Integrated Drug Efficacy Surveillance (iDES):

Using routine case management and follow-up to monitor drug efficacy and resistance in Thailand

Present at JITMM 2018
S14 Current Status of Antimalarial Resistance and its Impact on Clinical Practice

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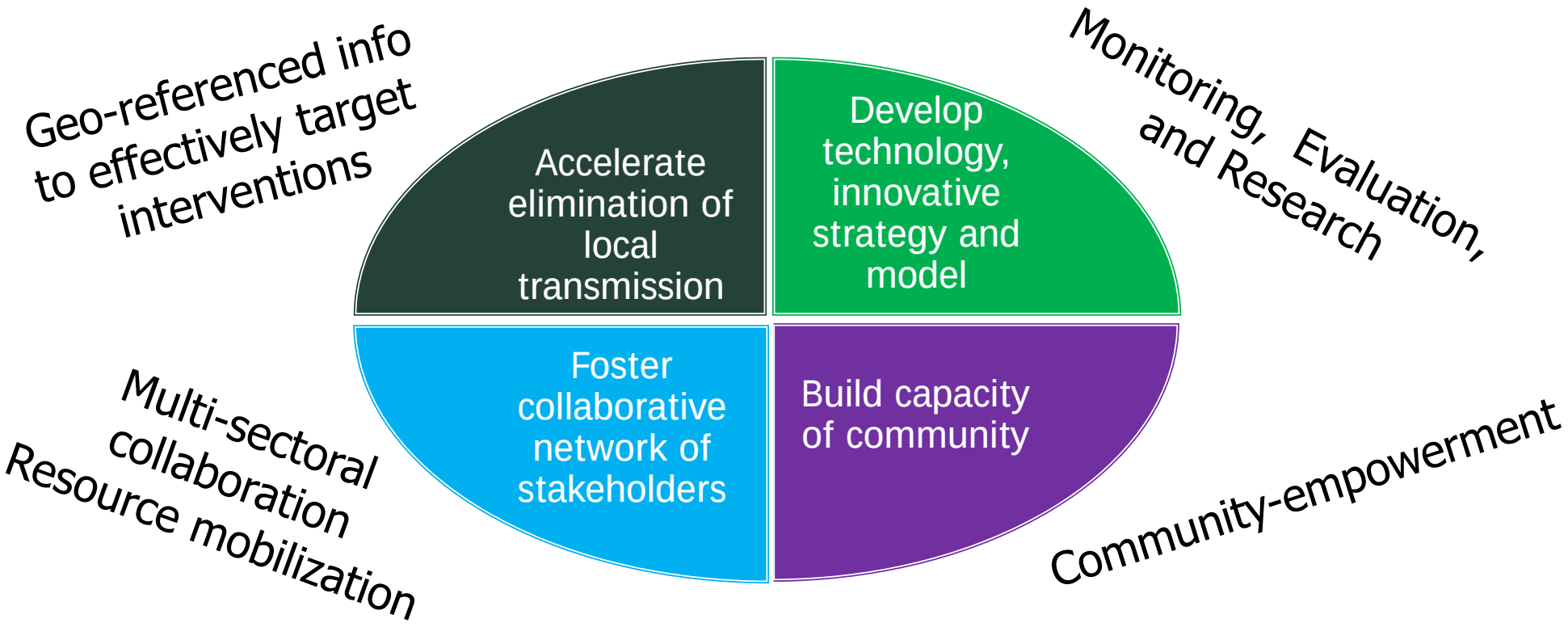
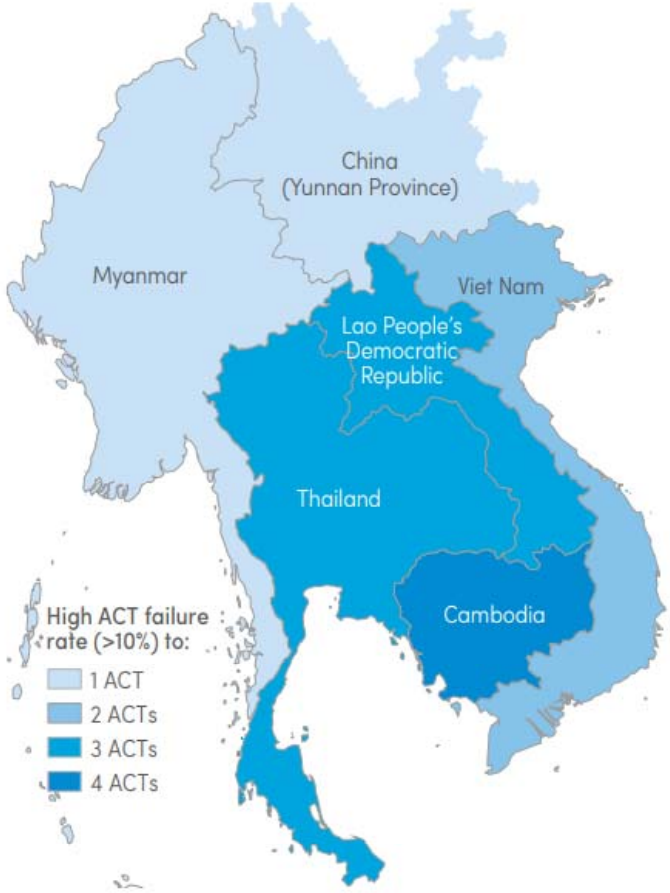
National Malaria Elimination Strategy: 2017-2026



Fiscal Year	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026
Percent and number of district / subdistrict with NO active foci	75 (696)	80 (743)	85 (789)	90 (836)	95 (882)	98 (910)	100 (928)	100 (928)	100 (928)	100 (928)

Current Malaria Situation and Drug Policy – 1

- Malaria cases declined from 23,668 to 7,209 (-70%) in Thailand from FY2015 to FY2018
- In 2014, WHO Therapeutic Efficacy Study (TES) reported >10% treatment failure rates with Artesunate+Mefloquine (AS+MQ)
- In 2015, National treatment policy changed to Dihydroartemisinin-Piperaquine (DHA-PIP)

