Integrated approach to malaria control during malaria elimination in the Greater Mekong Sub-region

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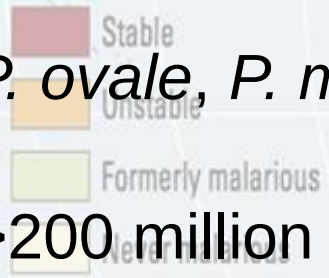
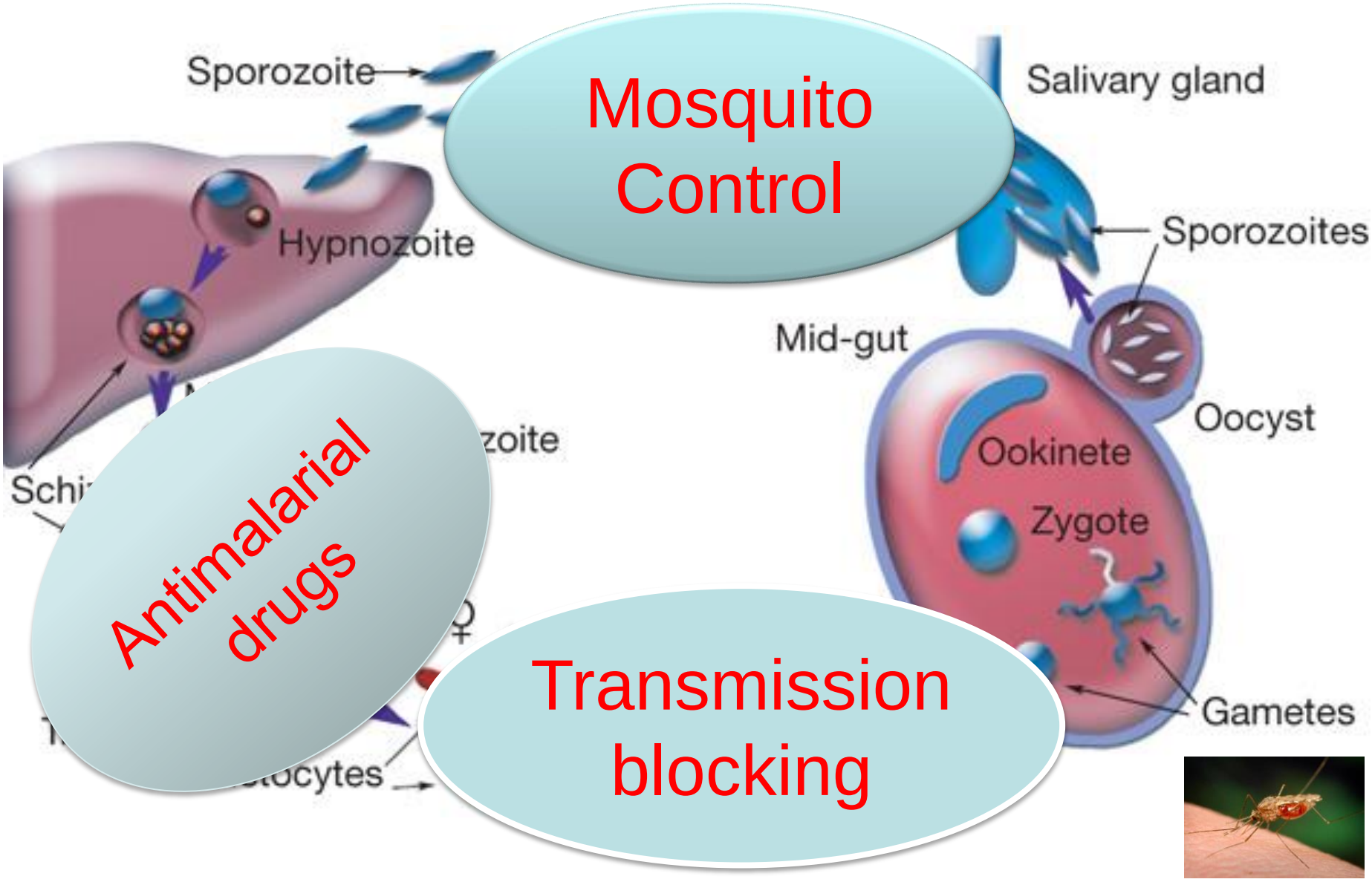
Human Malaria

- Malaria is a life-threatening vector-borne disease
- It is widespread in tropical and subtropical regions, including parts of Africa, Asia and the Americas
- Five species of *Plasmodium: P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae, P. knowlesi*
- >200 million cases and ~500,000 deaths (World Malaria Report 2018)

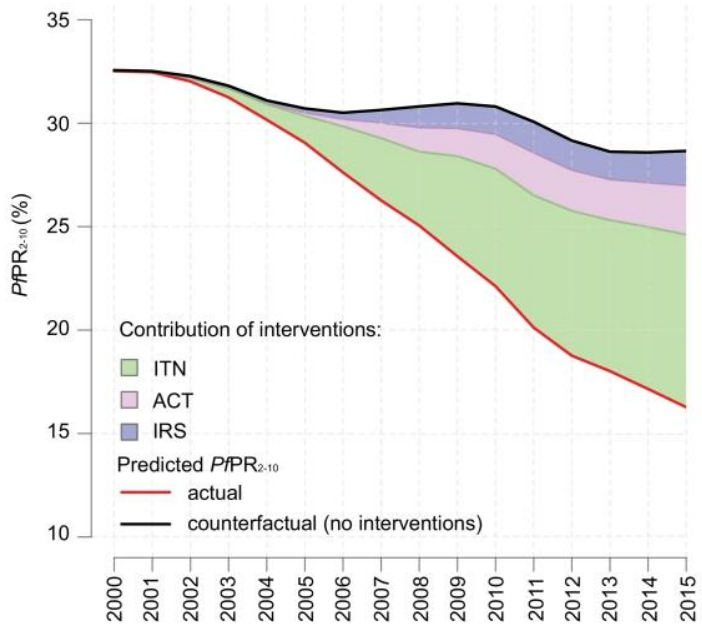


Malaria Parasite Life Cycle



EA Winzeler Nature 455, 756-751 (2008) doi:10.1038/nature07361

Effect of Control Efforts on Parasite Rate Reduction

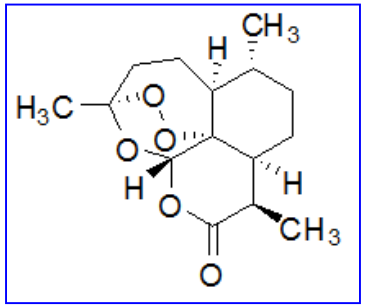


Parasite rate

Insecticide-treated nets

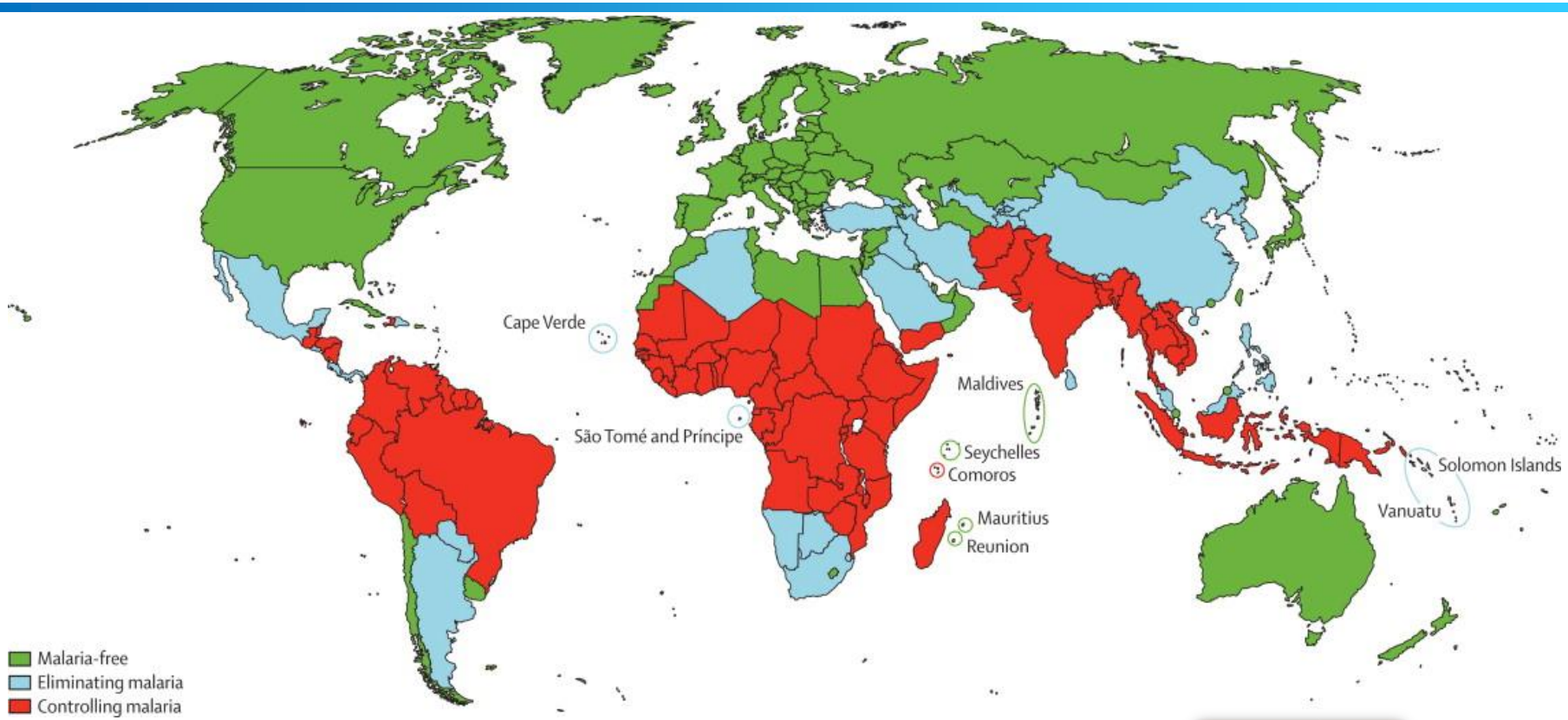
Indoor residue spray

Artemisinin combination therapy



Bhatt et al. 2015 Nature

From Malaria Control to Elimination



Slide Positive Rate <5% in fever cases

<1 case/1000 population at risk/year

0 locally acquired cases

WHO Certification

3 years

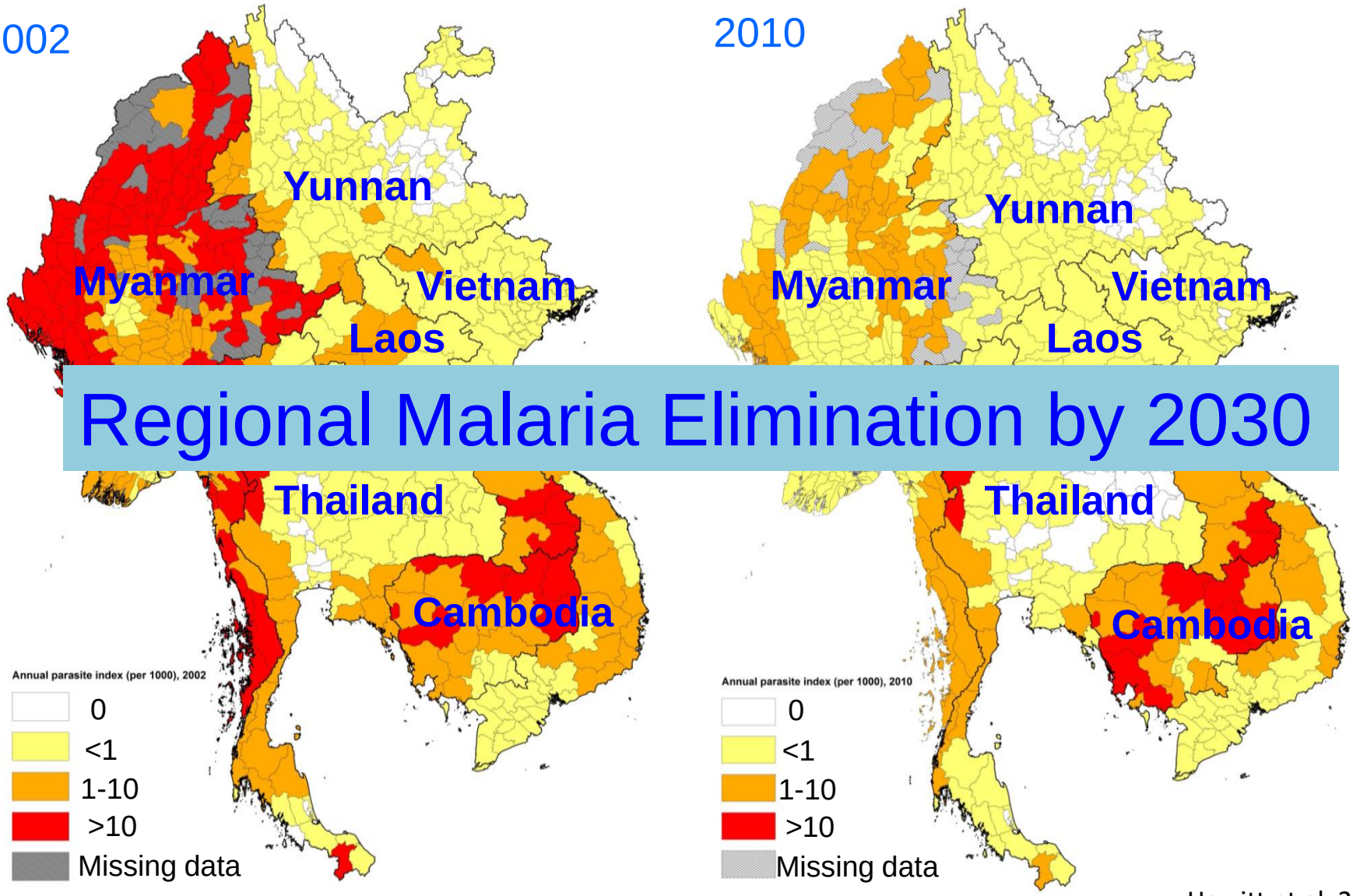
Control → **Pre-Elimination** → **Elimination** → **Prevention of Reintroduction**

