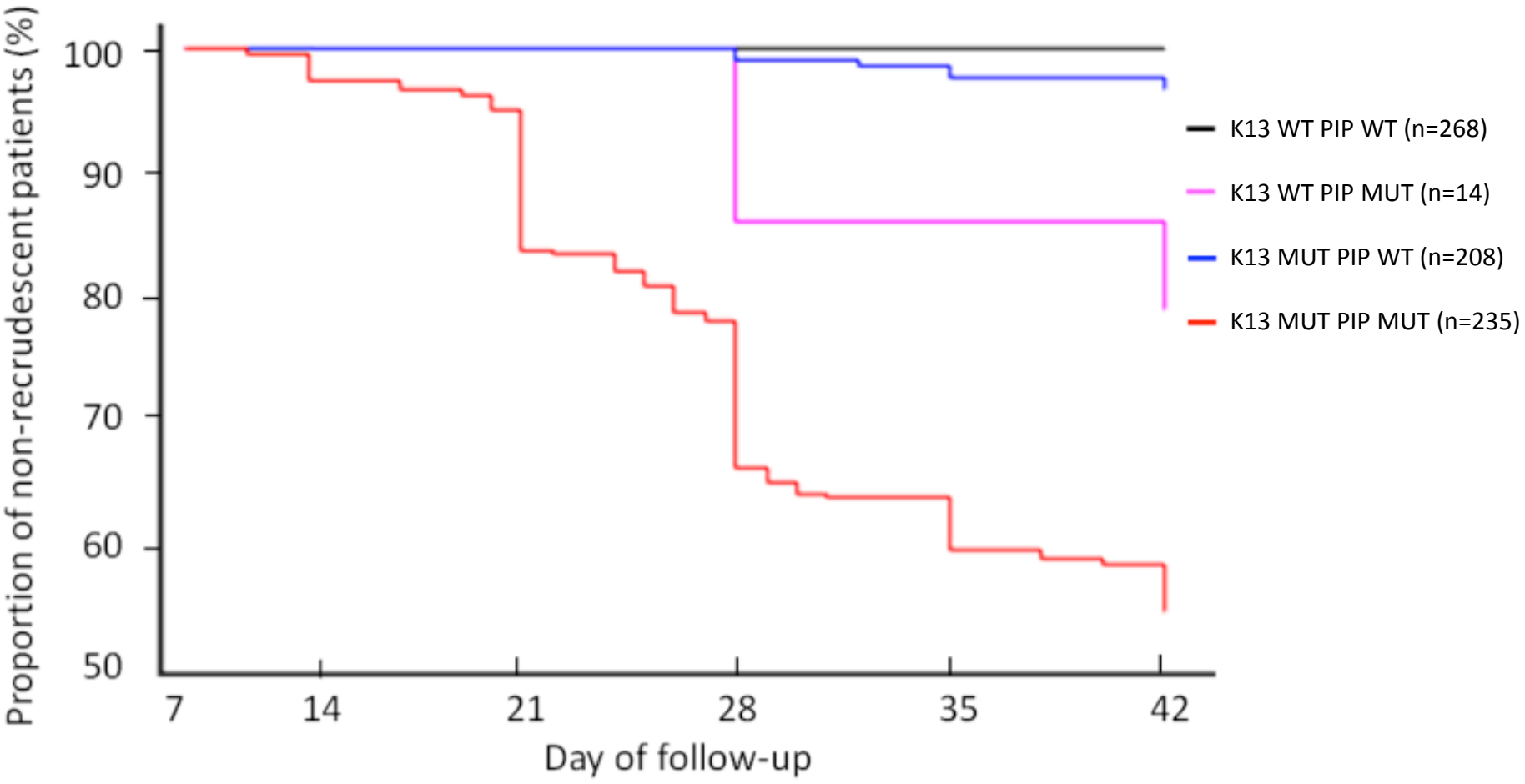
Relation between ACT efficacy and K13 mutations

Year	Site	ACT	N	Efficacy 28/42 days (%)	K13 mutant (%)	*Pfmdr1* (n > 1) (%)
2011	Pailin Cambodia	Artesunate-mefloquine	29	100	75.9 (C580Y)	6.9
2012-13	Dak Nong Viet Nam	Dihydro-piperaquine	33	100	72.7 (C580Y; Y493H)	N/A
2014	Yingjiang county Yunnan, China	Dihydro-piperaquine	23	100	91.3 (F446I)	N/A
2014-15	Champassak Lao PDR	Artemether-lumefantrine	29	93.2	83.3 (C580Y; R539T)	N/A
2014-16	Kratie, Siam Riep, Pursat, P. Vihear Cambodia	Artesunate-mefloquine	305	100	94.2 (C580Y)	< 5

Role of each markers in DHA-PIP efficacy in Cambodia (N = 725)



Witkowski et al., *Lancet Inf. Disease* 2016

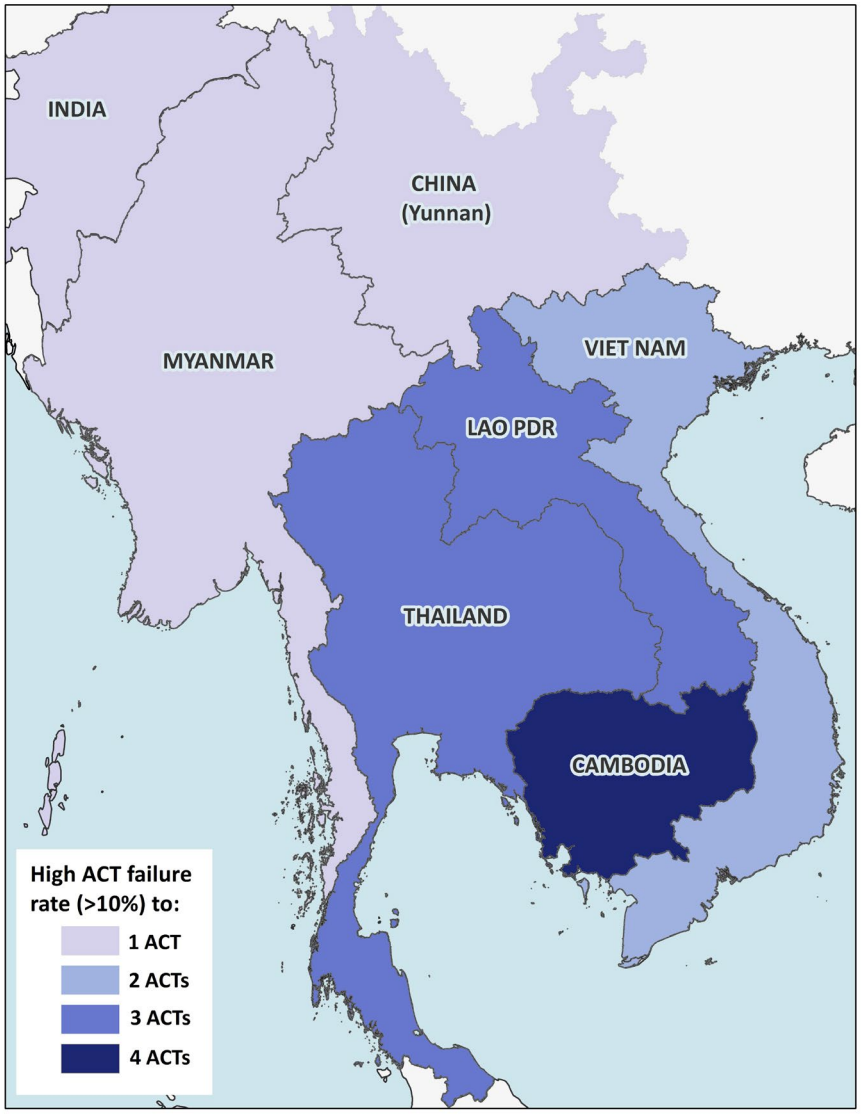
Clinical outcome after ACT treatment according to sensitivity pattern of each component