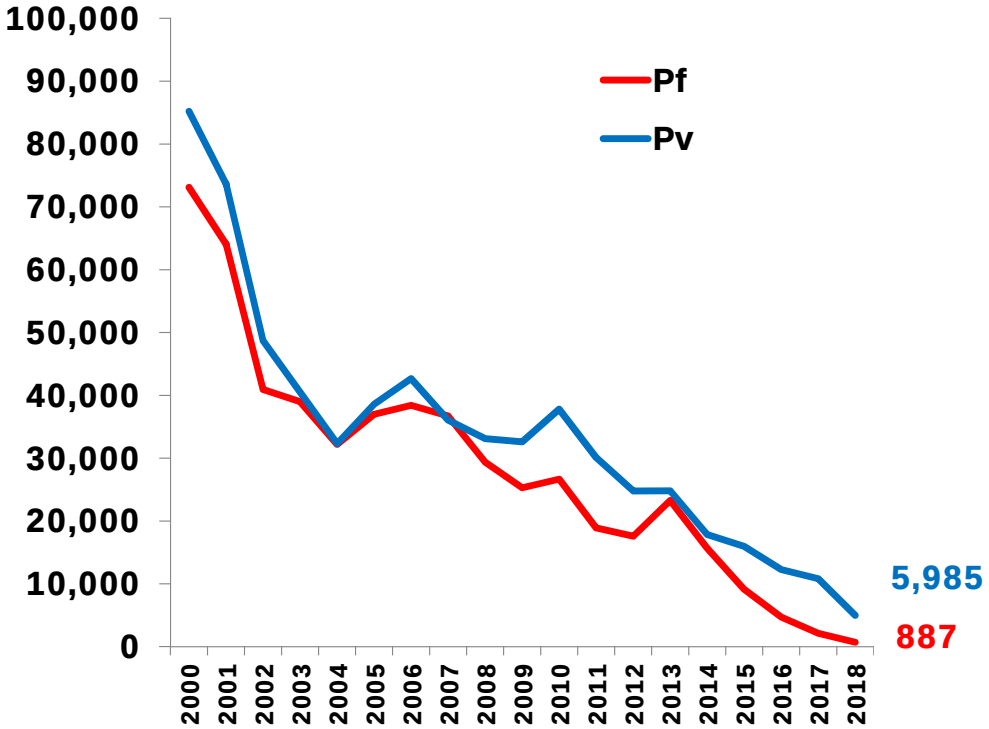


ACT, artemisinin-based combination therapy

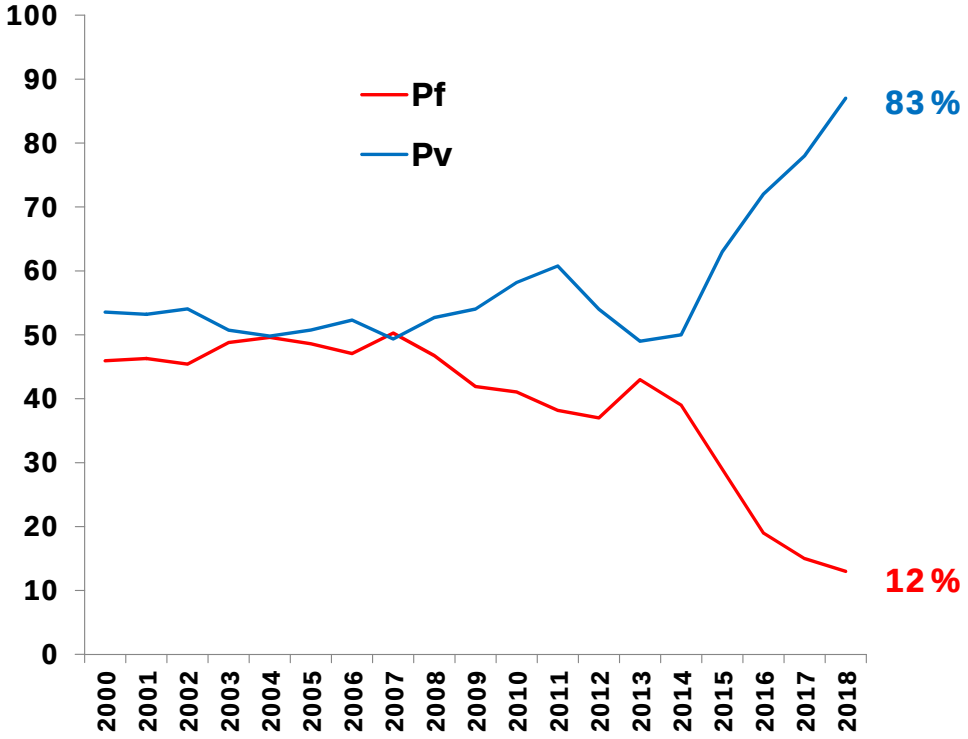
Source: WHO 2017, World Malaria Report

Current Malaria Situation and Drug Policy - 1

Malaria cases and proportion by species, 2000-2018



Source: BVBD, 13 December 2018



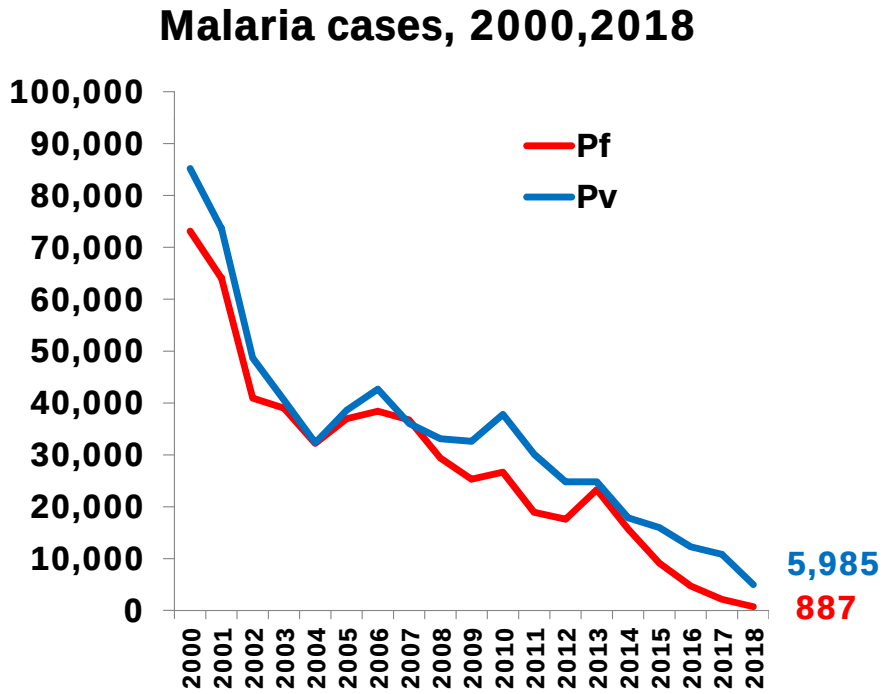
Source: WHO 2017, World Malaria Report

iDES in Malaria Elimination

- **Malaria elimination strategy**
  - All patient diagnosis by microscope or RDTs
  - Supervise treatment for all malaria cases
  - Ensure patient follow up and cure
- **From TES to iDES**
  - Low malaria cases
  - "Research to routine surveillance"

Objective

To utilize routine surveillance system for monitoring antimalarial drug efficacy for elimination



Source: BVBD, 13 December 2018