67 countries

23 countries

Malaria Program Phases and Milestones, WHO

Malaria in the Greater Mekong Subregion



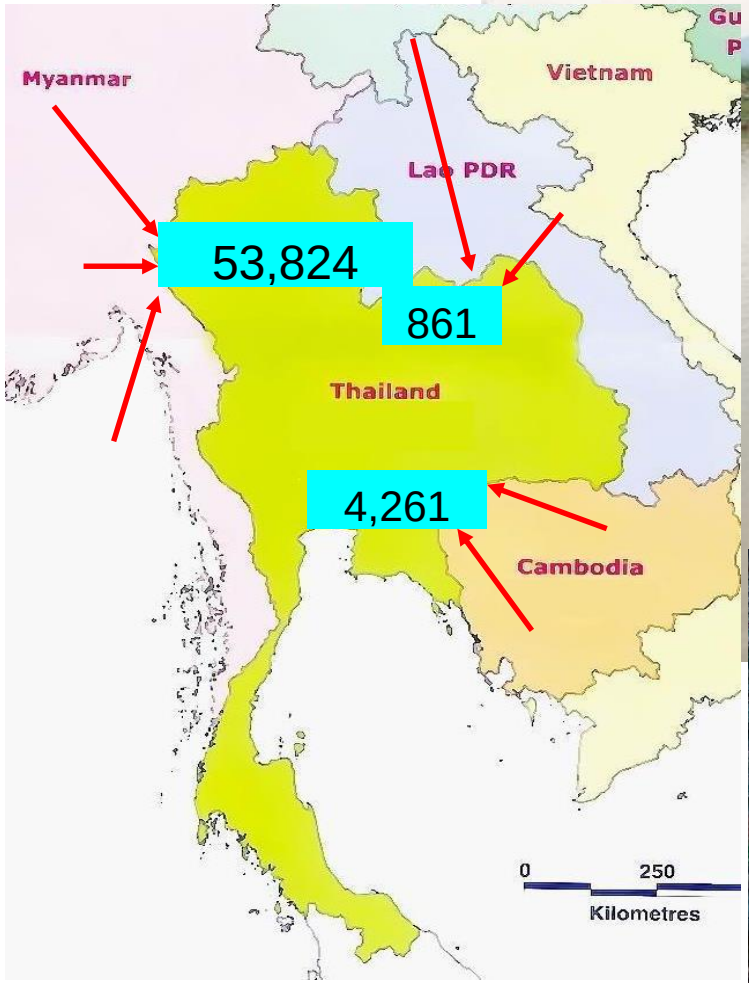
Regional Malaria Elimination by 2030

Hewitt et al. 2013

The Challenges

- Malaria epidemiology: border malaria
- Complex vector systems: outdoor transmission
- Epicenter of multidrug resistance
- Fake artemisinins

Border Malaria: Introduction by Migrants



Malaria among Ethnic Minorities

A large proportion of the hill-tribe ethnic minorities (~1/3) live in the remote, often hilly and forested border areas

Wa – 5,000
Ximeng, Yunnan

Shan-Lahu-Aka – 15,000
Tachileik, Eastern Shan

Karen – 2,400
Sopmeoi, Maehongson

Map 1: Project Target Population in the GMS Countries

Brau-Taliang – 3,000
Phouvong, Attapeu

Kreung – 3,000
Rattanakiri

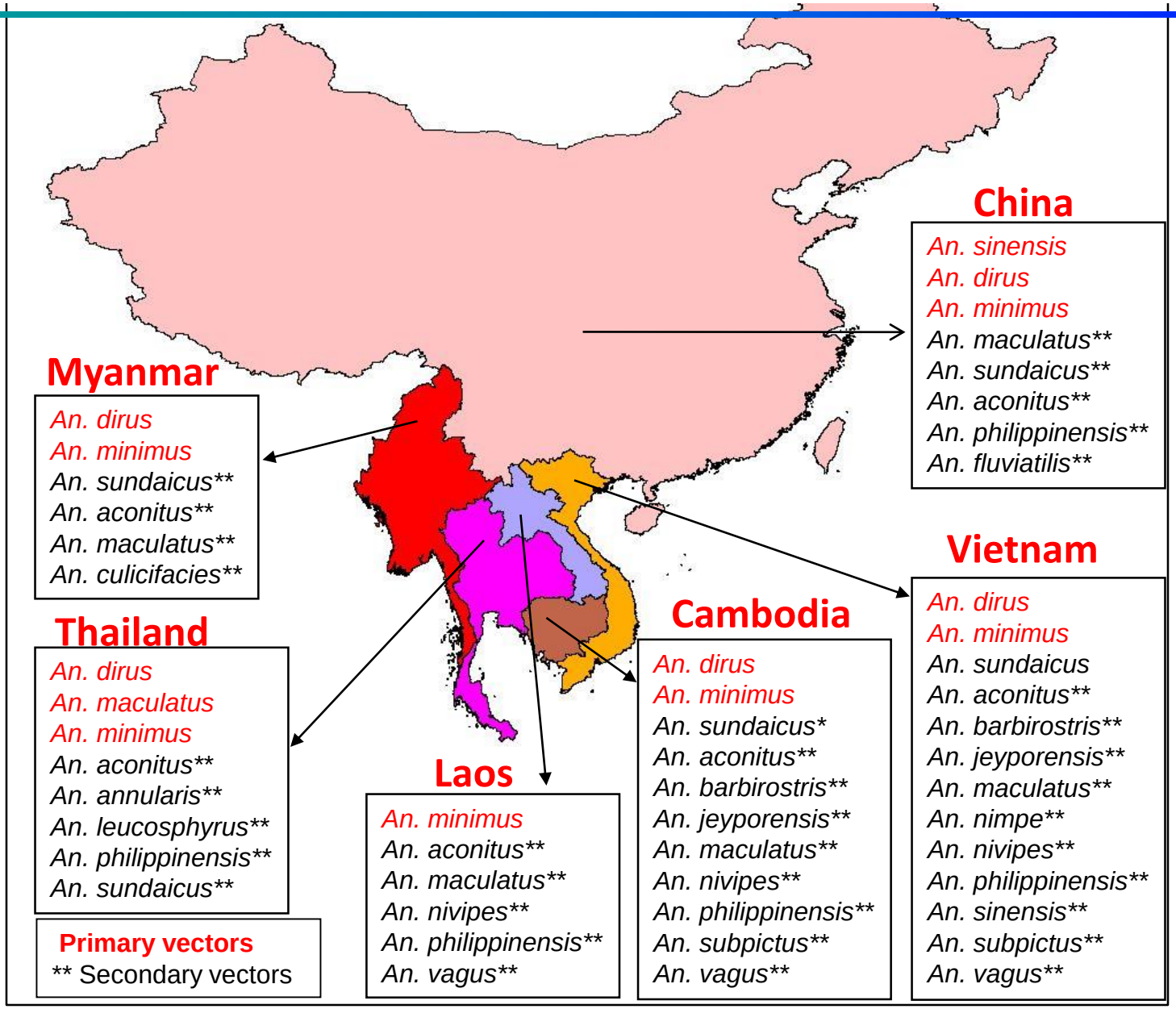
Raglai – 4,000
Khan Vinh, Khan Hoa

Border Malaria

Kachin village, Myanmar

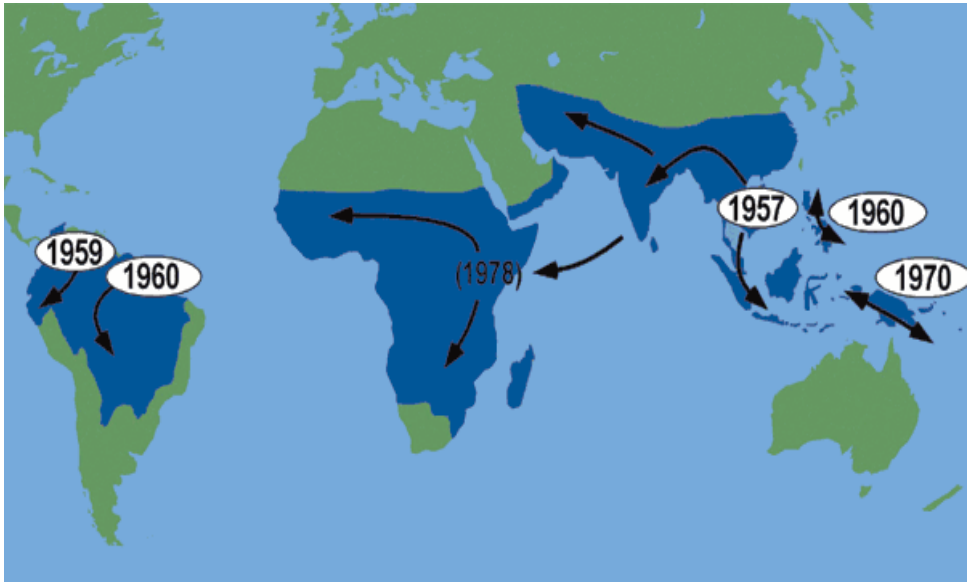
Karen village, Thailand

Diverse Malaria Vector Species



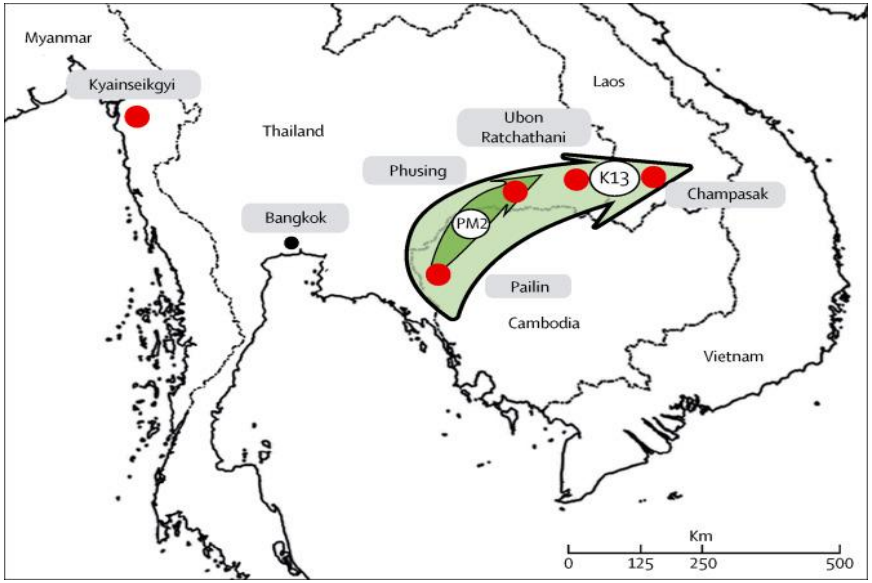
Epicenter Antimalarial Drug Resistance

Intercontinential Spread of Chloroquine Resistance



Wellems, 2004

Spread of Artemisinin Resistance in the GMS



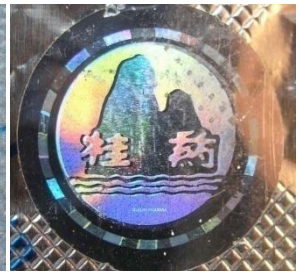
Imwong et al. 2017

Spread of Drug Resistance: An Imminent Threat

Counterfeit and Substandard Artemisinins

- **Multiple types of counterfeit artesunate tablets**
- **38-53% of artesunate blister packages sampled contained no active ingredients (Newton et al. 2003)**
- **Fake malarial drugs in Africa – global crisis**



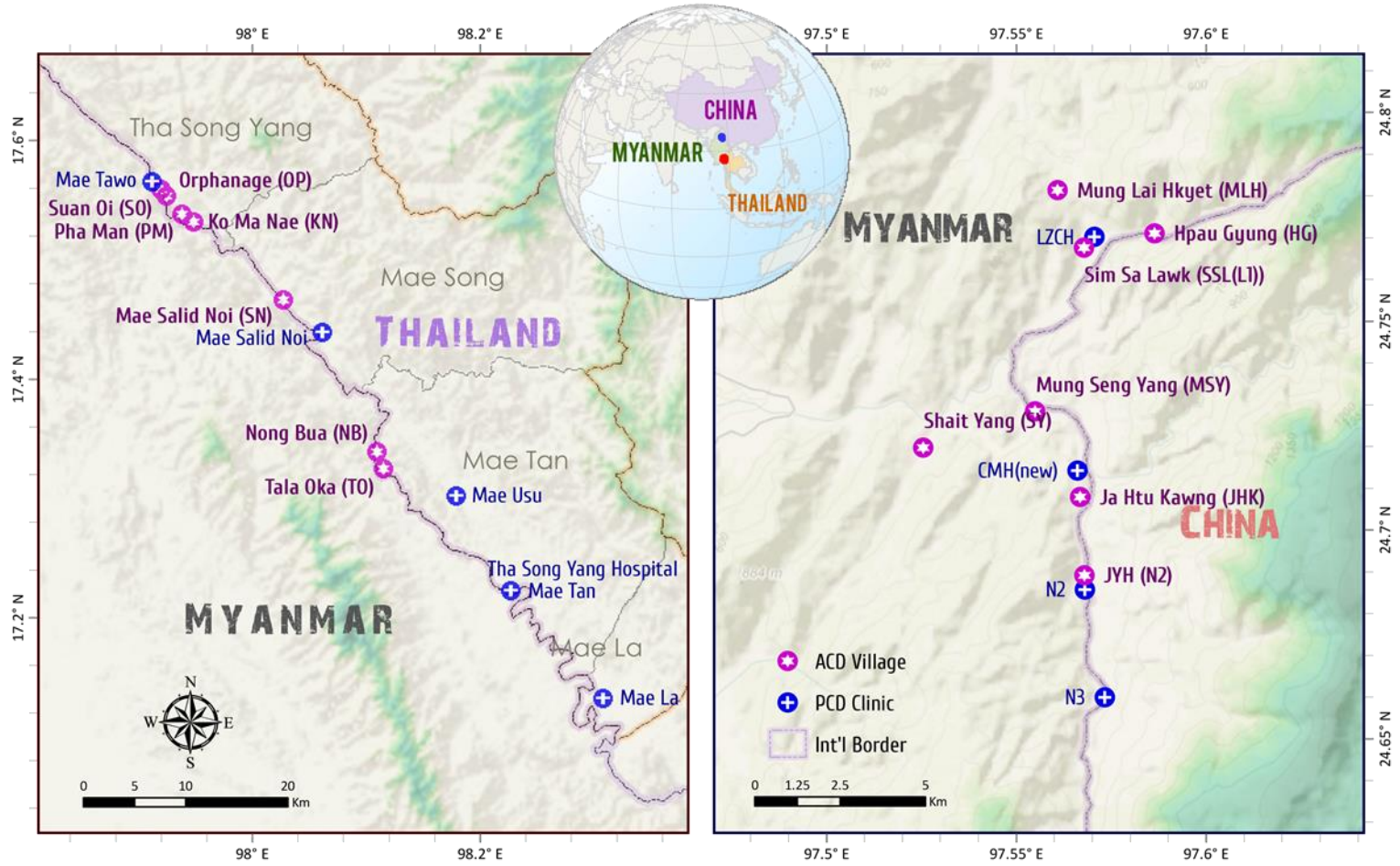




SE Asian ICEMR

- **Malaria Epidemiology:** Accurate quantitation of malaria epidemiology
- **Vector Biology:** effective management of vectors
- **Drug Resistance:** mechanism and surveillance of artemisinin resistance
- **Fake Artemisinins Detection Methods**