Artemisinin*	Partner drug	Treatment outcome
Sensitive	Sensitive	Treatment success (ACPR)
Resistance (partial - delayed clearance)	Sensitive	Treatment success (ACPR)
Sensitive Sensitive	Resistance (low grade)** Resistance (high grade)	Treatment success (ACPR) Treatment failure *
Resistance (partial - delayed clearance)	Resistance	Treatment failure (high rate)

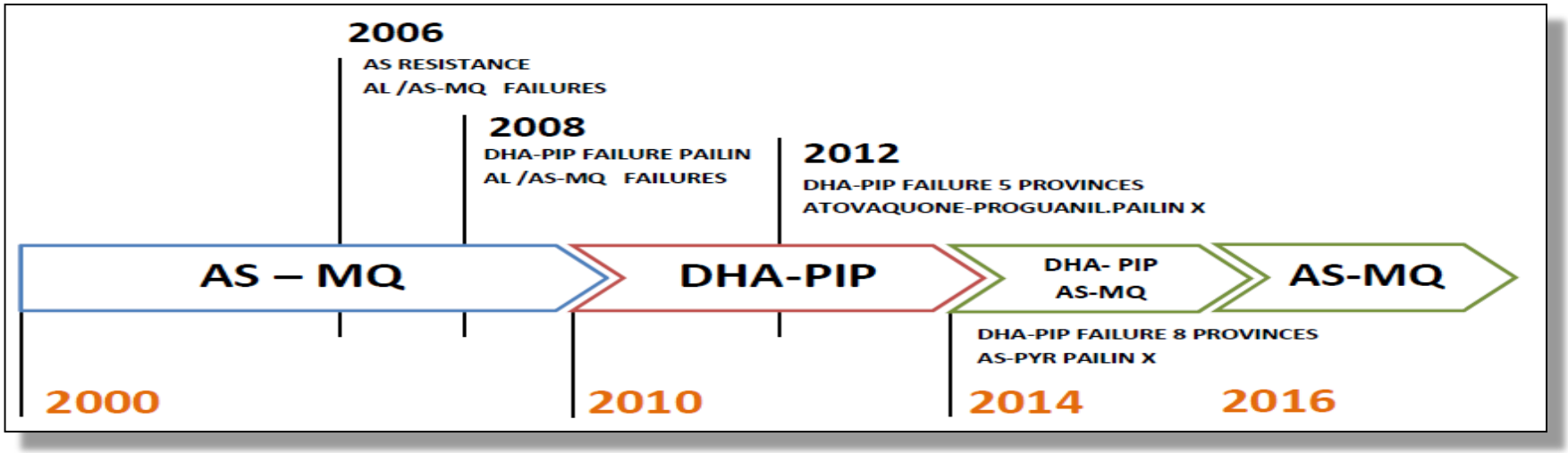
*** A 3-day treatment with artesunate used as monotherapy may cure up to 50% of patients;**

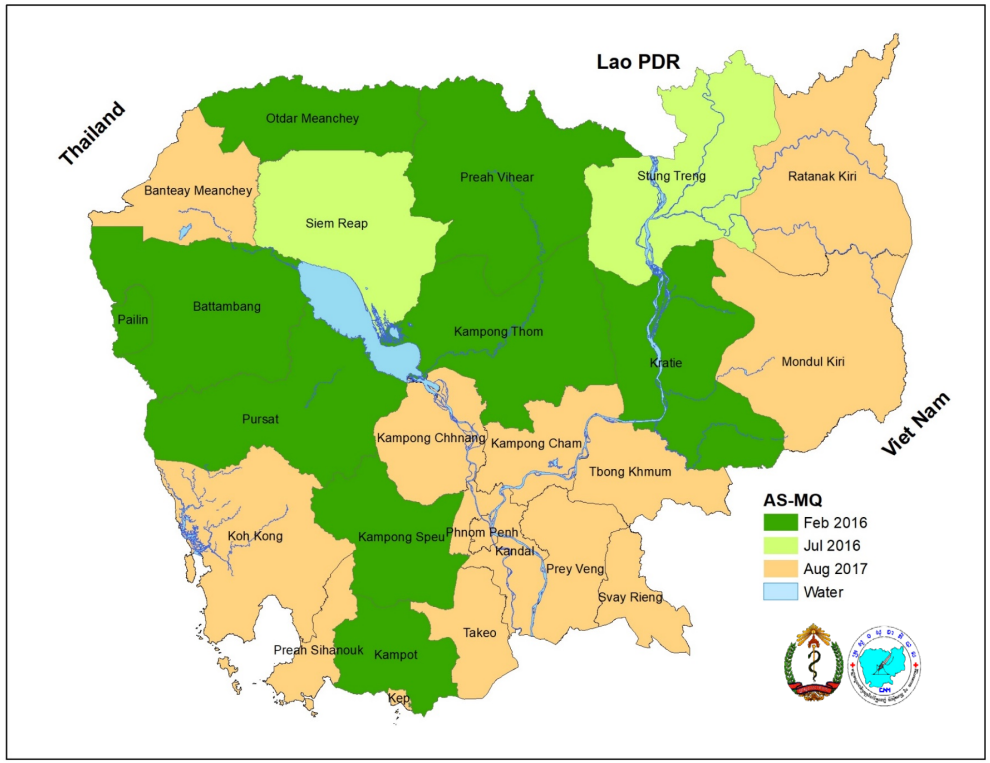
**** For amodiaquine and SP, treatment response was still adequate despite 20-30% of AQ or SP resistance in absence of artemisinin resistance**