Work Flow for iDES

Registration
Suspected patients

Blood test
Microscope or RDT

Negative

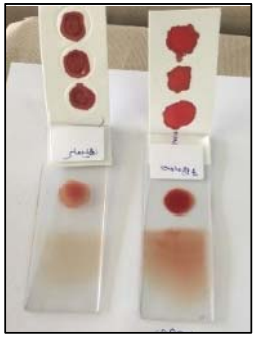
Refer to hospital

Positive (D0)
Thick/thin films
Blood spots

G6PD test

Deficiency

Normal



Supervise Treatment
- *Pf*: D 0, 1, 2
- *Pv*: D 0, 1, 2, 3-13

Follow up on schedule
- *Pf*: D 3, 7, 28, 42
- *Pv*: D 14, 28, 60, 90

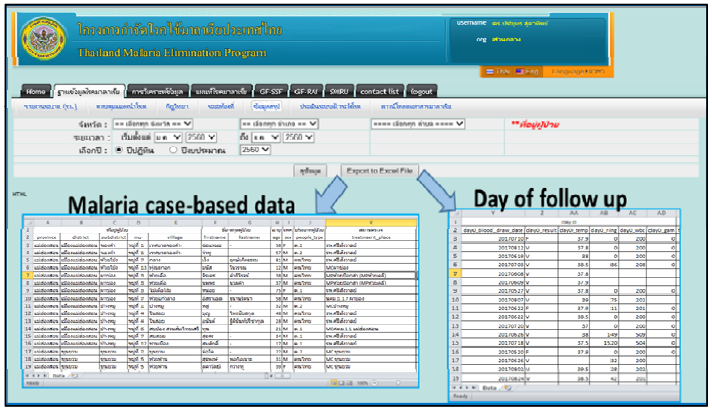
Thick/thin films
Blood spots

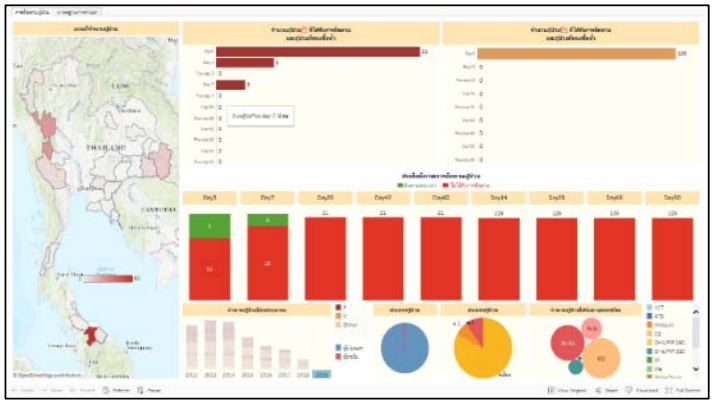
Parasite positive

Parasite clear

Monitoring and Supervision

- **Malaria online (login / password)**
  - Individual case → export to excel file
  - http://malaria.ddc.moph.go.th
- **Performance dashboards on MIS**
  - District level for local monitoring
- **Supervisory visits by regional and provincial health officers**