Addressing the Problem of Border Malaria

Thailand-Myanmar Border China-Myanmar Border



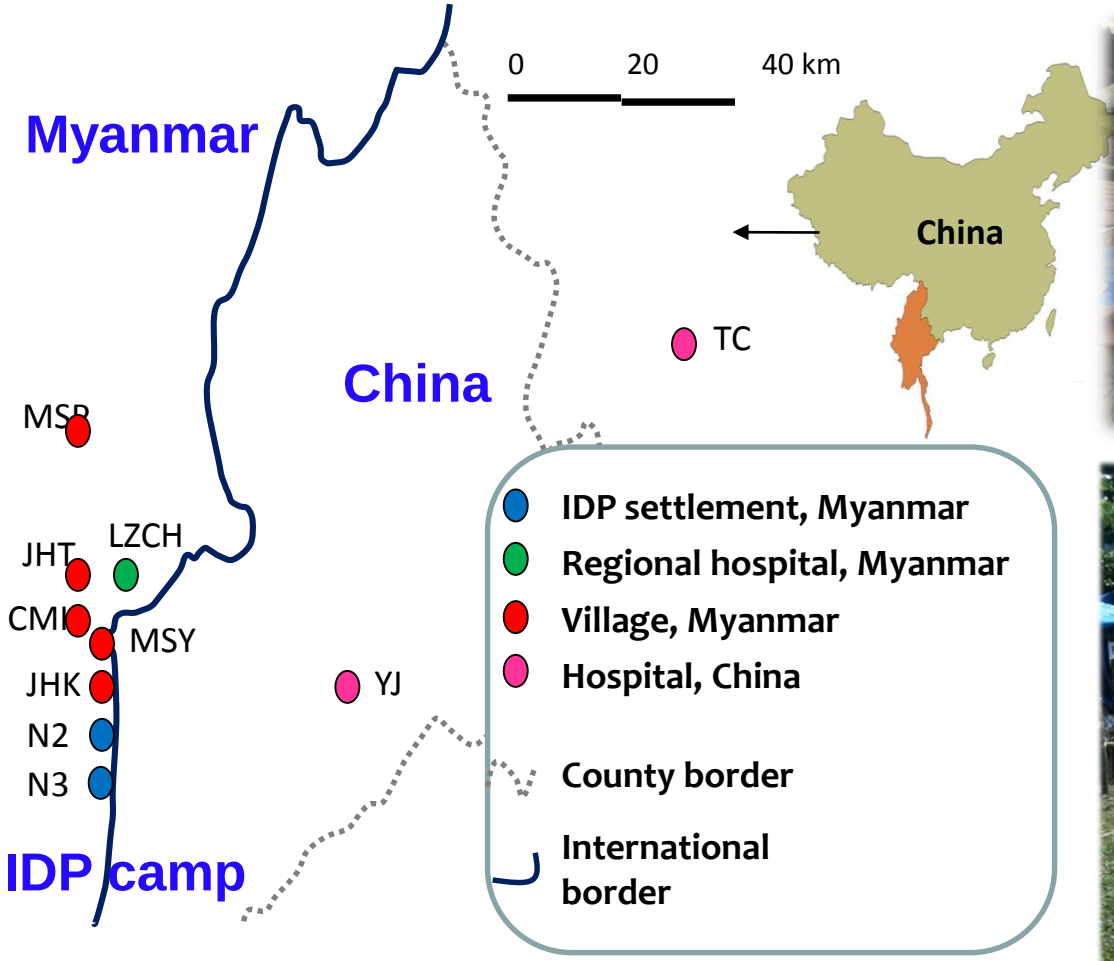
Malaria Surveillance at Study Sites along International Borders

PCD: Passive case detection in hospitals and clinics

ACD: Active case detection in border village communities (weekly and biweekly visits)

CSS: Cross-sectional surveys of prevalence of infections (pre-, peak- and post-peak seasons)

Camps for Internally Displaced People



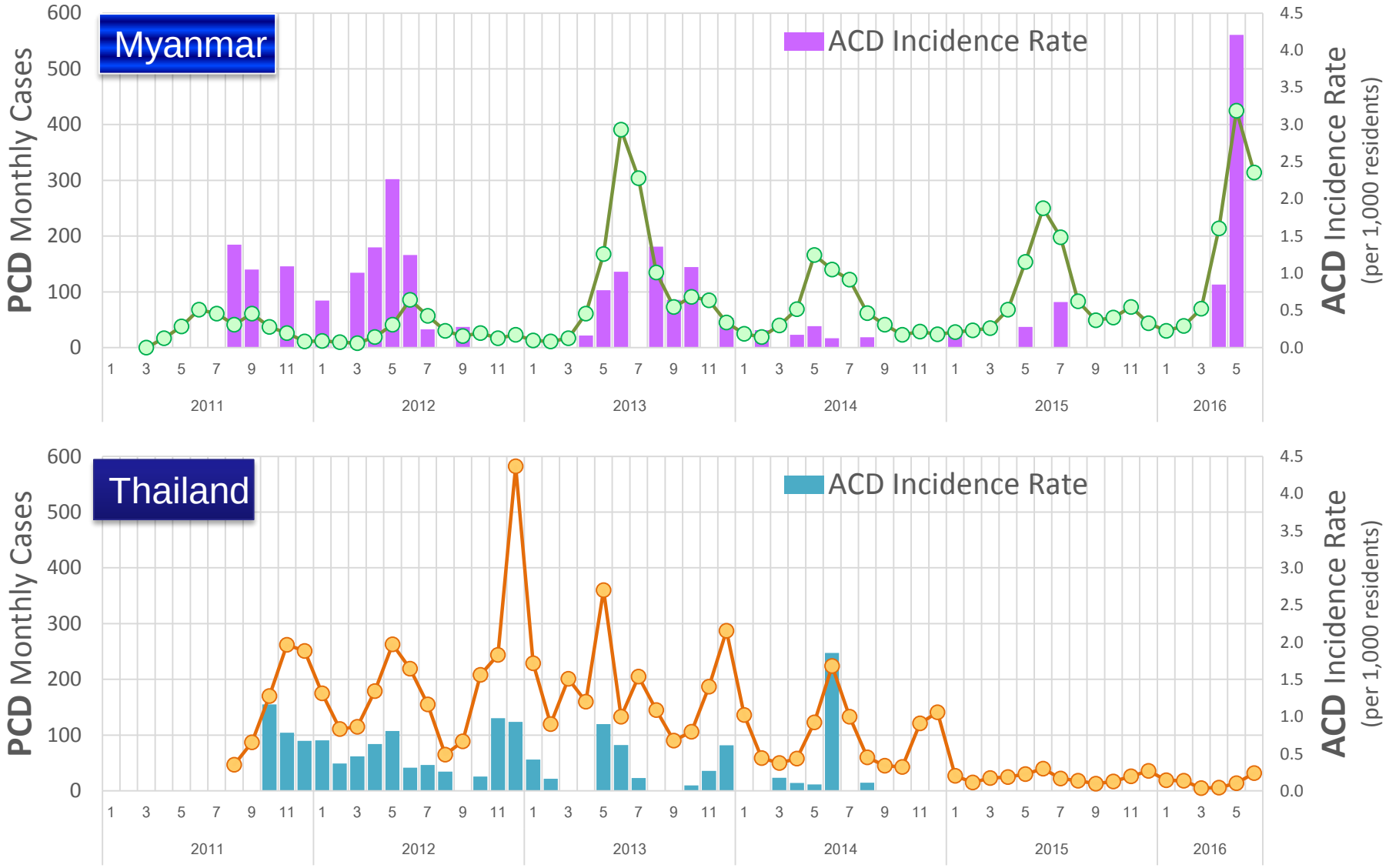
Establishment of Database Allows Timely Analysis of Malaria and Vectors

- Use case report forms and tablets for data collection and entry
- Online database allows effective sharing of data
- Timely data analysis to notify malaria control agencies