Number of ACTs failing in the Greater Mekong Subregion



Changes in Cambodia national malaria treatment policies





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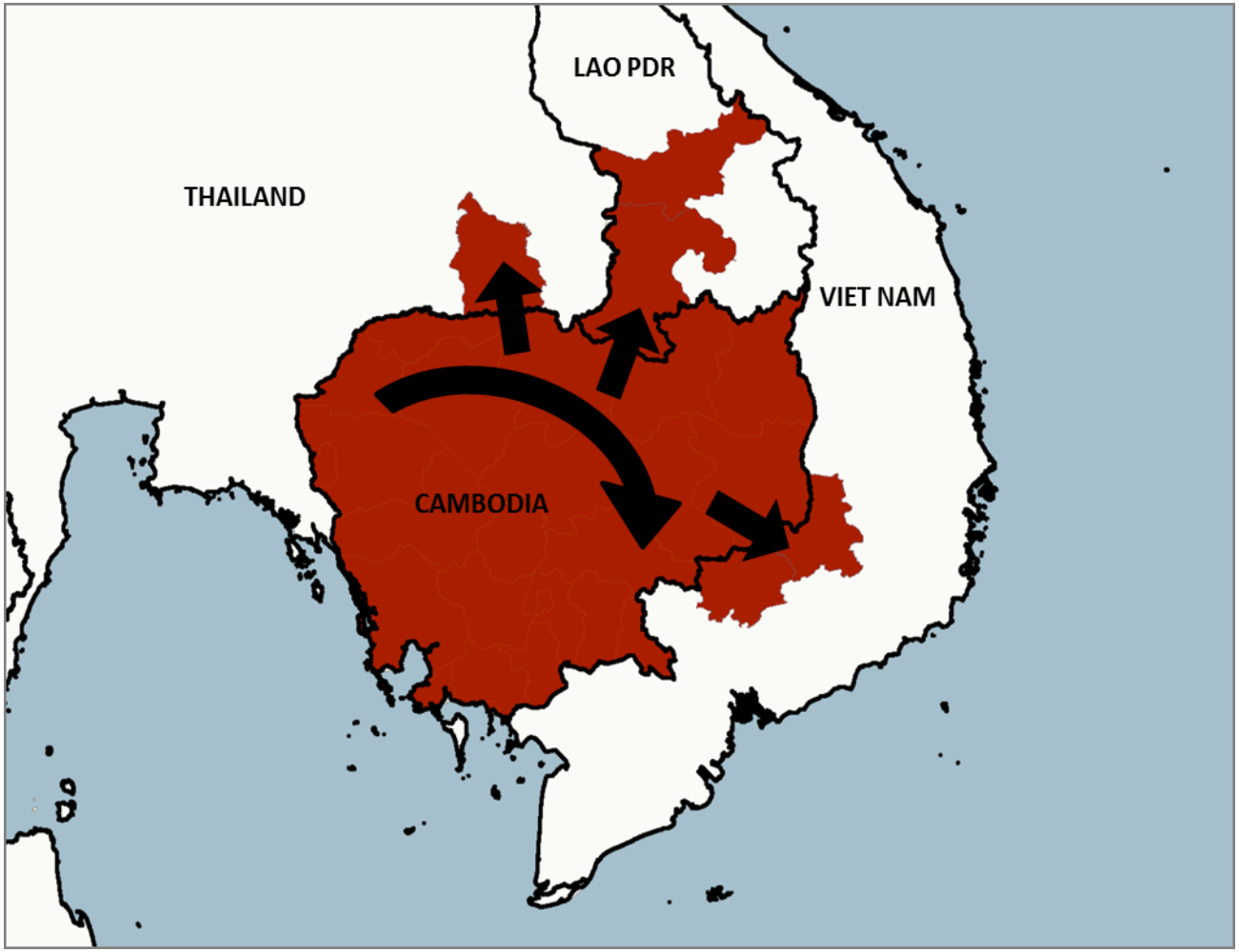
Spread of DHA-piperaquine in GMS

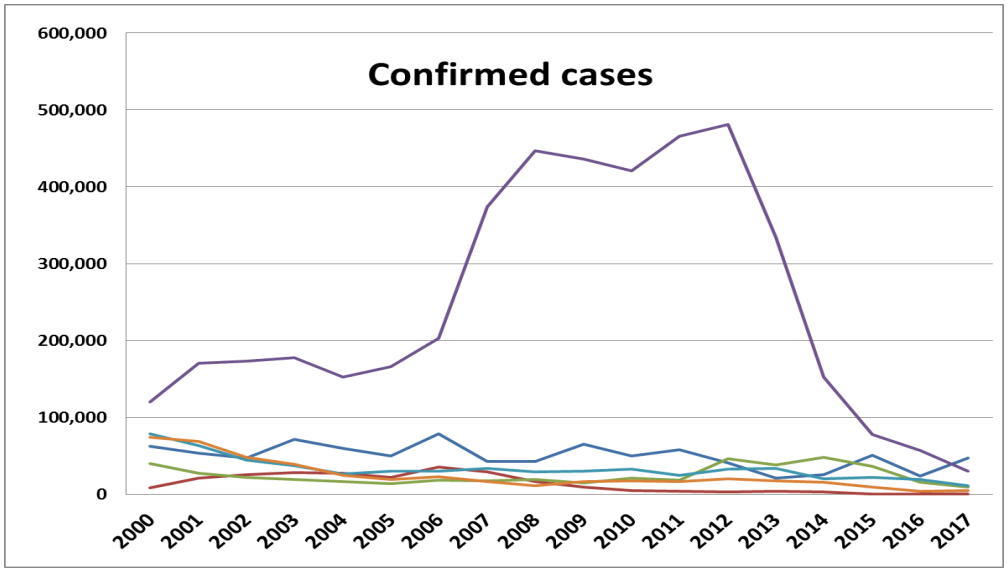
Spread of a single multidrug resistant malaria parasite lineage to Viet Nam