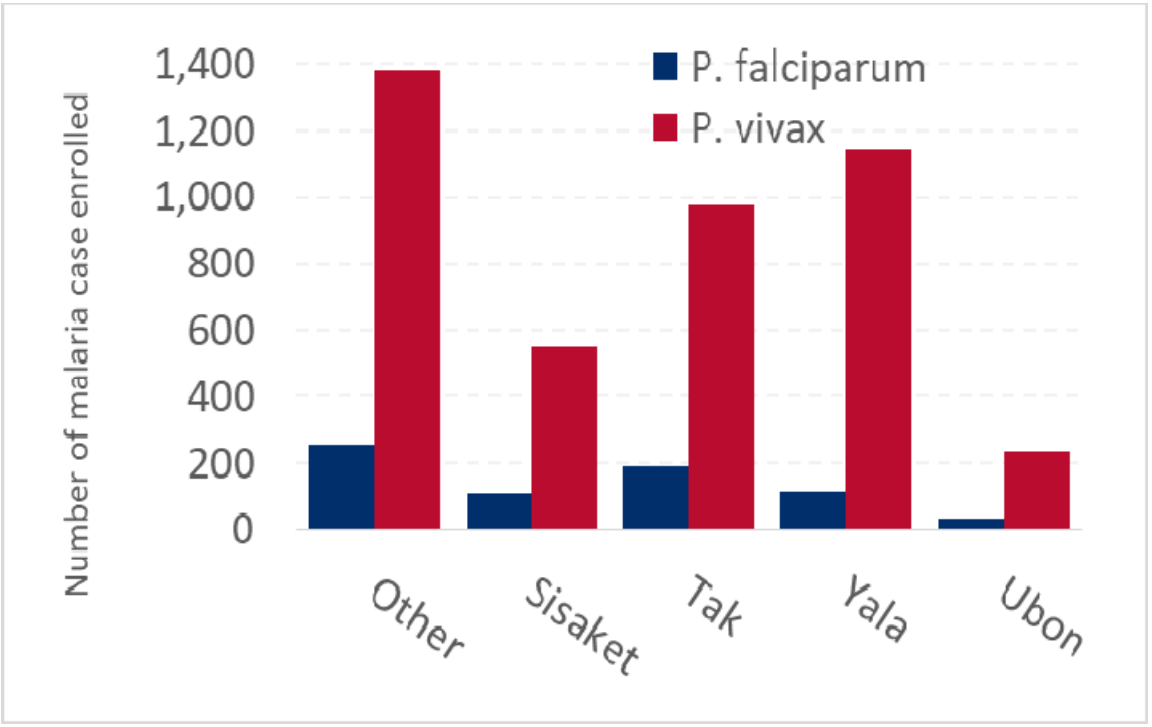


Drug Efficacy Evaluation Methods

- Start point: October 1st 2017
- Endpoint:
  - PV: up to August 29th 2018 (Day 90)
  - PF: up to October 16th 2018 (Day 42)
- Cases from all facilities
- Malaria results based on microscopy
- National Treatment Guideline (NTG)
  - ***P.f.*** = Dihydroartemisinin-Piperaquine + Primaquine
  - ***P.v.*** = Chloroquine + Primaquine
- Follow-up schedule
  - Pf = Day 0, Day 3, Day 7, Day 28, Day 42
  - Pv = Day 0, Day 14, Day 28, Day 60, Day 90

- Survival analysis for treatment efficacy (not PCR corrected)
- Modified intent-to-treat, ITT
  - Pf: endpoint day 42
  - Pv: endpoint day 90
- A treatment recurrent failure was defined as any of the following:
  - Recurrent parasitaemia i.e. a conversion from a positive to a negative smear result
    - Recurrent Pf within 42 days
    - Recurrent Pv within 90 days
- Molecular analysis (planned activity)
  - PCR confirm parasite detection and species
  - *P. falciparum* detect K13, *msp1, msp2*

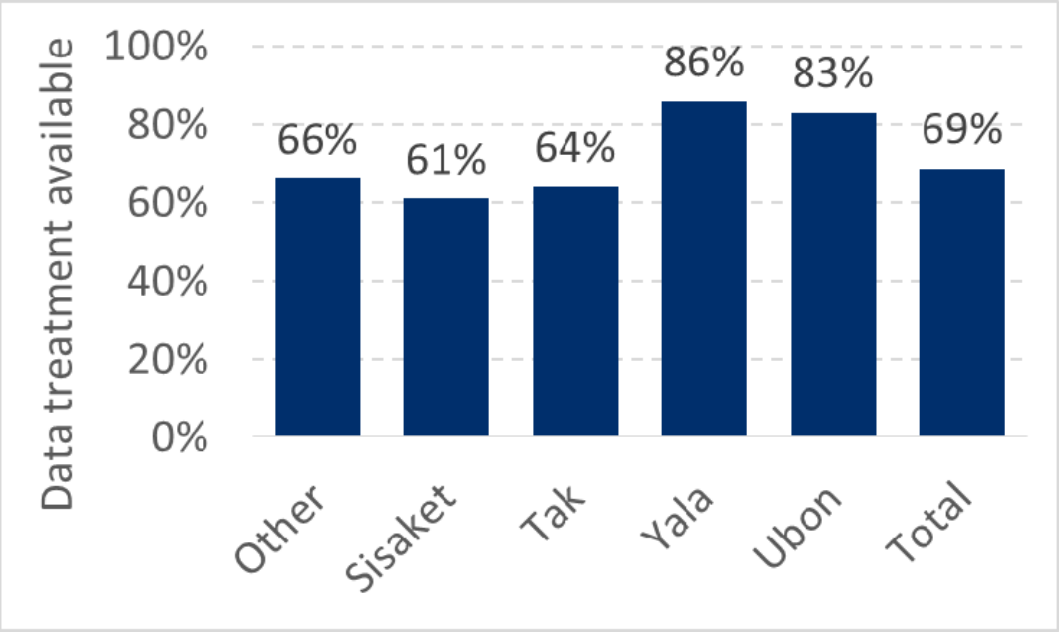
Malaria case characteristics



- By endpoint Oct 2018
  - 5,101 cases
    - 699 Pf cases
    - 4,287 Pv cases
    - 59 other spp.
- 14% of Pf cases
- Greatest number of cases in Tak (23%) and Yala (25%)
- Median age: 30 years old
- 20% of the cases were women
- 78% of the cases were Thai nationals
- 80% treatment data available