Monthly Case Dynamics: ACD & PCD

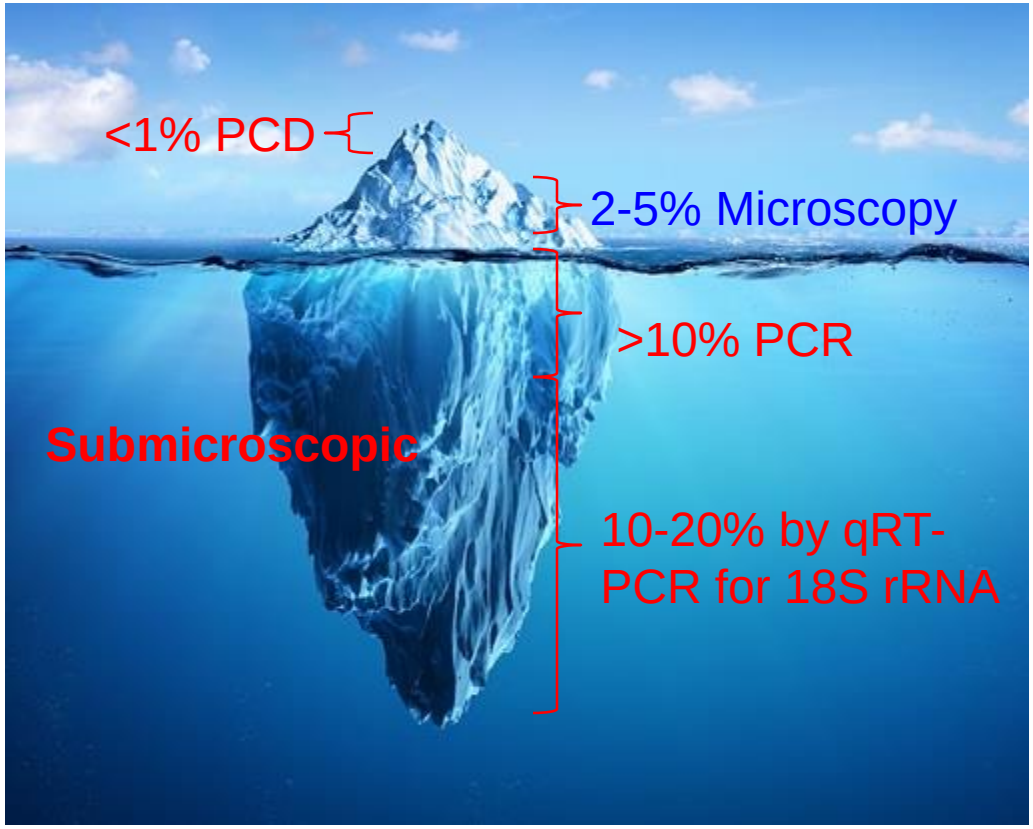
Data update: July 1, 2016



Changing Malaria Epidemiology – *P. vivax*

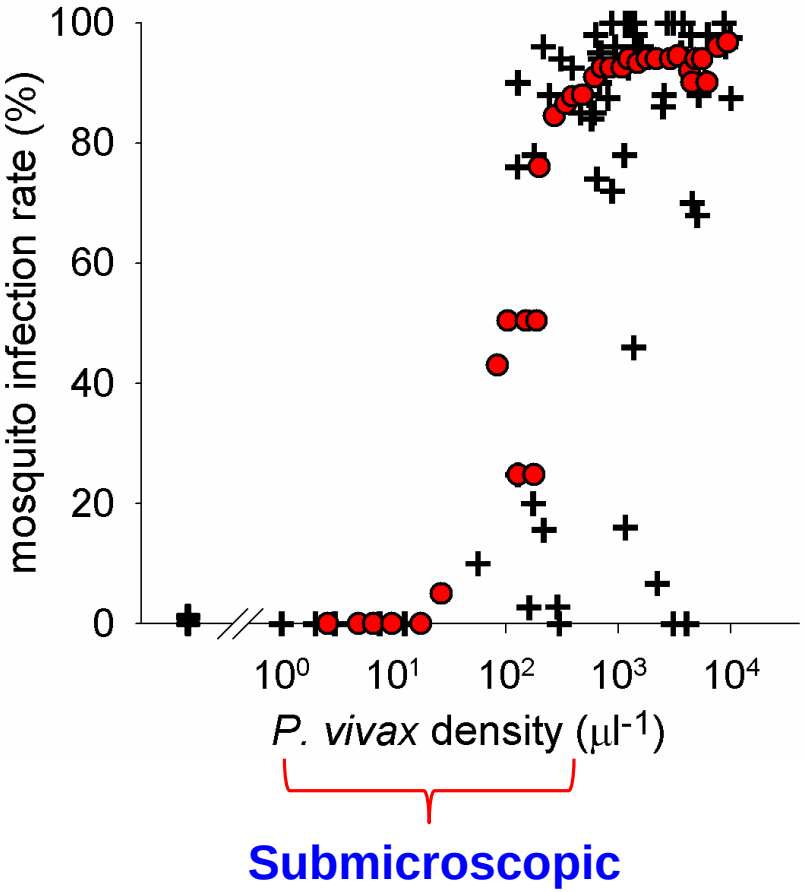
CSS: Microscopy vs. qPCR

Acute Asymptomatic

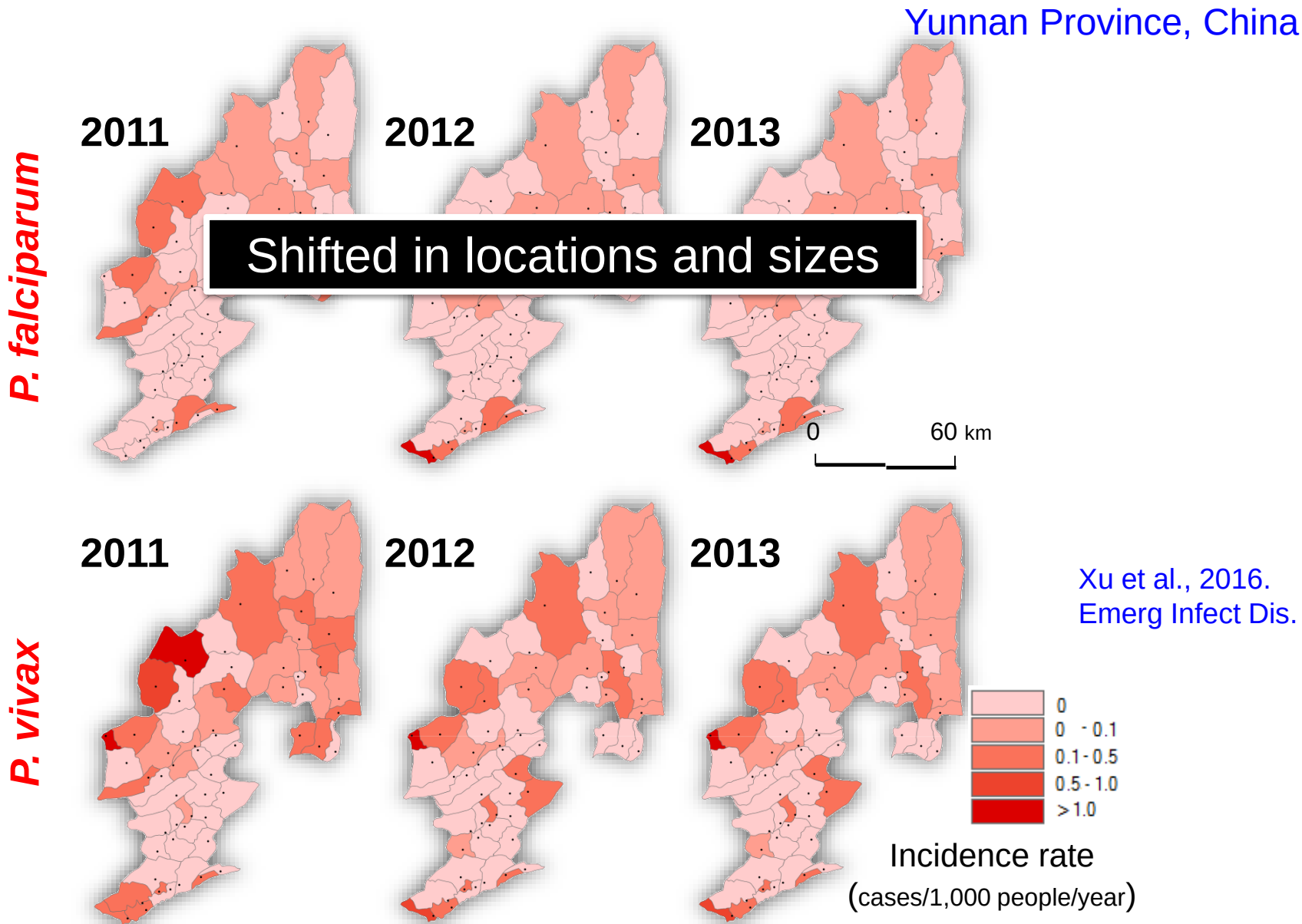


Total could reach 35%

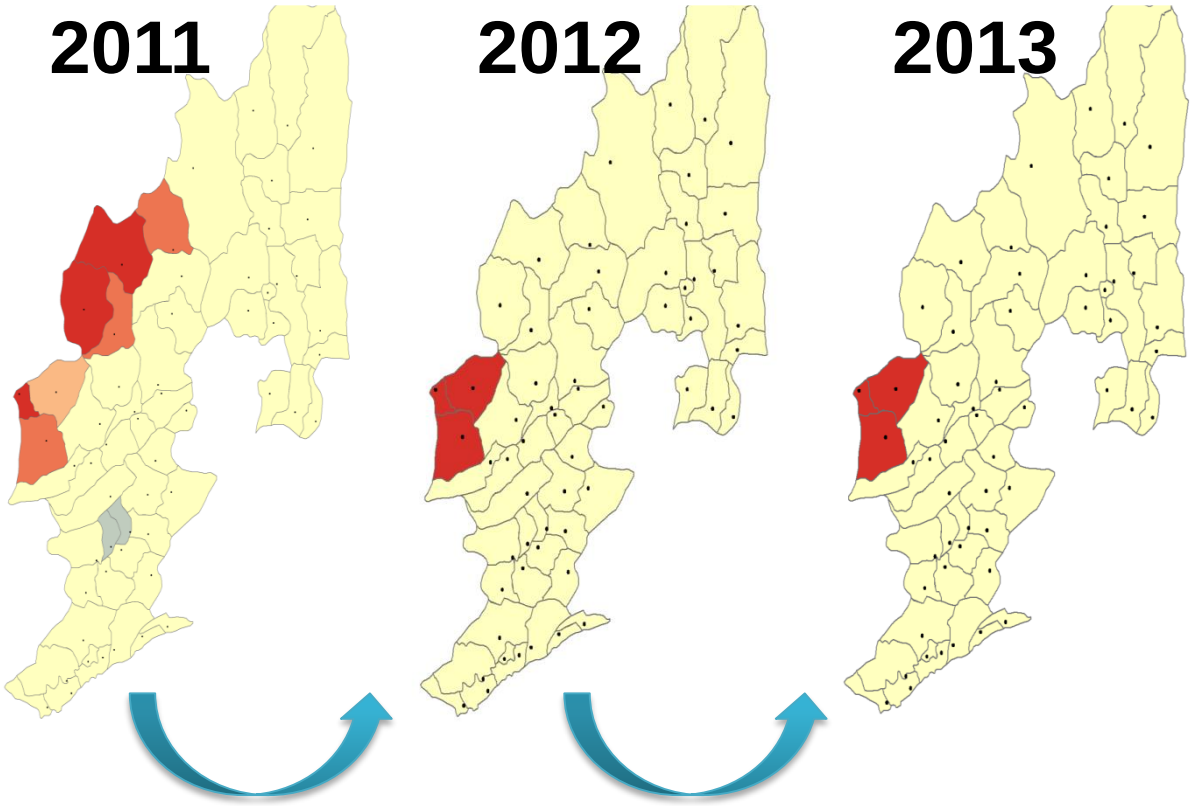
Membrane Feeding



Incidence Rate Spatiotemporal Distribution

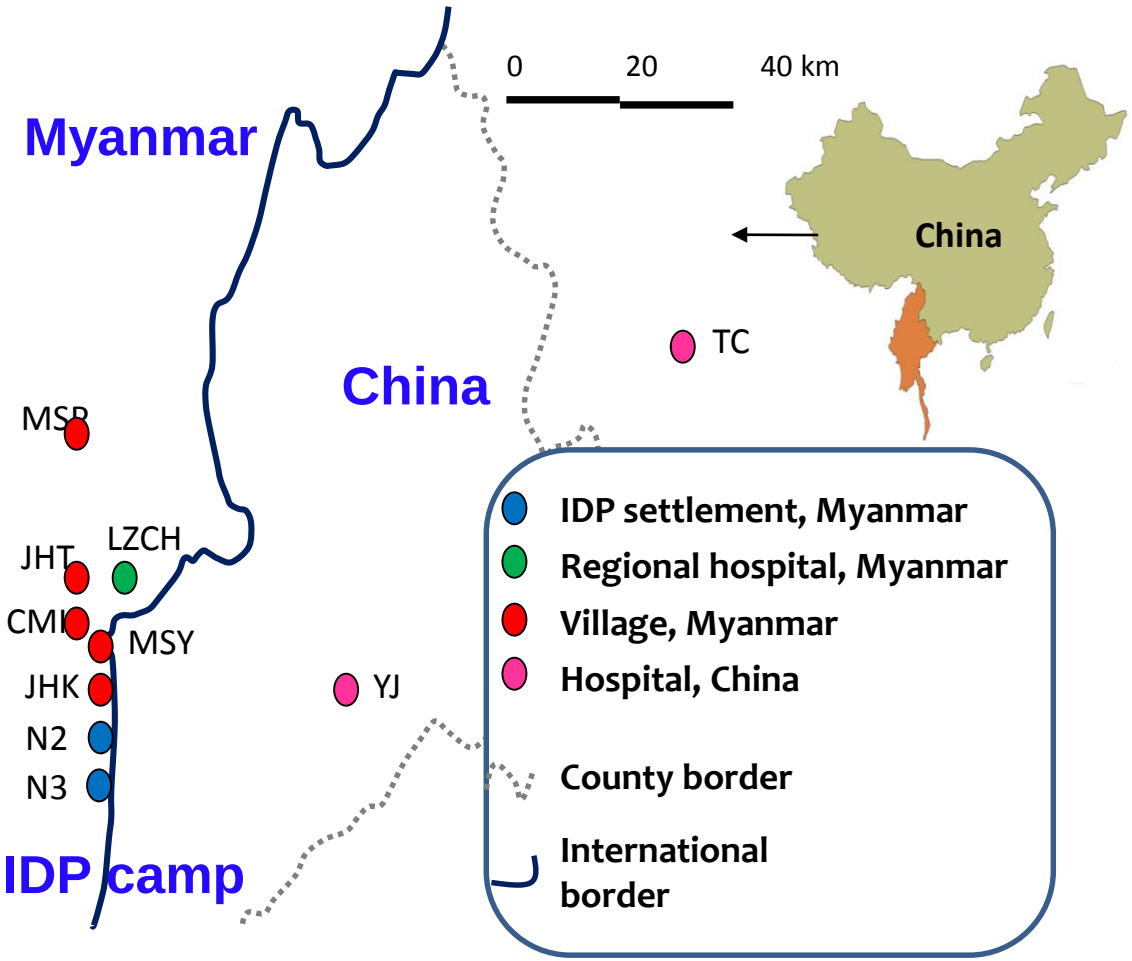


Spatiotemporal Clustering of *P. vivax*

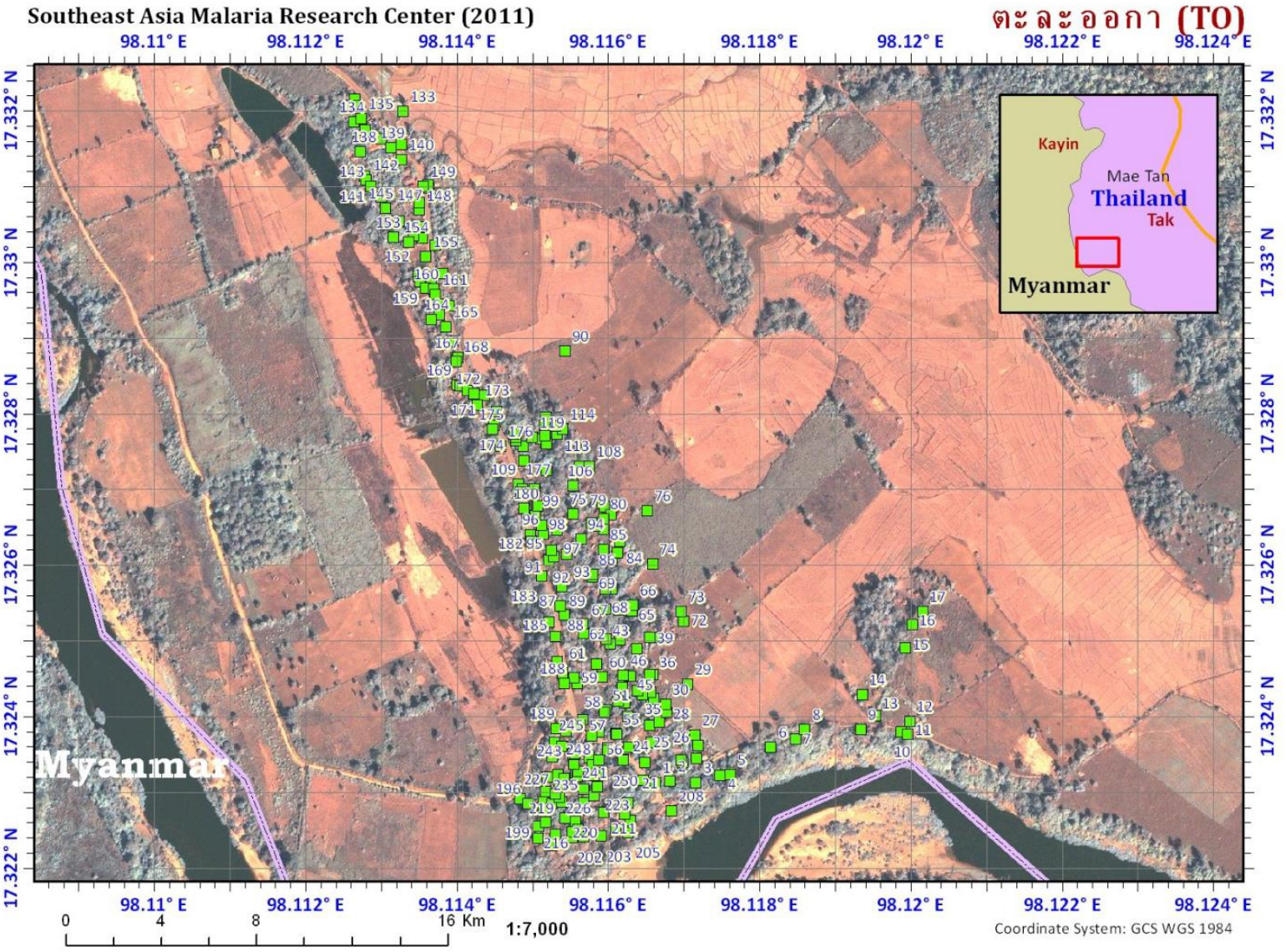


Xu et al., 2016.
Emerg Infect Dis.