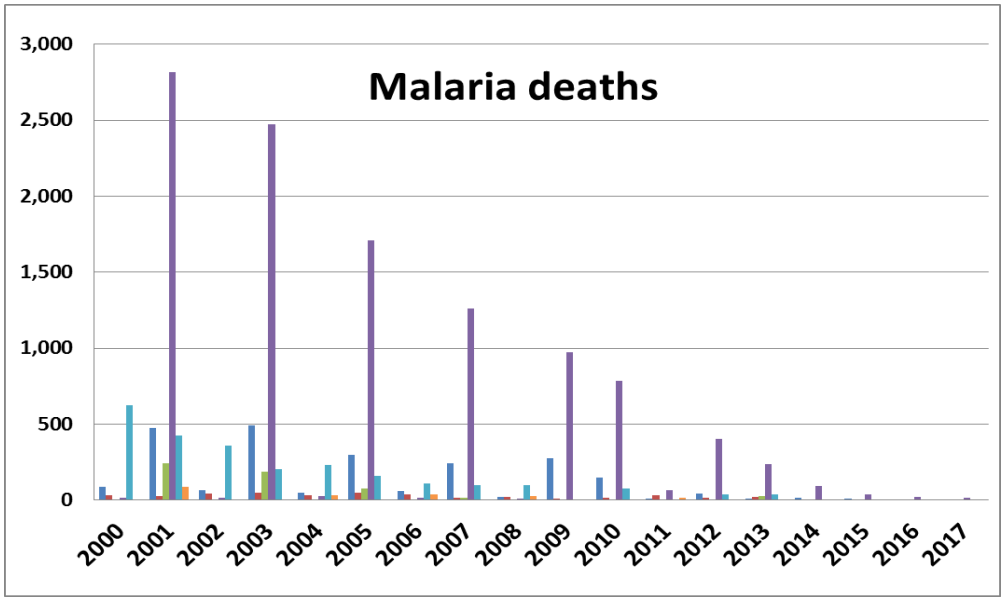


- The spread of resistant parasites across the region linked to massive drug pressure including through MDAs.

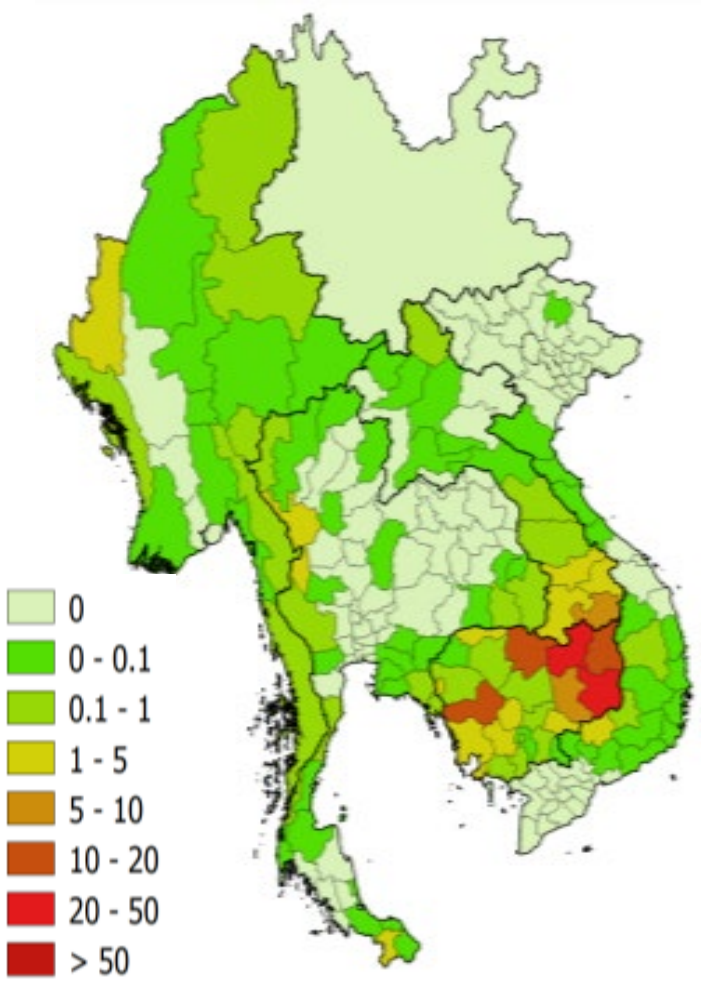
Adapted based on Imwong et al. 2017 Lancet Inf Dis.

Eliminating malaria in the GMS





Parasite incidence Jan-Jun 2018 (per 1000 population)



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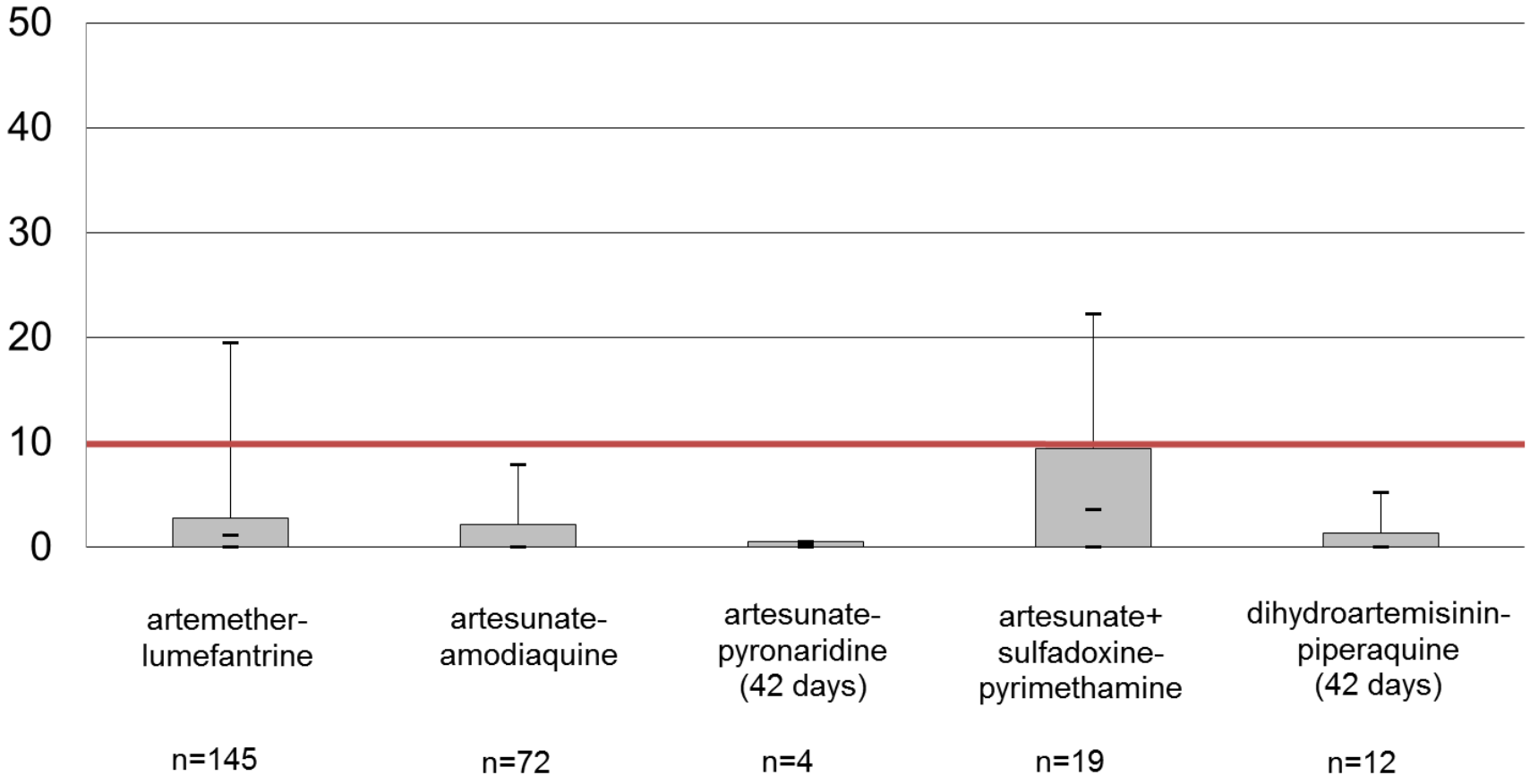
ACT treatment failure rates in the WHO African Region (2010-2016)