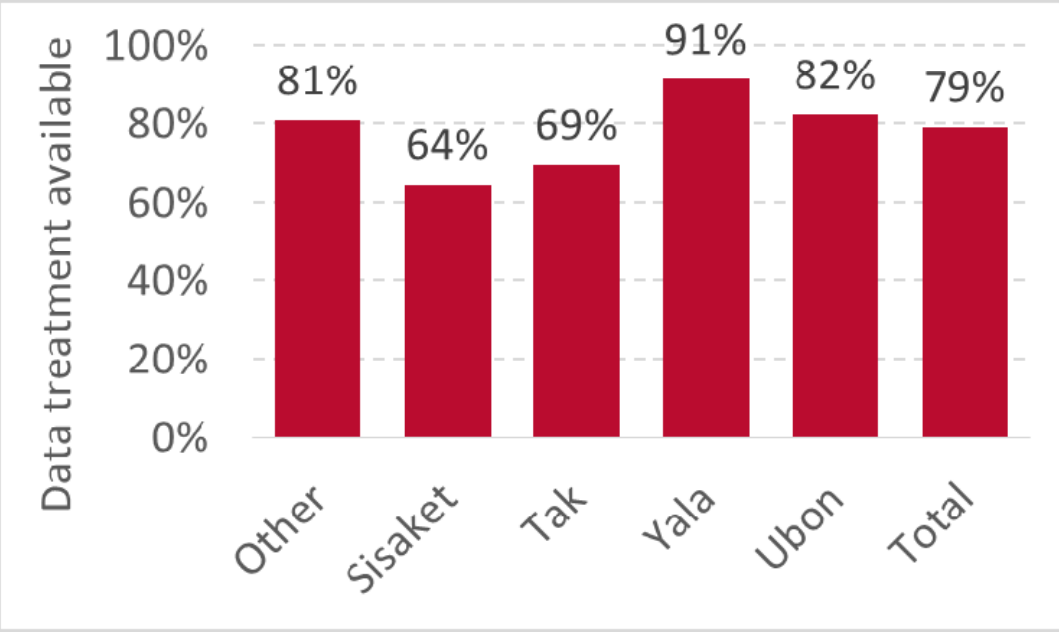
NTG treatment compliance by province

- *P. falciparum*
  - 69% compliance to NTG



Total Pf cases	253	110	189	112	32	699

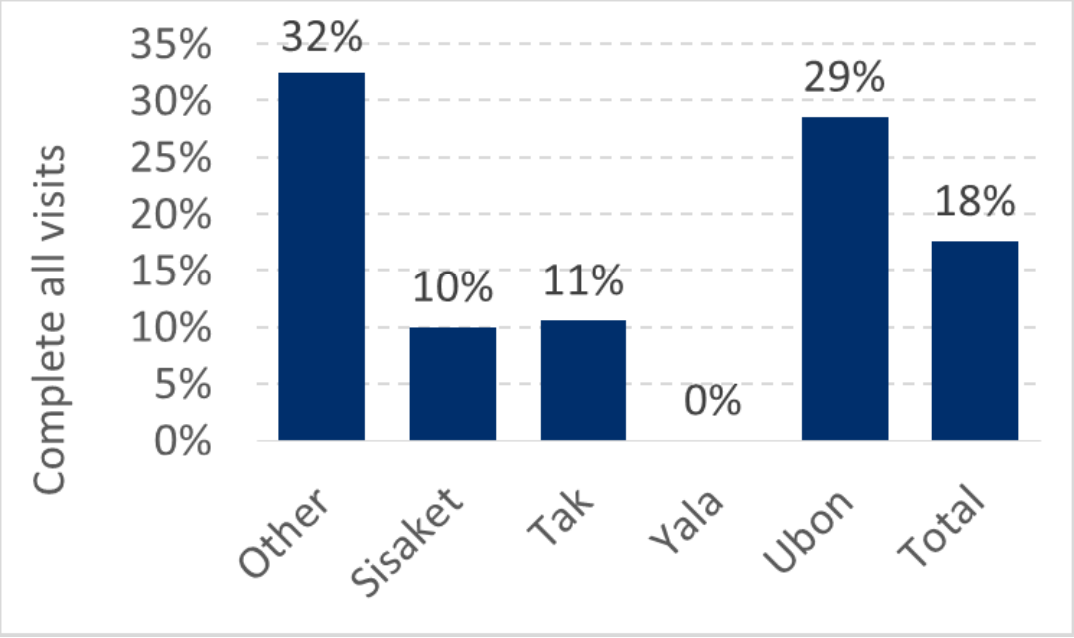
- *P. vivax*
  - 79% compliance to NTG



Total Pv cases	1381	551	974	1145	236	4287

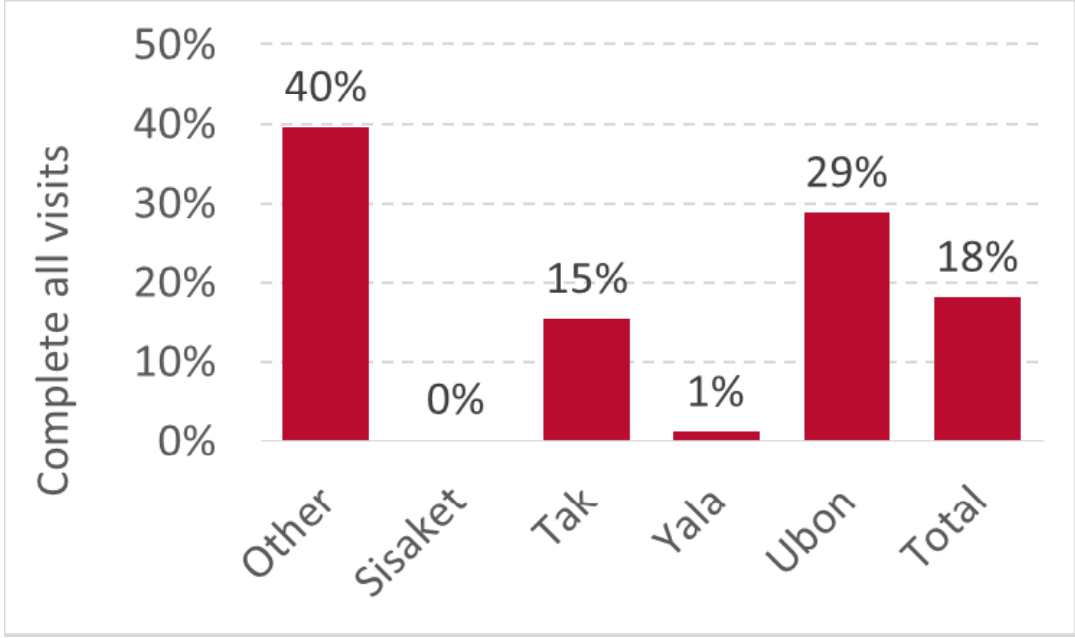
Completeness of FU schedule according to NTG (4 visits) by province