Case Clusters and Parasite Spread: Microgeographical Scale

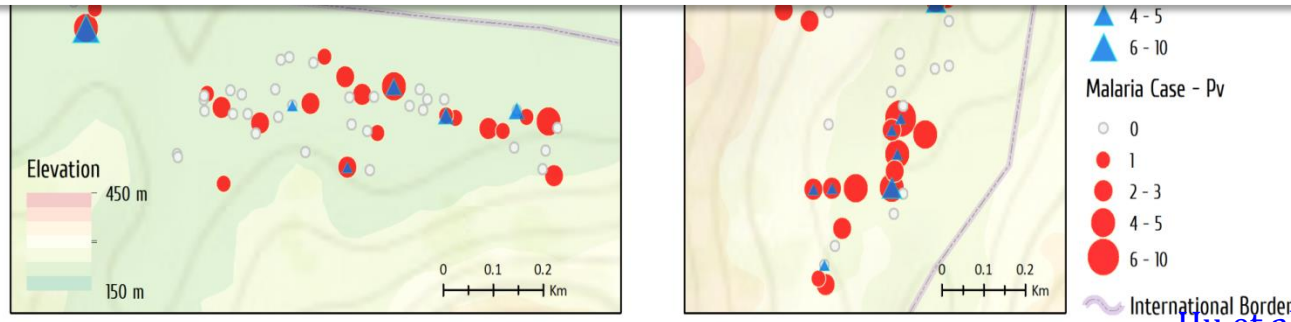


GPS Information



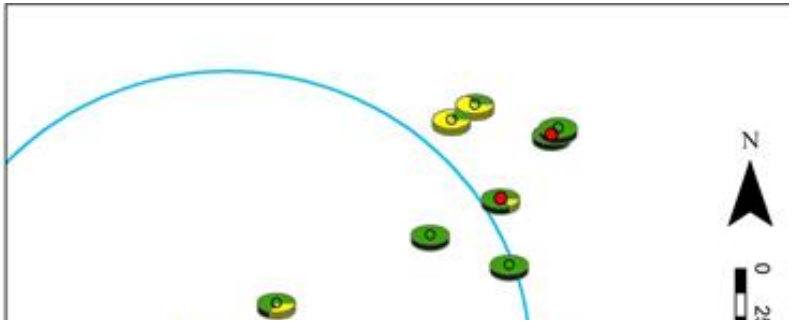
Spatial Clustering of Malaria Cases:
China-Myanmar Border

- Average villages monthly incidence rates in China is 3-8 folds lower than in Myanmar
- Spatial analysis revealed the presence of clinical malaria hotspots in four villages.
- Malaria seasonal dynamics and transmission hotspots should be harnessed for planning targeted control



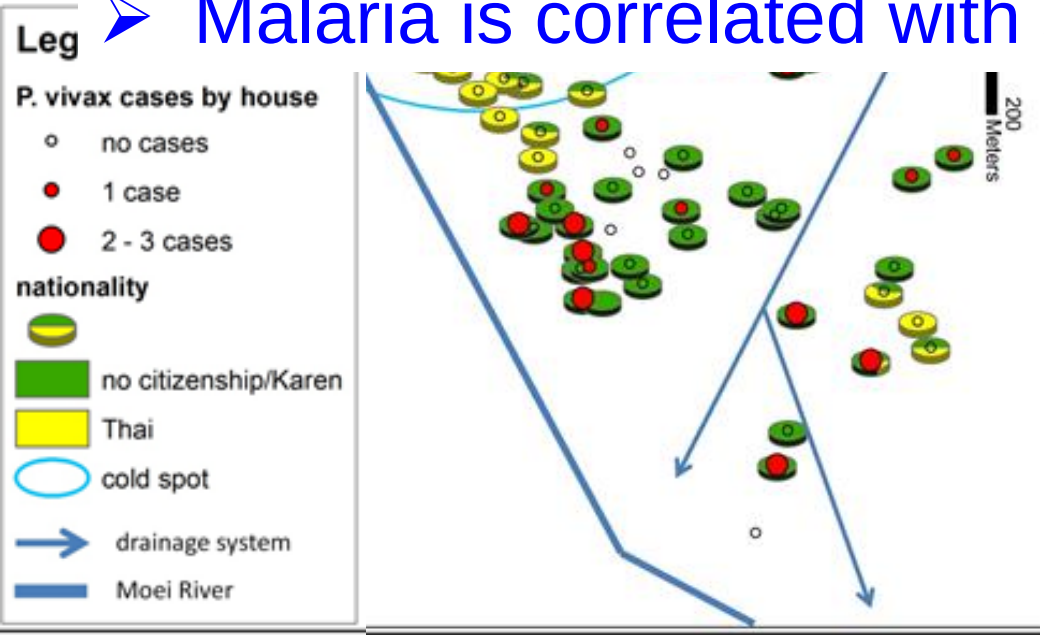
Hu et al., Acta Trop. 2016

Spatial Clustering of Malaria Cases:
Thai-Myanmar Border



- Malaria is associated with migrant populations

- Malaria is correlated with socio-economic status



Cross-Border Parasite Introduction

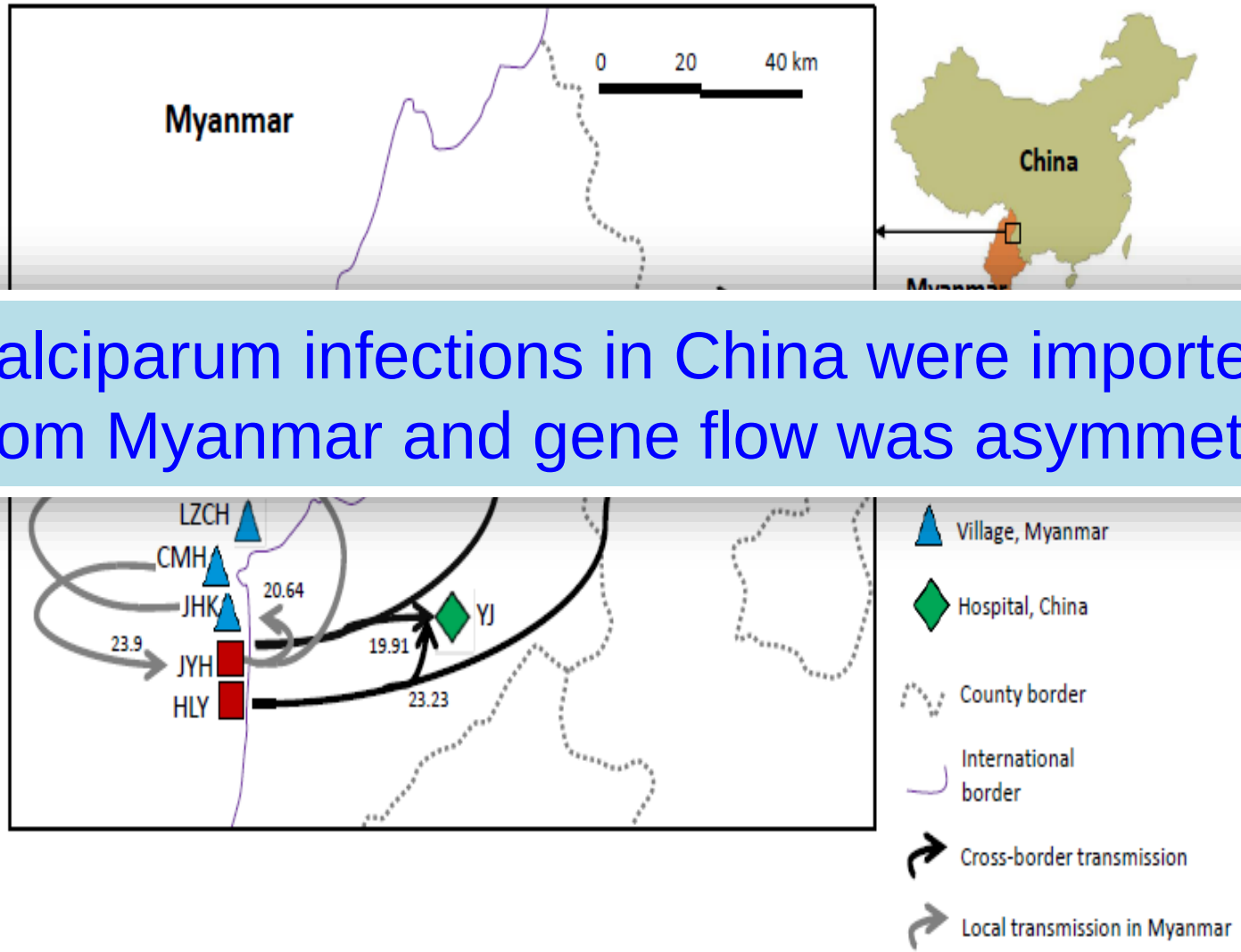
Year	Site	Latitude, longitude	Locality setting	Sample size§
2011	JHK	24.71°N, 97.57°E	Myanmar village	15
	MSP	24.83°N, 97.55°E	Myanmar village	24
	LZCH	24.77°N, 97.57°E	Myanmar regional hospital	33[b]
	N2	24.69°N, 97.57°E	IDP settlement	29
	N3	24.66°N, 97.57°E	IDP settlement	2

P. falciparum Samples (N=352)

Analysis using 13 microsatellite markers

	N2	24.69°N, 97.57°E	IDP settlement	47
	N3	24.66°N, 97.57°E	IDP settlement	7
	TC	25.03°N, 98.49°E	China hospital	25
	YJ	24.71°N, 97.93°E	China hospital	7
			Total	**162**
2013	JHK	24.71°N, 97.57°E	Myanmar village	5
	LZCH	24.77°N, 97.57°E	Myanmar regional hospital	42
	N2	24.69°N, 97.57°E	IDP settlement	40
			Total	**87**

Migration Pathways of *P. falciparum*



- Falciparum infections in China were imported from Myanmar and gene flow was asymmetrical

Key Points

- Extensive spatial heterogeneity on both large and micro-geographical scales – targeted control
- Clustering of malaria cases associated with ecological settings, economic status and migrants
- Asymptomatic carriers as potential reservoirs for persistent transmission at borders
- Cross-border migration – contributing factors to parasite introduction

What Are the Malaria Vectors?

- **Sampling methods:**
  - CDC light trap, no CO_2 bait
  - CDC light trap with CO_2 bait
  - Electric motor catches (EMC)
  - Human landing catches (HLC)





Diverse Malaria Vectorial System

Surveillance of malaria vectors

Adult

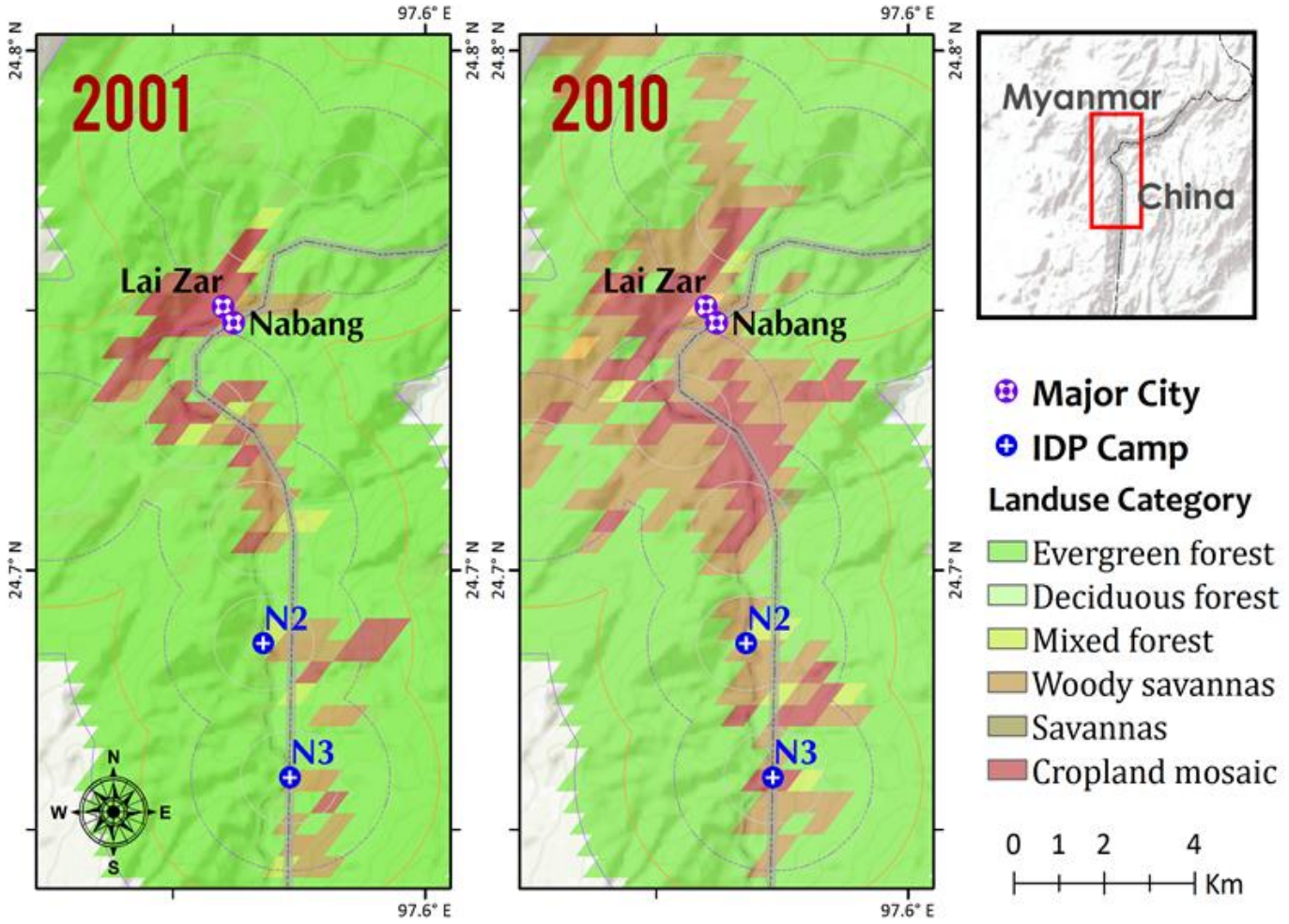
Larval

How Does Environmental Change Affect Vector Development?