* Includes: Angola, Burkina Faso, Benin, Cameroon, CAR, Chad, Comoros, Congo, Côte d'Ivoire, DRC, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, Somalia, Sudan, Togo, Zambia and Zimbabwe

Update on antimalarial drug efficacy and drug resistance

Prevalence of *Pfplasmepsin2-3* increased copy number

Year	Countries	Prevalence	Study
2013	Comoros	3/46 (6.5%)	TES
2015	Mozambique	0/87 (0%)	TES
2015	Mozambique	1/88 (1.1%)	TES
2015	Mozambique	1/89 (1.1%)	TES
2015	Mozambique	2/87 (2.3%)	TES
2015	Mozambique	3/61 (4.9%)	Pre-MDA
2016	Mozambique	1/19 (5.3%)	Post-MDA

Recommendations of the TEG

- presence of multicopy *Pfplasmepsin 2-3* in Africa is a potential concern in terms of the use of DHA-PIP;
- additional information is required regarding the in vivo and ex vivo piperaquine-resistant phenotype in African parasites;
- additional African data are needed to assess the relationship between DHA-PIP treatment failures and molecular markers (*Pfkelch13*, *Pfplasmepsin 2-3*, and *Pfcrt*).

Conclusions

- Surveillance for artemisinin and partner drug resistance needs to be continued and strengthened in the GMS;
- There is a critical need for surveillance outside the GMS to detect potential de novo resistance or the potential introduction of resistant parasites;
- Where surveillance signals a potential threat to nationally recommended ACTs, effective alternative ACTs should be identified and implemented before resistance reaches critical levels.

Antimalarial drug efficacy and drug resistance WHO website

WHO website
http://www.who.int/malaria/areas/drug_resistance/en/

Malaria threats maps

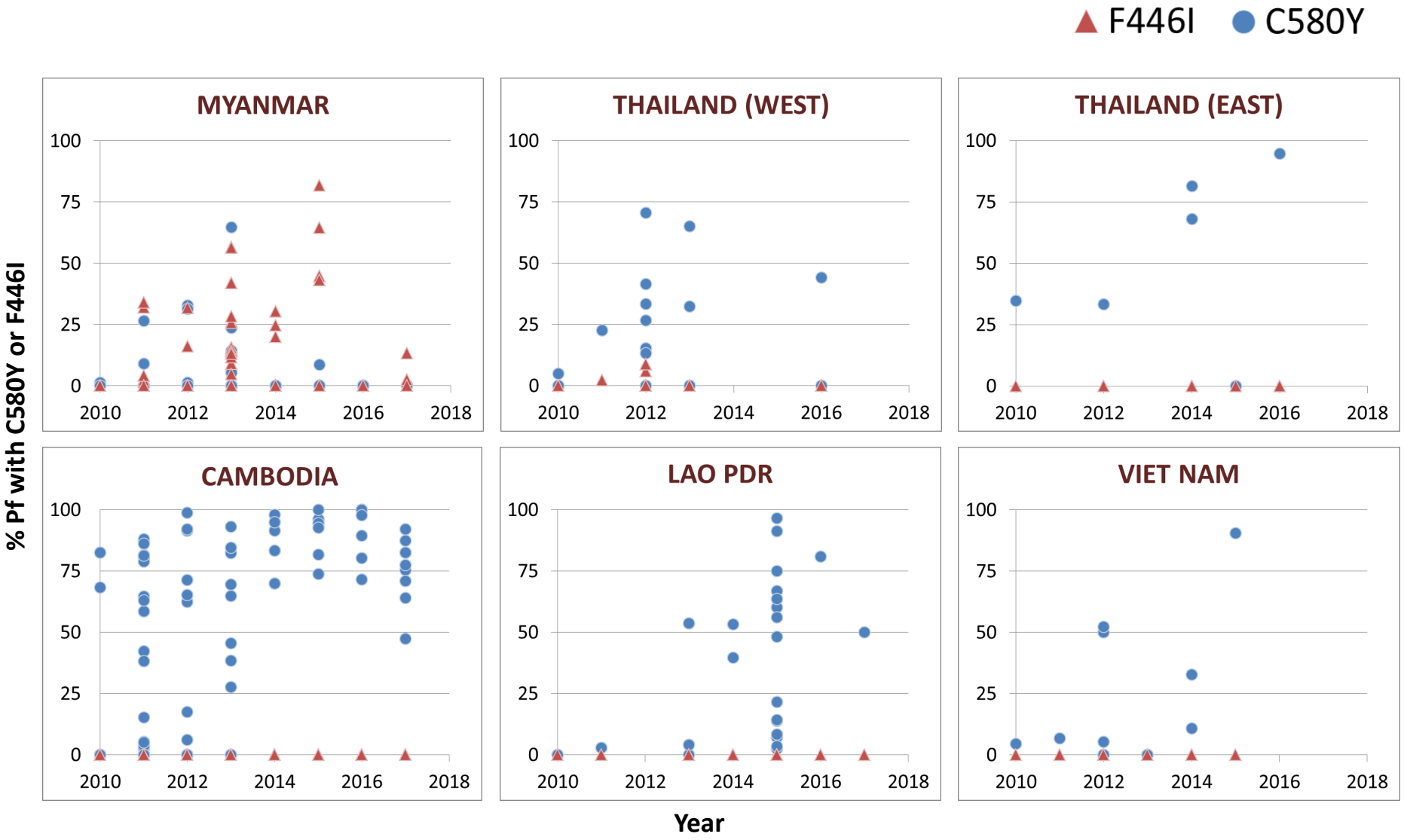
http://apps.who.int/malaria/maps/threats/