- ***P. falciparum*** **: 18 %**



Total *Pf* case	253	110	189	112	32	699

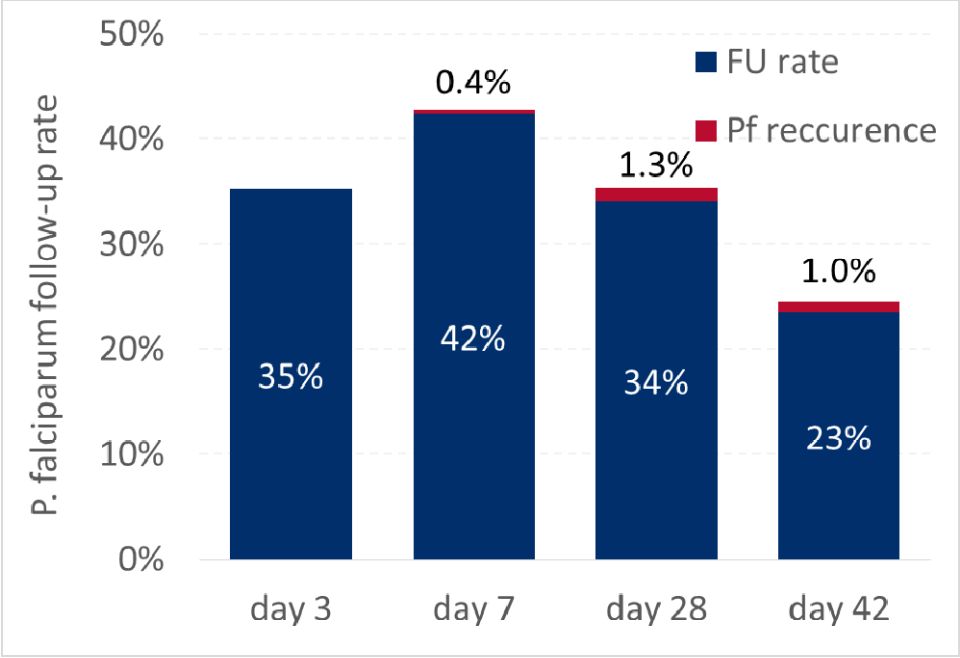
- ***P. vivax:*** **18 %**



Total *Pv* case	1,381	551	974	1,145	236	4,287

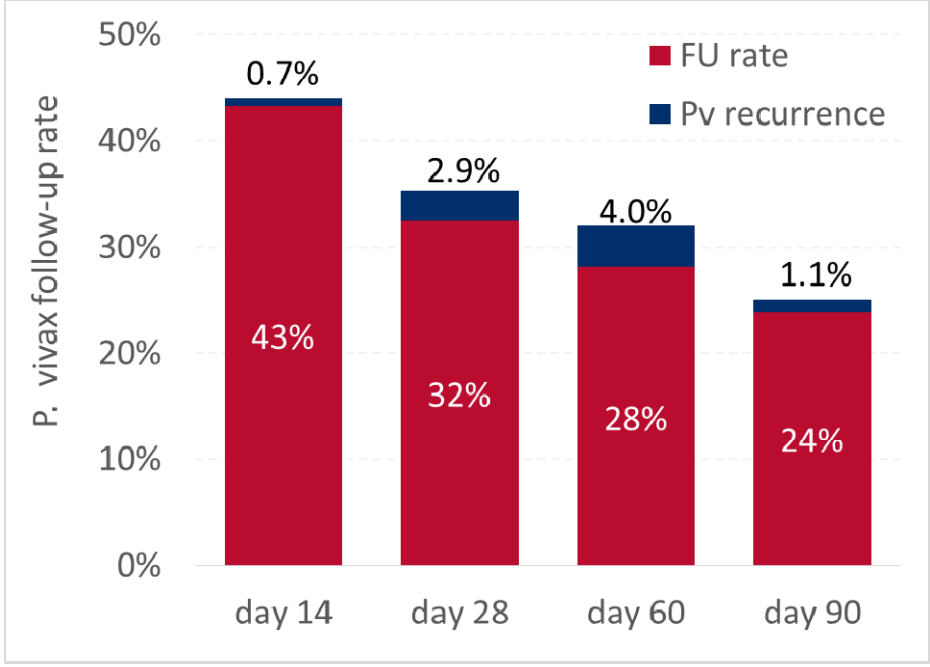
Follow-Up Rate and Parasite Recurrence (All regimens)

- *P. falciparum* (n= 699)
- *P. falciparum* parasitological recurrence occurred between Day 7 and Day 42



FU Day	Day 3	Day 7	Day 28	Day 42
No. *Pf* FU	246	296	238	164
Pf Recurrence	0	3	9	7

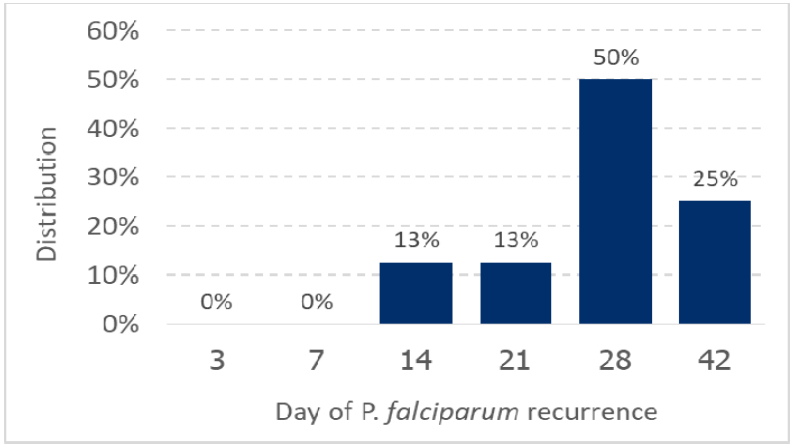
- *P. vivax* (n= 4,287)
- P. *vivax* parasitological recurrence occurred between Day 14 and Day 90



FU Day	Day 14	Day 28	Day 60	Day 90
No. *Pv* FU	1,854	1,391	1,201	1,022
Pv Recurrence	5	20	28	8