Survivorship
Species composition

Environmental Changes Lead to Major Changes in Vector System

- Deforestation
- Urbanization



How Do Environmental Conditions Affect Adult Mosquito Survival?

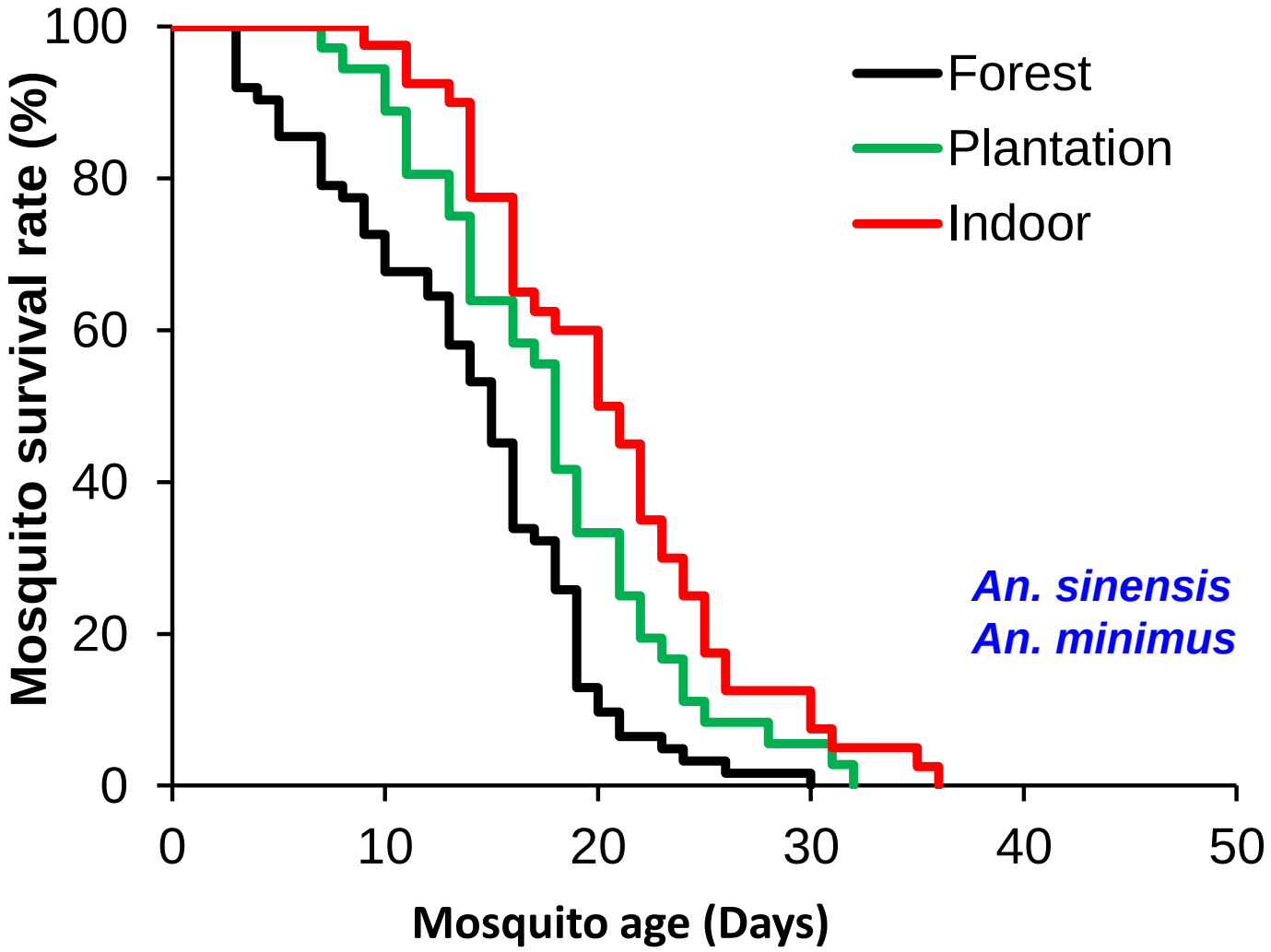
- Environmental conditions:
  - Microclimate variation due to land use and land cover differences

Deforested

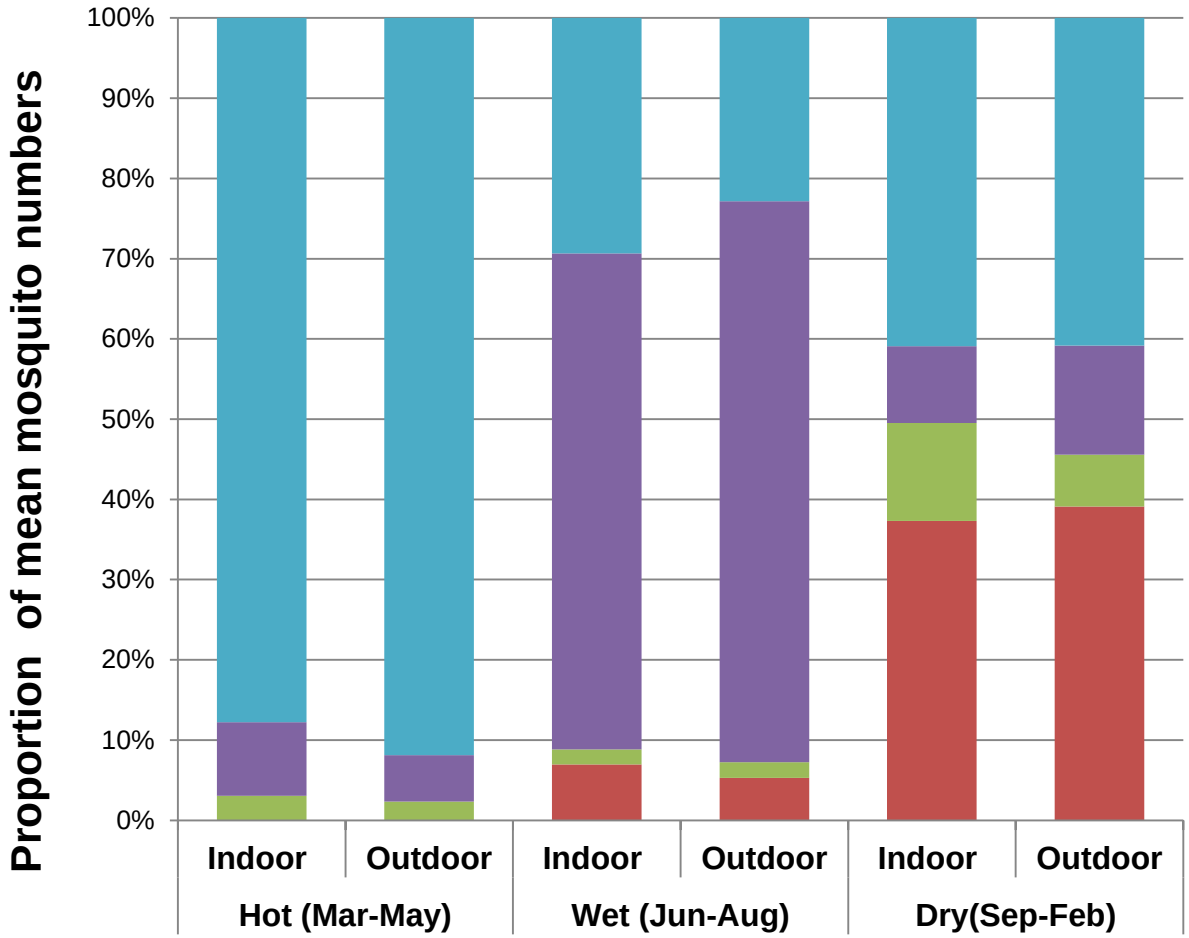
Plantation

Forest

Mosquito Kaplan-Meier Survivorship



Changes in Malaria Vectorial System

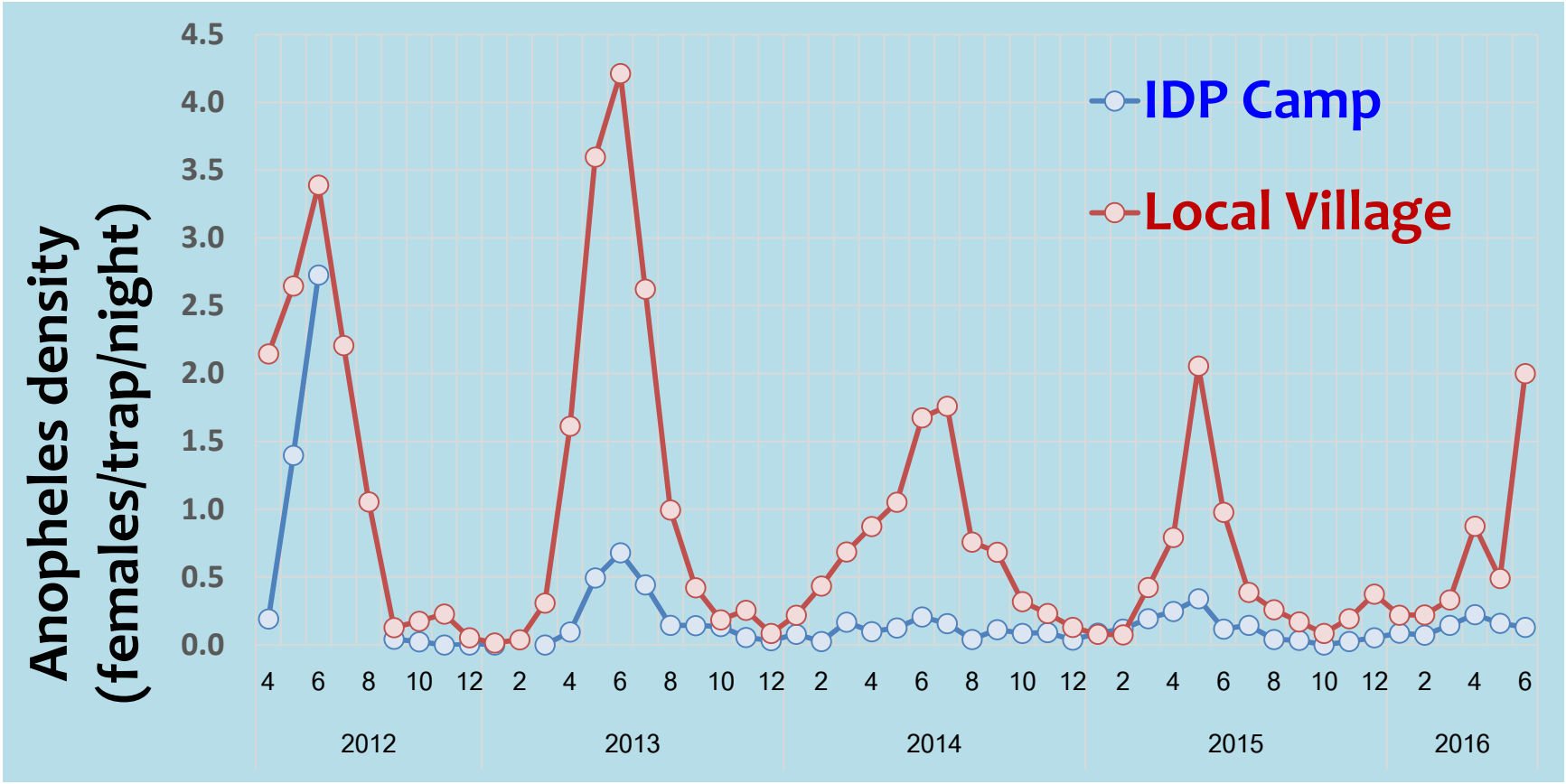


Sporozoite positivity

An. minimus	0.76%
An. maculatus	0.37%
An. barbirostris	0.72%
An. annularis	1.74%

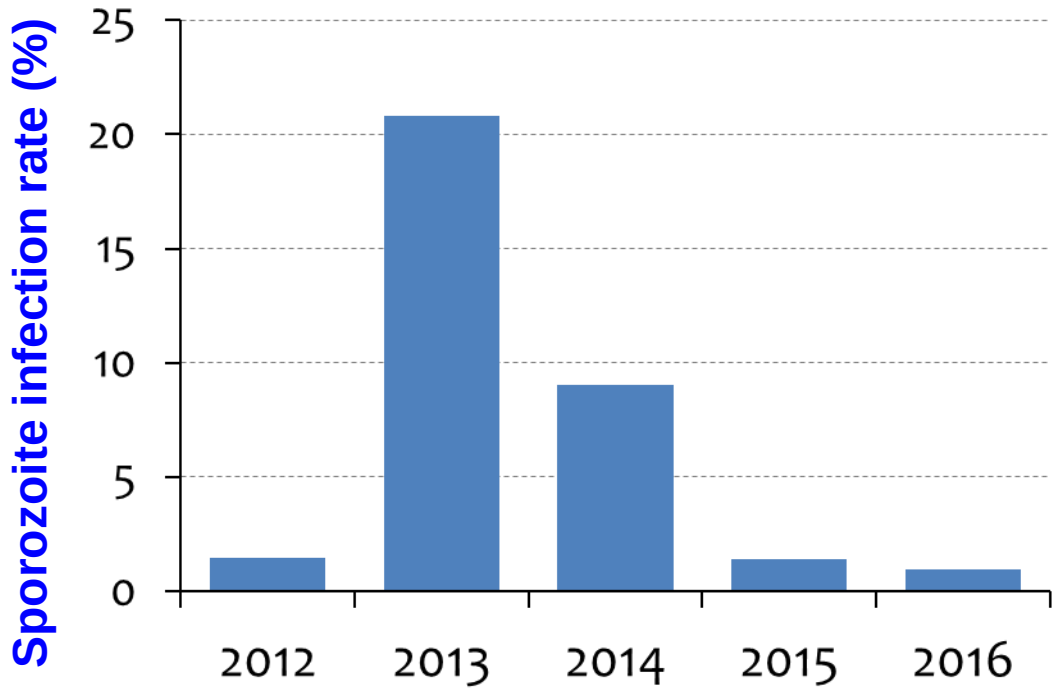
Thai-Myanmar border

Seasonal Dynamics of Vector Population



Vector density in local villages were 6-folds higher than the IDP Camps

P. vivax Sporozoite Infection Rate in *An. minimus* from Myanmar



High rate of *P. vivax* sporozoite infection was detected in samples collected in 2013 in *An. minimus* from Myanmar (higher malaria case reported in 2013)