Update on drug resistance
http://www.who.int/malaria/publications/atoz/artemisinin-resistance-august2018/en/

Thank you for your attention

BACK-UP SLIDES

Percentage F446I and C580Y



Source: WHO database. Includes all studies with n>14 and a study start-year between 2010 and 2018

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NAYPYITAW, 8 December 2017

Ministerial Call for Action to Eliminate Malaria in the Greater Mekong Subregion before 2030

MALARIA FREE MEKONG

We, the Ministers of Health and delegates attending the High level Meeting to Accelerate Elimination of Malaria in the Greater Mekong Subregion, Nay Pyi Taw, 8 December 2017,

ACKNOWLEDGING the commitment of the governments of all countries in the Greater Mekong Subregion (GMS) to the United Nations Sustainable Development Goals, adopted in September 2015, including the target to eliminate malaria by or before 2030, as reflected in the 2014 declaration at the 9th East-Asia Summit in Myanmar, the Strategy for Malaria Elimination in the Greater Mekong Subregion (2015-2030), GMS countries' national malaria strategic plans, and the essential commitment and contributions of the Global Fund and other development partners providing financial, technical and programmatic support;

DRAWING the urgent attention of policy makers and partners, civil society and the public, to the fact that though the burden of malaria has been substantially lowered in many areas of the GMS, the malaria burden is concentrated in some areas, including development project sites, hard to reach areas, and international borders with at risk populations, which imposes significant human, financial and developmental costs, may lead to the continued high transmission of malaria including further spread of multi-drug resistance, and may jeopardize the 2030 GMS regional malaria elimination goals as well as national goals;

RECOGNIZING that multiple factors contribute to malaria vulnerability, including but not limited to challenges facing health systems, coverage gaps in prevention and case management efforts, civil unrest and humanitarian emergencies, development projects not accounting for health impact as well as climate change, and that the malaria burden is primarily borne by the economically and otherwise vulnerable households and communities, underscoring the importance of coordinated multi-sectoral action to achieve elimination of malaria;

NOTING that malaria multi-drug resistance, including resistance to artemisinin-based combination therapies (ACTs), threatens regional and international health security, requiring urgent implementation of the Strategy for Malaria Elimination in the Greater Mekong Subregion (2015-2030);

NOTING that in light of the threat posed by multi-drug resistance, the subregional strategy was amended in 2015 to move beyond containment of malaria to elimination, specifically with the goals to eliminate *Plasmodium falciparum* from the GMS by 2025 and all malaria parasites by 2030 at the latest, countries should be ready for rapid implementation of changes in first line therapies for *Plasmodium falciparum* malaria;

NOTING that oral artemisinin monotherapies, substandard and falsified medical products continue to be available in some GMS countries - especially in the private health sector - which are key factors in the development of malaria multi-drug resistance, and that stock-outs of quality-assured ACTs and malaria rapid diagnostic tests continue to deny at risk populations ready, universal, reliable access to malaria diagnosis and appropriate case management, and hamper surveillance and rational use of antimalarials;

RECOGNIZING that the strengthening of malaria surveillance systems and the expansion of case- and foci-based surveillance, management and response, which are key requirements for malaria elimination, is in the most areas not progressing as fast as required;

NOTING the transition in the Region from malaria responses that are donor-led to responses that are country-owned and country-led;

RECOGNIZING also that partner coordination is often inadequate, leading to duplication of efforts, insufficient targeting of underserved and difficult-to-reach populations and areas, and insufficient focus on operational research to guide programmes;

RECOGNIZING that strong collaboration with other key relevant sectors of government as well as with the private and corporate sector and affected communities is essential for effective implementation and sustainability of the Strategy for Malaria Elimination in the Greater Mekong Subregion (2015-2030) as well as the national strategic plans, notably in terms of domestic funding, ready access to affordable quality pharmaceuticals, community involvement, multi-sectoral action to reduce vulnerability, access to malaria interventions for indigenous, mobile and migrant populations, and cross-border collaboration;

And **ACKNOWLEDGING** the international visibility and interest that the malaria problem in the GMS has attracted, and the unprecedented partner and financial support this has elicited;

COMMIT OURSELVES THIS DAY to exceptional action, specifically including the following essential, high-impact steps:

1. **REAFFIRM** the "One Region, One Strategy" as our guiding principle for malaria elimination in the GMS, with strong country ownership;
2. **SECURE** full and sustainable financing through:
   a. Overseeing the full implementation of planned activities and related funds;
   b. Committing our national governments to adequate domestic budgetary allocations for malaria elimination efforts;
   c. Urging global and regional partners to sustain financing for malaria elimination;
3. **IMPLEMENT** a multi-sectoral response in every country to ensure that policies are effectively translated into time-bound, result-oriented actions at every level of administration, with ownership and access to real-time monitoring and collaboration across borders ensuring information exchange and joint actions along borders where required;
4. **ENABLE**, using innovative communication tools to engage and promote health literacy among communities on malaria elimination, and provide – as part of Universal Health Coverage (UHC) – the best possible prevention, diagnosis and care to all persons at risk of malaria, including development project sites, hard to reach areas and international borders with at risk populations;
5. **STRENGTHEN** existing malaria drug supply management systems to ensure that oral artemisinin monotherapies, substandard and falsified antimalarials as well as ACTs which are not proven effective or quality assured are no longer available both in the public and private sector in any of the GMS countries, and that stock-outs of essential malaria supplies no longer occur;
6. **TRANSFORM** malaria surveillance into a core intervention in each GMS country, including effective information collection, analysis and dissemination systems, and switch to case-based surveillance for malaria elimination where appropriate and feasible as soon as possible;
7. **STRENGTHEN** national malaria elimination strategies and interventions and the coordination of partners and stakeholders and adapt them to changes in epidemiology and environment through utilization of technical leadership and support from WHO and support from other partners, and for oversight, establish national elimination committees;
8. **WORK** together with relevant entities as a sub-region to:
   a. Develop and implement cross-border elimination strategies and action plans that concretely address the malaria-related needs and challenges of populations at risk of malaria living in border areas and cross-border mobile and migrant populations;
   b. Under the concept of UHC, ensure that everyone is eligible for and can be reached by malaria prevention and diagnosis and treatment interventions, including the provision of free malaria services to mobile and migrant populations, ethnic minority groups and other vulnerable populations;
   c. Exchange core surveillance data on malaria, including but not limited to imported or cross-border malaria cases and drug resistance;
   d. Build collaboration among Member States for sharing and transferring 'good practices', and for strengthening technical and managerial expertise in malaria elimination;
   e. Promote collaborative research and share best practices amongst countries;
   f. Strengthen continuous monitoring of the sub-regional progress through the regional surveillance network for malaria, coordinated by WHO;
   g. Ensure that all research efforts are nationally coordinated and adhere to international standards, and translate operational research findings into policy and action;
   h. Establish an independent sub-regional malaria elimination oversight body, empowered by GMS countries, for which WHO would act as the secretariat;
   i. Ensure that all major development activities are preceded by a health impact assessment and that projects include measures to minimize malaria transmission, including provision of malaria related services and access to diagnostics and treatment for all workers on such projects;
   j. Engage in regional regulatory partnerships aimed at improving the efficacy and quality of the regulatory review for new antimalarial treatments and diagnostic tests;
   k. Strengthen GMS regulatory functions through increased convergence and reliance mechanisms to improve the accessibility of quality assured malaria commodities, including post marketing surveillance.

1 For the People's Republic of China this would include the areas of Yunnan Province and Guangxi Zhuang Autonomous Region.

We call upon all leaders, policy-makers, partners, civil society and the public in the Greater Mekong Subregion and around the world to actively support this Call for Action to Accelerate Efforts to Eliminate Malaria in the Greater Mekong Subregion before 2030.

WORKING TOGETHER, WE WILL DEFINITELY ELIMINATE MALARIA IN THE GREATER MEKONG SUBREGION BEFORE 2030.

H.E. Prof. Eng Huot — Secretary of State for Health, Ministry of Health, Government of the Kingdom of Cambodia

Mme Cui Li — Vice Minister of National Health Commission, Government of the People's Republic of China

H.E. Ass. Prof. Dr Bounkong Syhavong — Minister for Health, Government of the Lao People's Democratic Republic

H.E. Dr Myint Htwe — Union Minister for Health and Sports, Government of the Republic of the Union of Myanmar

H.E. Prof. Piyaskol Sakolsatayadorn — Minister of Public Health, Government of the Kingdom of Thailand

H.E. Prof. Le Quang Cuong — Vice Minister of Health, Government of the Socialist Republic of Viet Nam

Dr Poonam Khetrapal Singh — WHO Regional Director for South-East Asia

Dr Shin Young-soo — WHO Regional Director for the Western Pacific

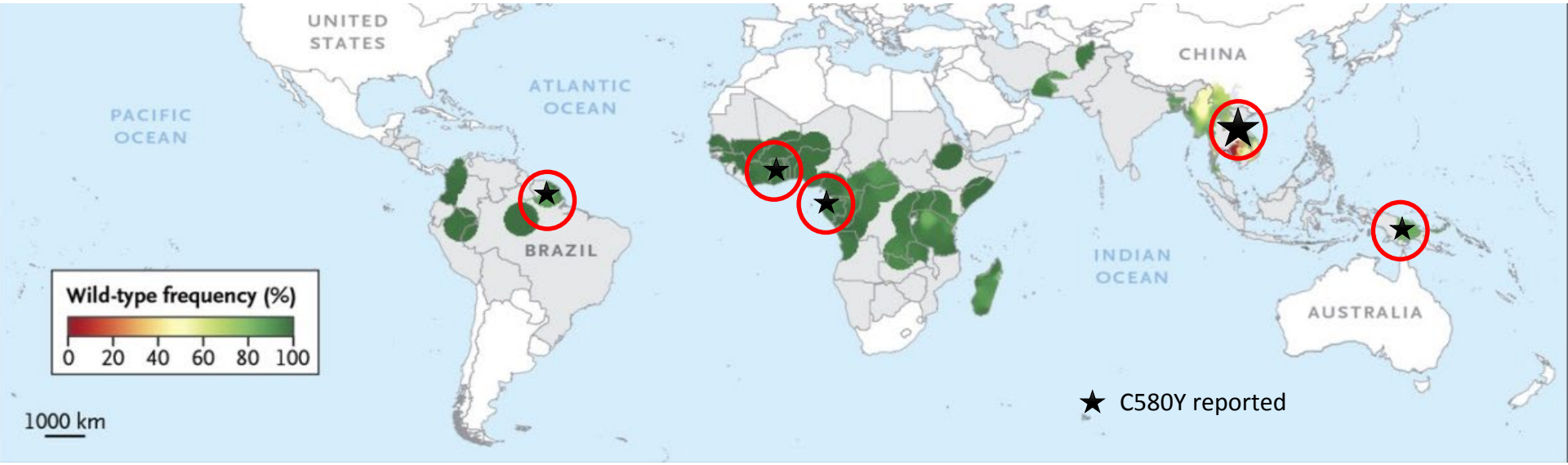
- During the World Health Assembly in May 2018, Health Ministers and Senior representatives from GMS countries signed the *Call for Action to Eliminate Malaria*
- Reconfirmed the commitment to malaria elimination by 2030 in the GMS