Parasite Recurrence for patients treated with NTG

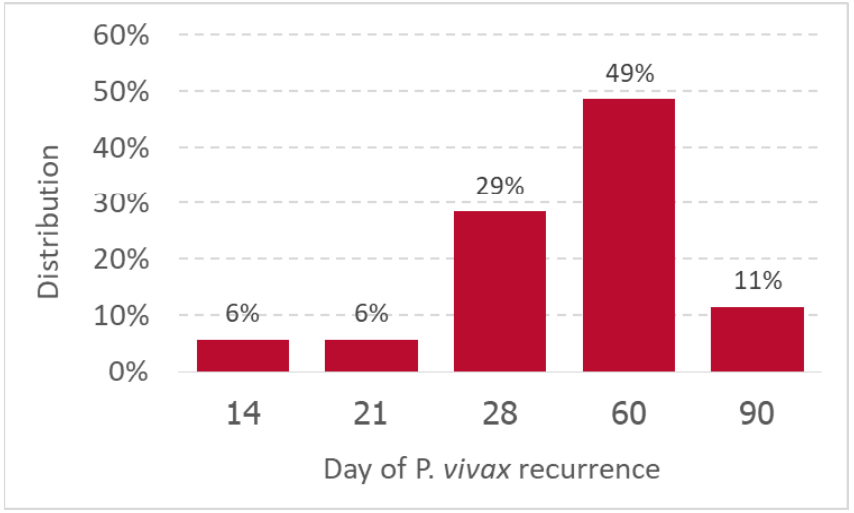
- *P. falciparum* (n= 8) DP+P
- *P. falciparum* parasitological recurrence occurred between Day 7 and Day 42
- Provinces with recurrence: Sisaket (5); Ubon Ratchathani (1); Suratthani (2)



Pf FU	163	202	61	145	102
No. Pf recurrence	0	1	1	4	2

D14 and D21: out-of-scheduled visits

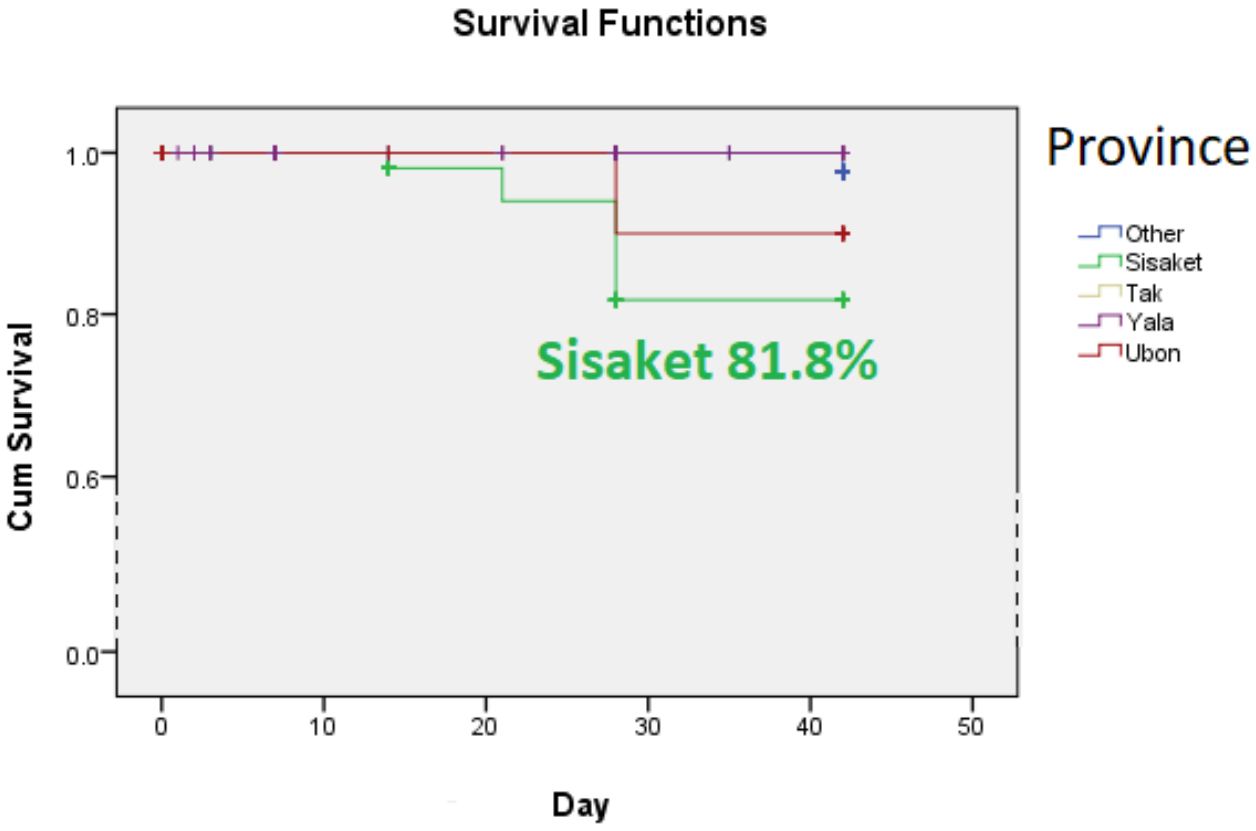
- *P. vivax* (n= 35) CQ+P
- P. *vivax* parasitological recurrence occurred between Day 14 and Day 90