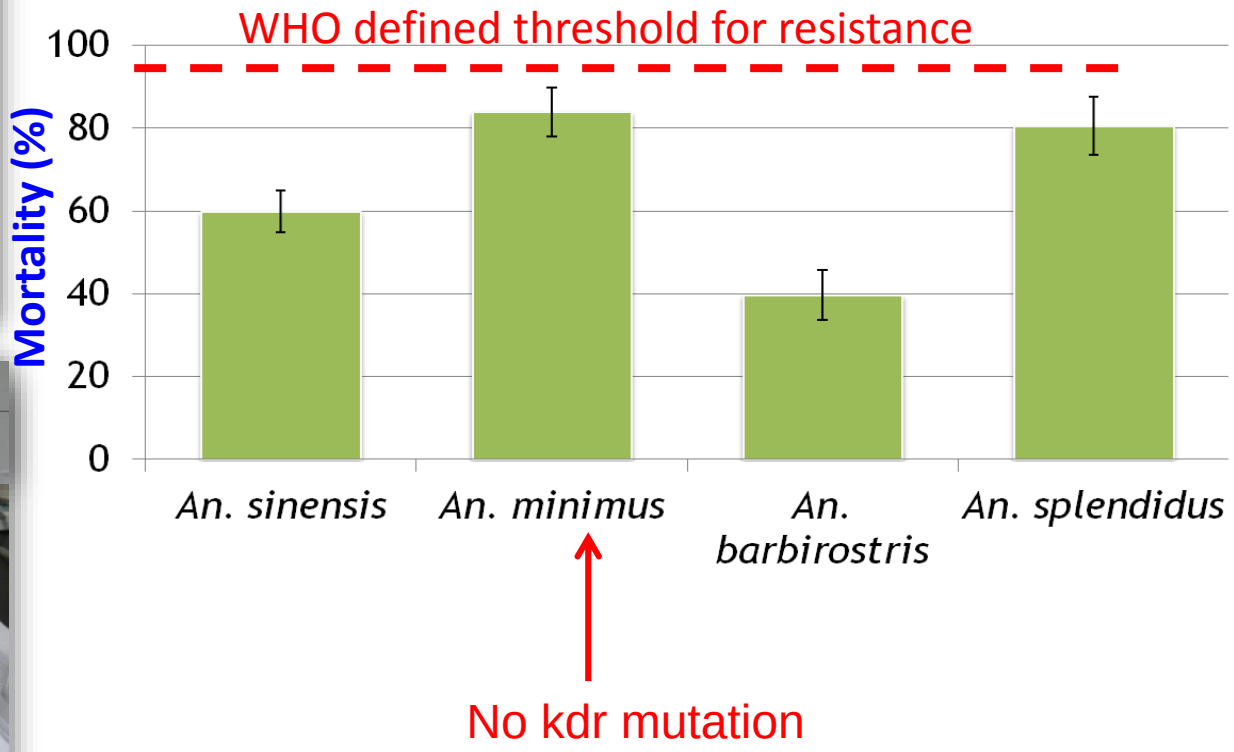
Blood Feeding Host Preference

No.	Species	Human	Pig	Cow	Other	PCR failed	Total (HBI,%)
1	*An. minimus*	61	6	48	16	31	162 (46.6)
2	*An. maculatus*	3	3	0	4	5	15 (30.0)
3	*An. kochi*	0	1	0	1	0	2 (0.0)
4	*An. splendidus*	3	1	2	7	3	16 (23.1)
7	*An. tessellatus*	0	0	0	1	0	1 (0.0)
8	*An. peditaeniatus*	10	15	11	17	3	56 (18.9)
9	*An. aconitus*	0	0	0	1	0	1 (0.0)
10	*An. pseudowillmori*	8	3	0	10	0	21 (38.1)
11	*An. sawadwongporni*	0	0	0	1	0	1 (0.0)
12	*An. willmori*	0	0	0	2	0	2 (0.0)
	Others	0	0	0	12	0	12
	Total	**131**	**45**	**101**	**88**	**52**	**417**

- *An. minimus* and *An. sinensis* are the major vectors
- Both feed almost equally on human and animals

Insecticide Resistance

Mortality rate 24 hrs after exposure to 0.05% deltamethrin

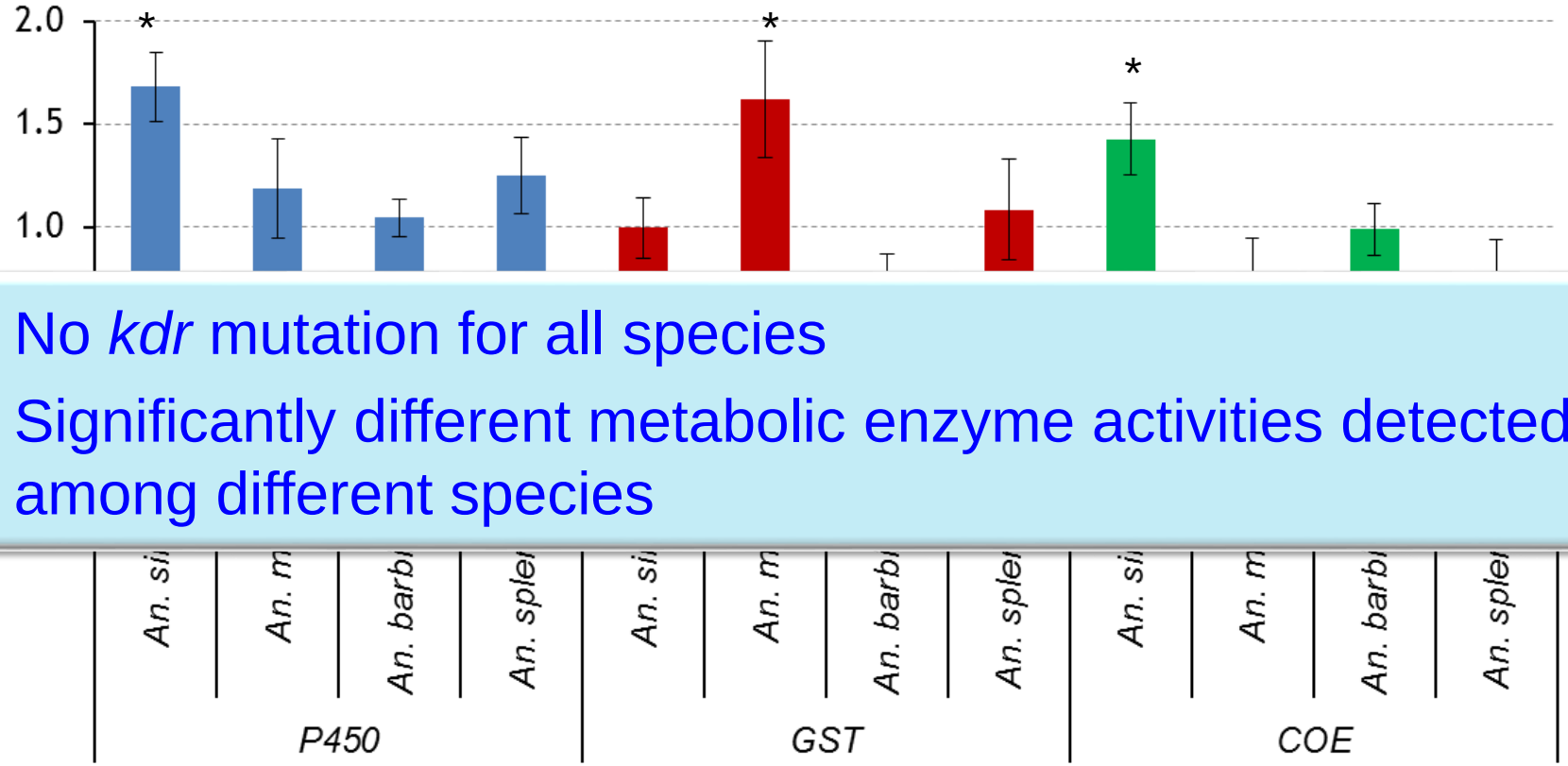


Insecticide Uses in Agriculture

Rotational use of insecticides for agricultural pest control

Deltamethrin **Cypermethrin** **Malathion**

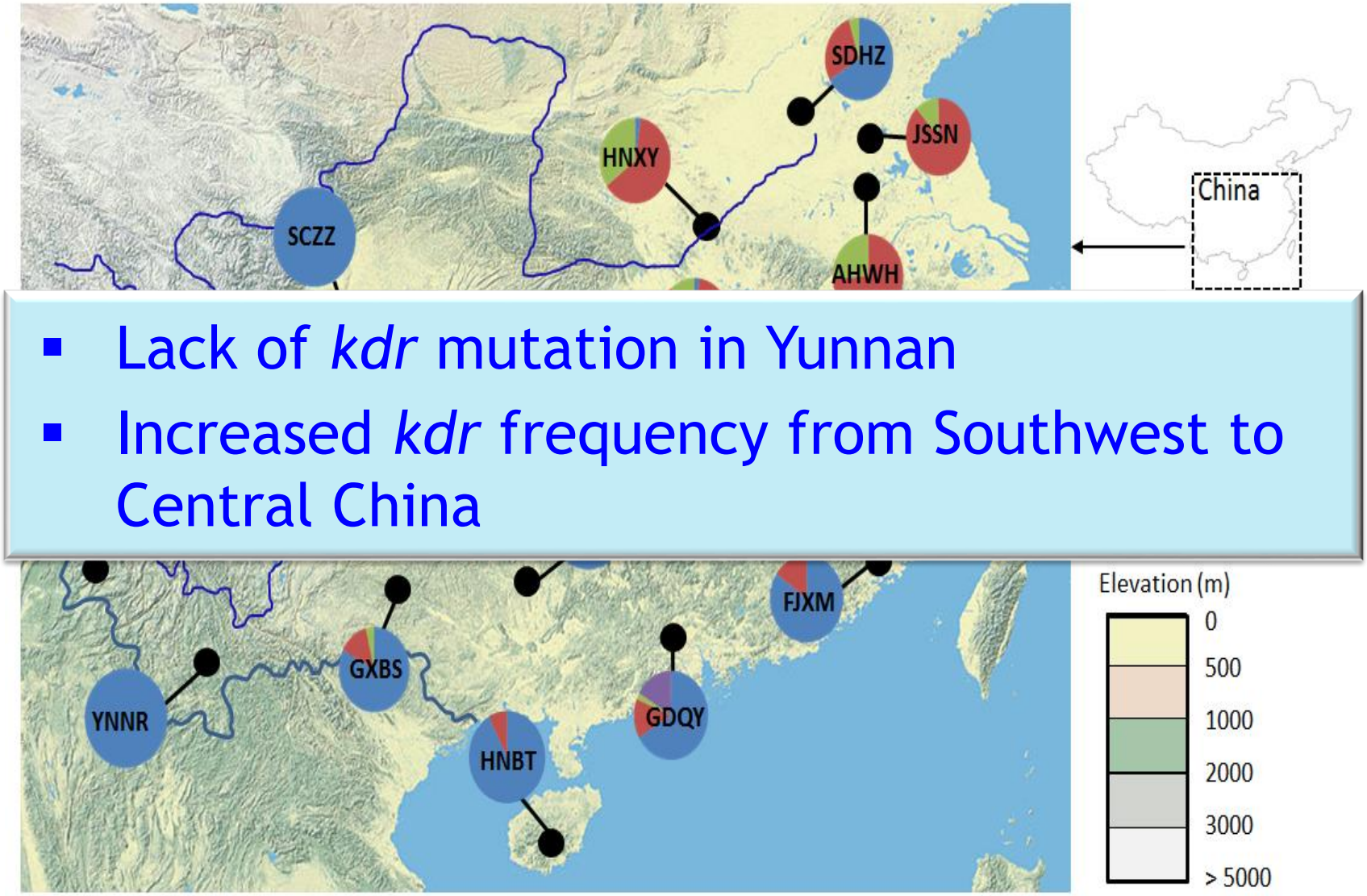
Ratio of Metabolic Enzyme Activity in Resistant to Susceptible Mosquitoes: Myanmar



- No *kdr* mutation for all species
- Significantly different metabolic enzyme activities detected among different species