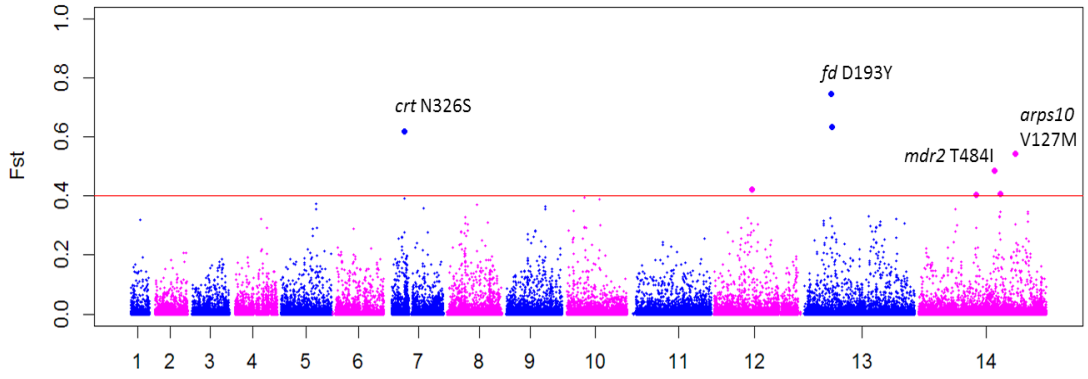
Validated	Candidates/ associated
F446I	P441L
N458Y	G449A
M476I	C469F
Y493H	A481V
R539T	P527H
I543T	N537I
P553L	G538V
R561H	V568G
C580Y	P574L
	F673I
	A675V

Relation between partner drug efficacy and K13 mutations

Year	Site	ACT	N	Efficacy 28/42 days (%)	K13 mutant (%)
2016	Kampong Speu, Kratie	Artesunate-mefloquine	69	100	95.6% (C580Y)
2017	Kampong Speu, Pursat, Stungtreng	Artesunate-mefloquine	170	99.5	78.2% (C580Y, R539T, Y493H)
2017	Ratanakiri, Mondulkiri	Artesunate-pyronaridine	123	97.6	72.4 (C580Y)
2017	Kachin, N. Shan	Artemether-lumefantrine	71	97.2	43.7 (F446I, R561H)

Distribution of C580Y mutations worldwide

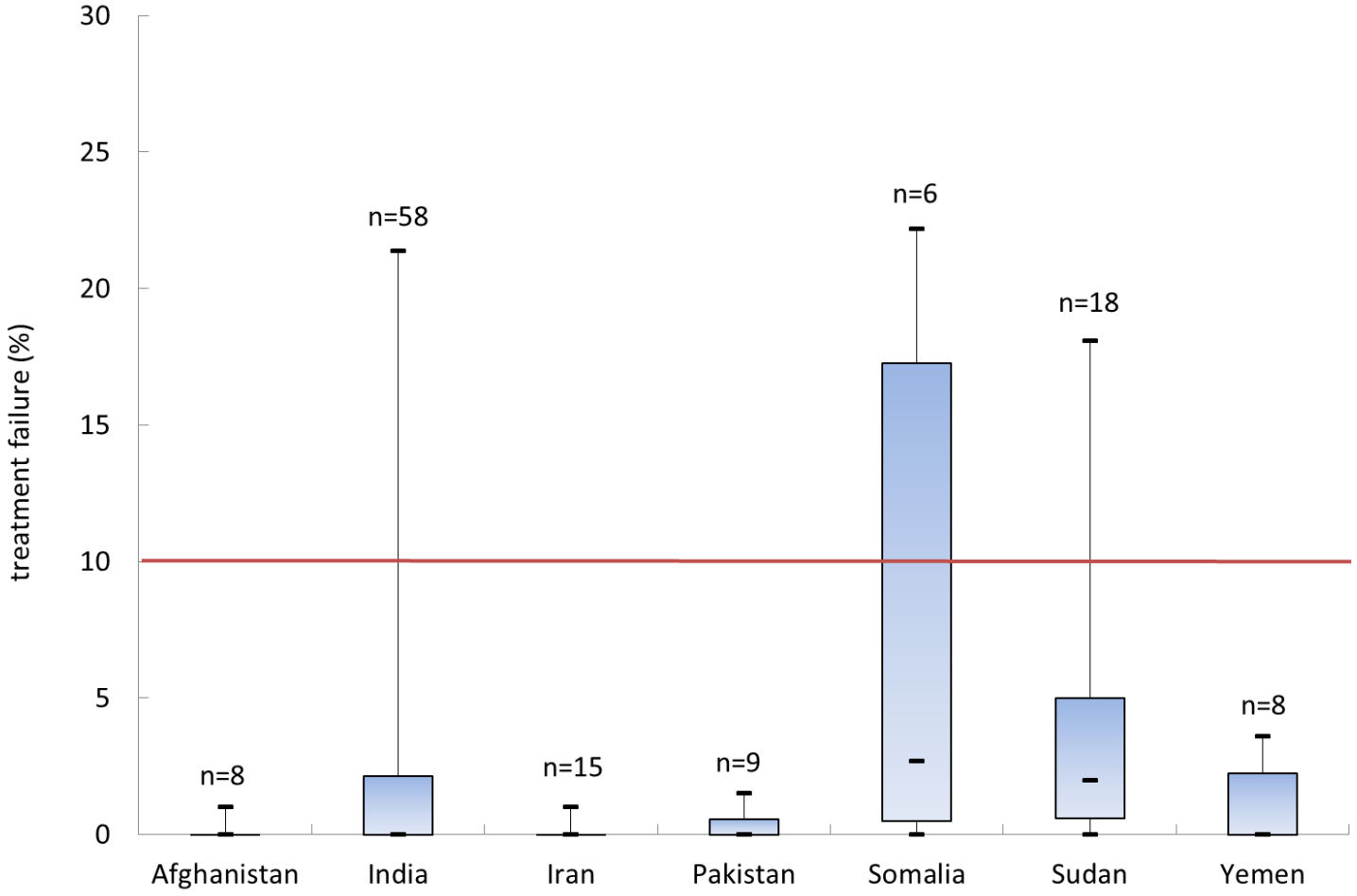




Possible “permissive” or compensatory background mutations

Miotto *et al.*, *Nature Genetics* 2015

Treatment failure rates with AS+SP (2005-2015)



- In India, Somalia and Sudan, treatment failure failures are associated with *Pfdhfr* and *Pfdhps* quadruple and quintuple mutants;
- These mutations are still rare in Afghanistan, IR Iran and Pakistan.

Consequences of artemisinin partial resistance

- Artemisinin resistance affects only ring stages of *P. falciparum* (no worsening seen over 15 years);
- Implication for the treatment of severe malaria (so far not increased mortality reported);
- 7-day artesunate > 90% efficacy;
- All 6 partner drugs are highly efficacious as monotherapy in absence of resistance;
- Increases the risk of de novo resistance to the partner drug and/or facilitate the selection of partner drug resistance: new evidence in GMS shows that artemisinin did not facilitate emergence of mefloquine or piperaquine resistance.

Recommended first-line treatment for falciparum