Pv FU	1,529	46	1,095	925	794
No. Pv recurrence	2	2	10	17	4

D21: out-of-scheduled visit

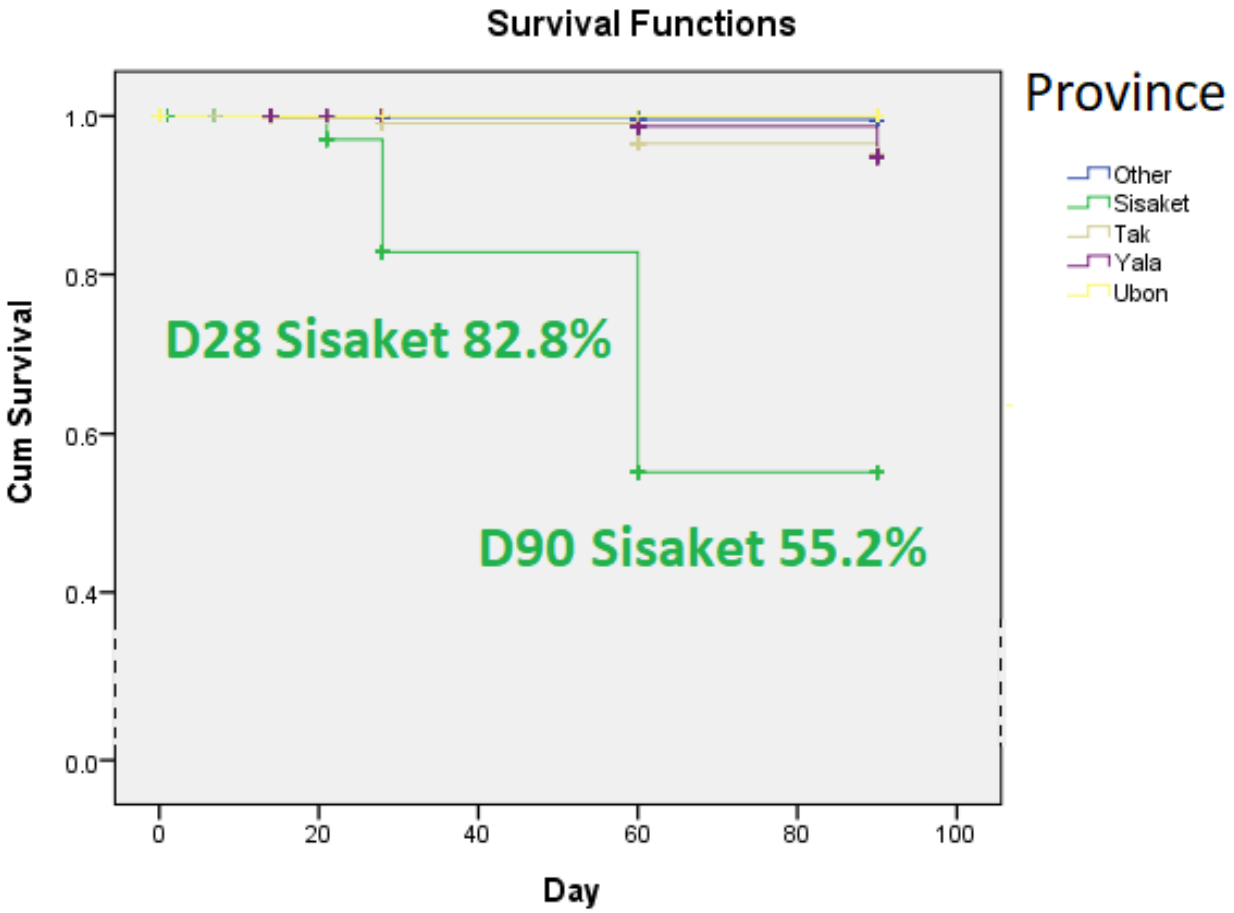
P. falciparum Drug Efficacy (Dihydroartemisinin-Piperaquine)



- P. *falciparum* (n=402)
- Modified ITT analysis
- Kaplan-Meier Survival analysis Day 42
- Overall DP: 94.7% (95%CI 89.9-98.9)
- Graph (95%CI, total number of cases):
  - Tak: 100% (95.6-100, n=67)
  - Yala: 100% (96.3-100n=79)
  - Ubon: 90.0% (71.4-100, n=27)
  - Sisaket: 81.8% (78.7-84.9, n=61)
  - Other: 97.6% (94.1-100, n=103)
  - p=0.003, log rank test

Remark: Not PCR corrected

P. vivax Drug Efficacy (Chloroquine + Primaquine)



- P. *vivax* only (n=3,386)
- Modified ITT analysis
- Day 90 Kaplan-Meier Survival analysis
- Overall: 99.1% (95%CI 98.5-99.7)
- Graph (95%CI, total number of cases):
  - Ubon 100% (98.5-100, n=194)
  - Other: 99.4% (98.8-100, n=1116)
  - Tak: 95.0% (91.9-98.1, n=676)
  - Yala: 94.7% (86.9-100, n=1045)
  - Sisaket: 55.2% (39.1-71.3, n=355)
  - p=0.001, log rank test

Remark: Not PCR corrected

OTHER RESEARCH

AFRIMS

- Cases in MIS in Sisaket (2018): 15% military; 13% traveled to Cambodia/border; 95% in 3 districts border with Cambodia
- Molecular analysis of Sisaket samples
  - Increased *plasmepsin2* copy number (CN) and *Pf crt* F145I mutations
  - Low frequency of parasites with multiple copy number of *Pf mdr1*

MORU

- Clinical trial in Phusing hospital (Aug 2017) in Sisaket showed treatment failures with DHA-PIP

Conclusion

- Preliminary results suggested that iDES has benefit for monitoring drug efficacy in Thailand for malaria elimination
- Overall, first line treatment for *P. falciparum* and *P. vivax* performed well except in Sisaket province, Cambodian border
- Other lines of evidence suggest treatment failure of DHA-PIP in Sisaket, but more analysis is needed.
- Use patient ID to match routine surveillance with clinical research (20% failure rates in iDES vs much higher (~80%) in studies

Next steps

- Need more analysis for Sisaket and provinces along the Cambodian border
  - Treatment compliance (patients and health staff)
  - Confirmation of slides and QA/QC microscopy
  - Molecularly analyses of DBS
- Conduct TES for alternative antimalarial drugs for Pf treatment in Sisaket
- Need to improve treatment compliance and follow-up rates (health staff and patients)
  - Involve village health volunteers to conduct case follow-up
  - Improve notification of cases treated at the hospitals and community-based clinics

THANK YOU

FOR YOUR ATTENTION

Acknowledgement:

- Hospitals and malaria program staff
- Inform Asia: USAID's Health Research Program
- Julien Zwang, RTI International
- Dr. Pascal Ringwald WHO GMP HQ