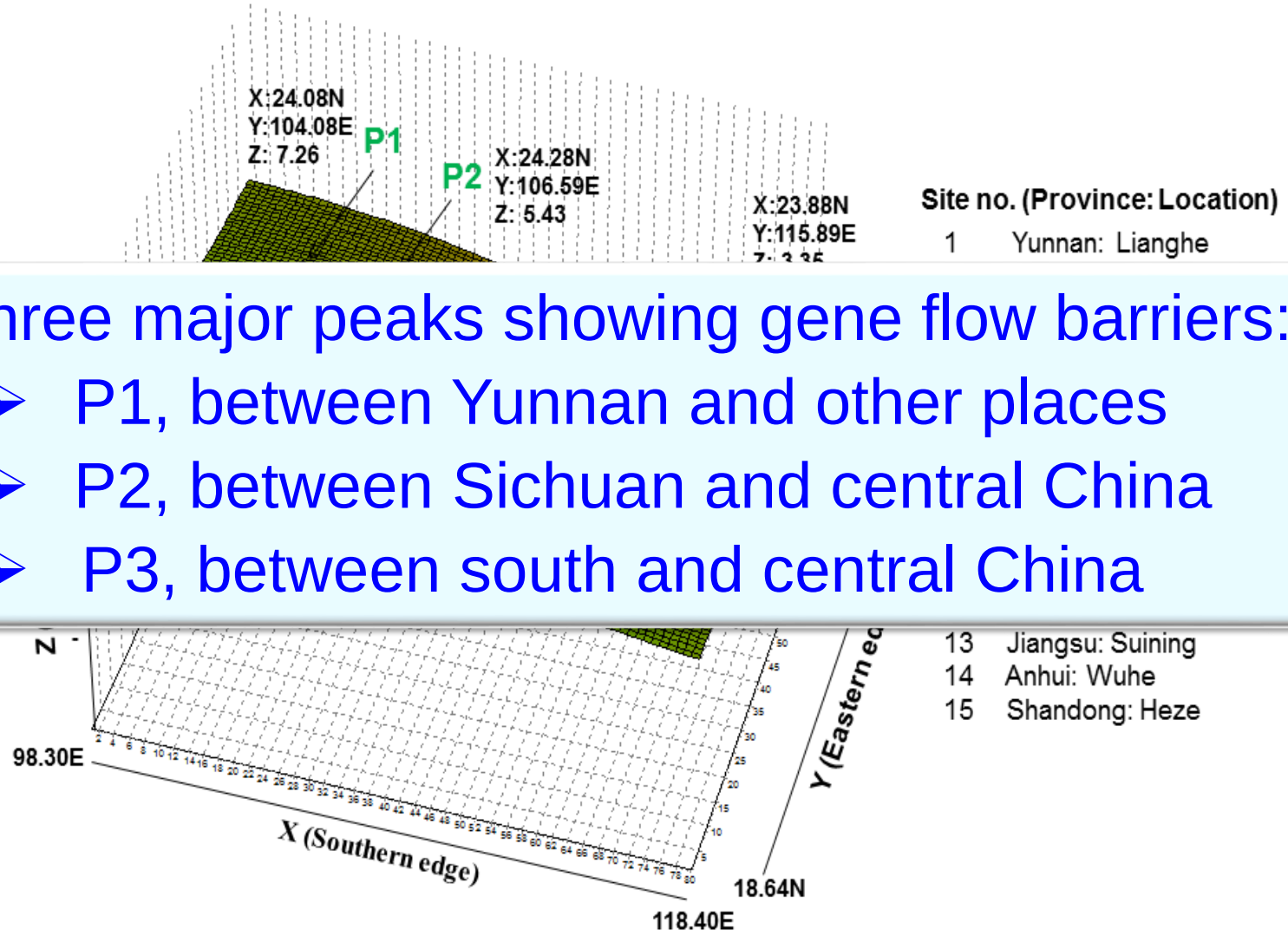
- **P450:** monooxygenases **GST:** glutathione S-transferase
- **COE:** carboxylesterases "*" $p < 0.05$

Population Genetics: *Kdr* in *An. sinensis*



- Lack of *kdr* mutation in Yunnan
- Increased *kdr* frequency from Southwest to Central China

Landscape Genetic Analysis



- Three major peaks showing gene flow barriers:
  - P1, between Yunnan and other places
  - P2, between Sichuan and central China
  - P3, between south and central China

Long-lasting Microbial Insecticide

5% Bti and 5%
Bacillus sphaericus

Large size: 10 grams, good for 10m² water surface

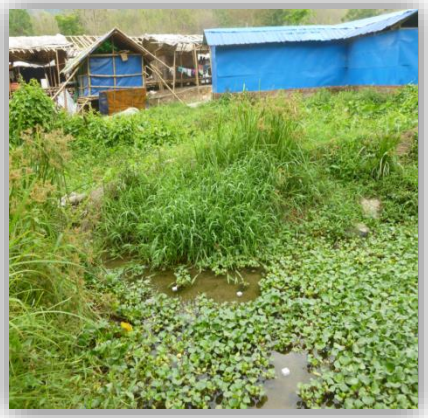
Small size: 1 gram, good for 1m² water surface

No toxin
(as control)

Treatment of Larval Habitats

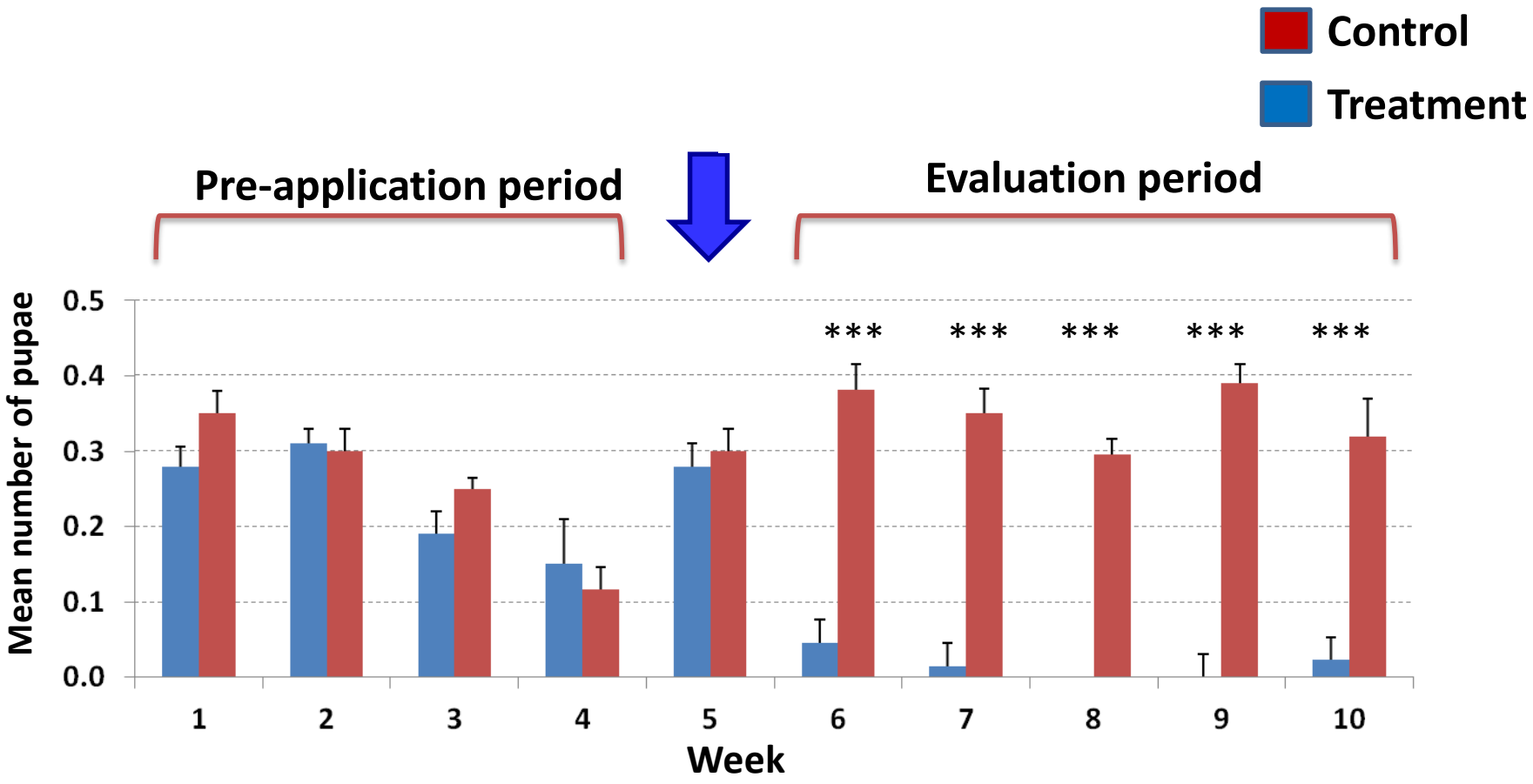
Density of the Briquette: 0.98, float on water





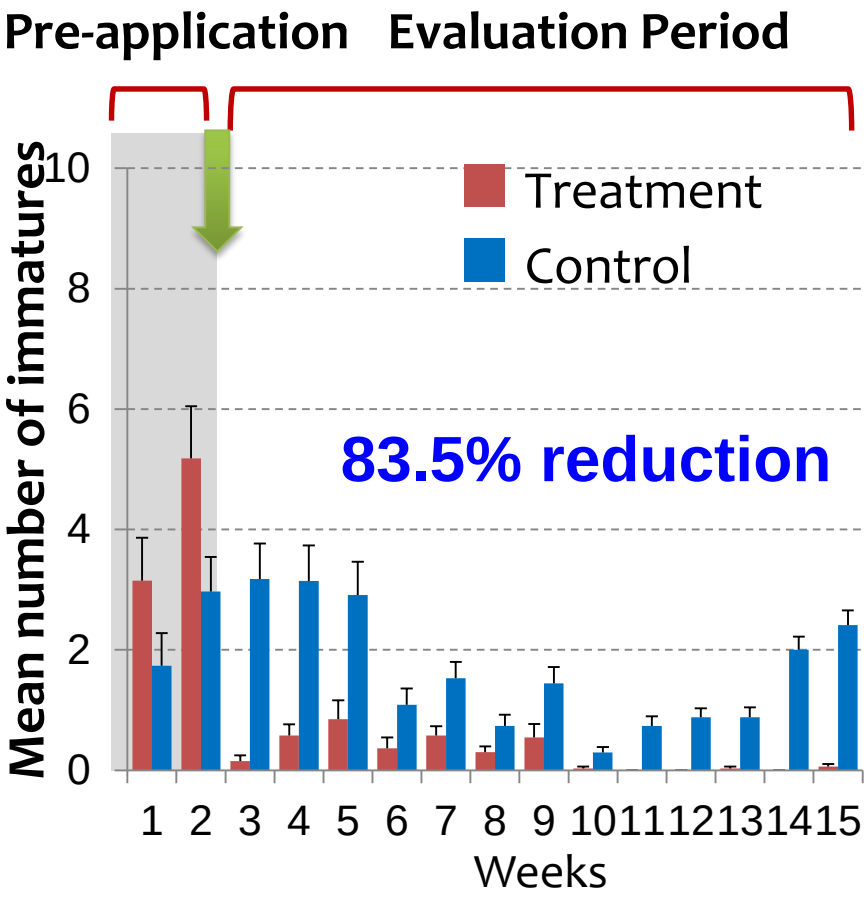
Randomized Field Study: Effect on Pupal Productivity



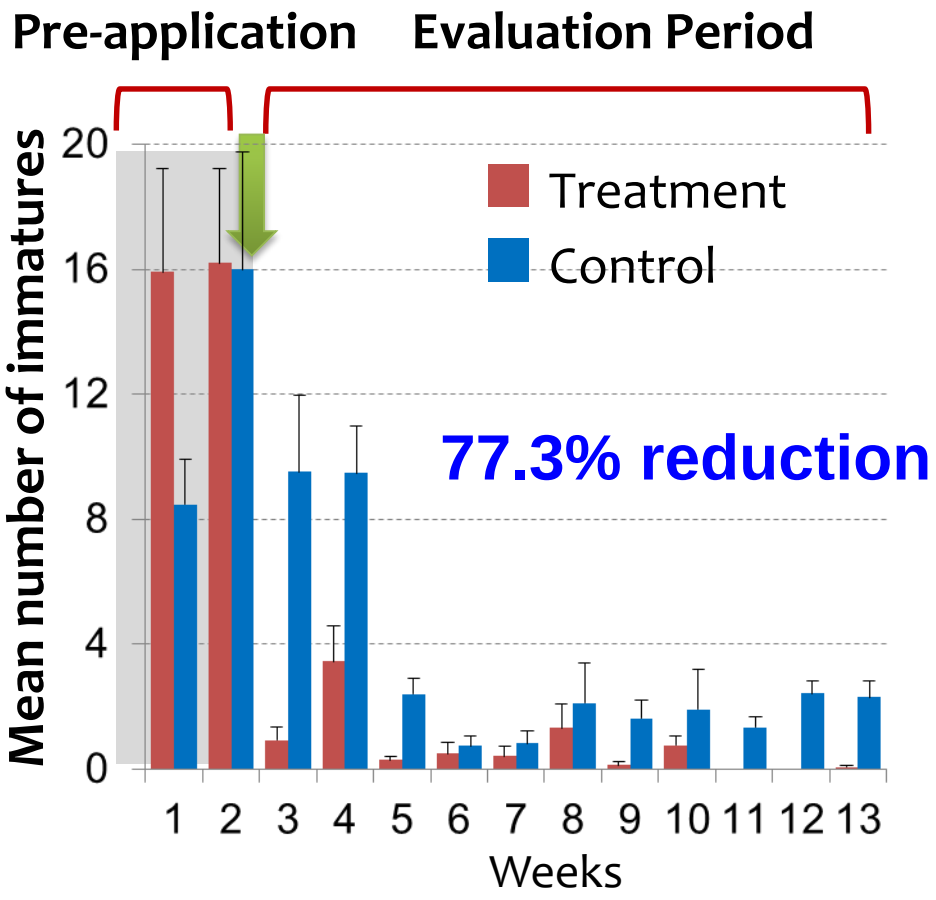
Habitat treatment every 3-5 months

Long-lasting Larvicide Efficacy: 2015

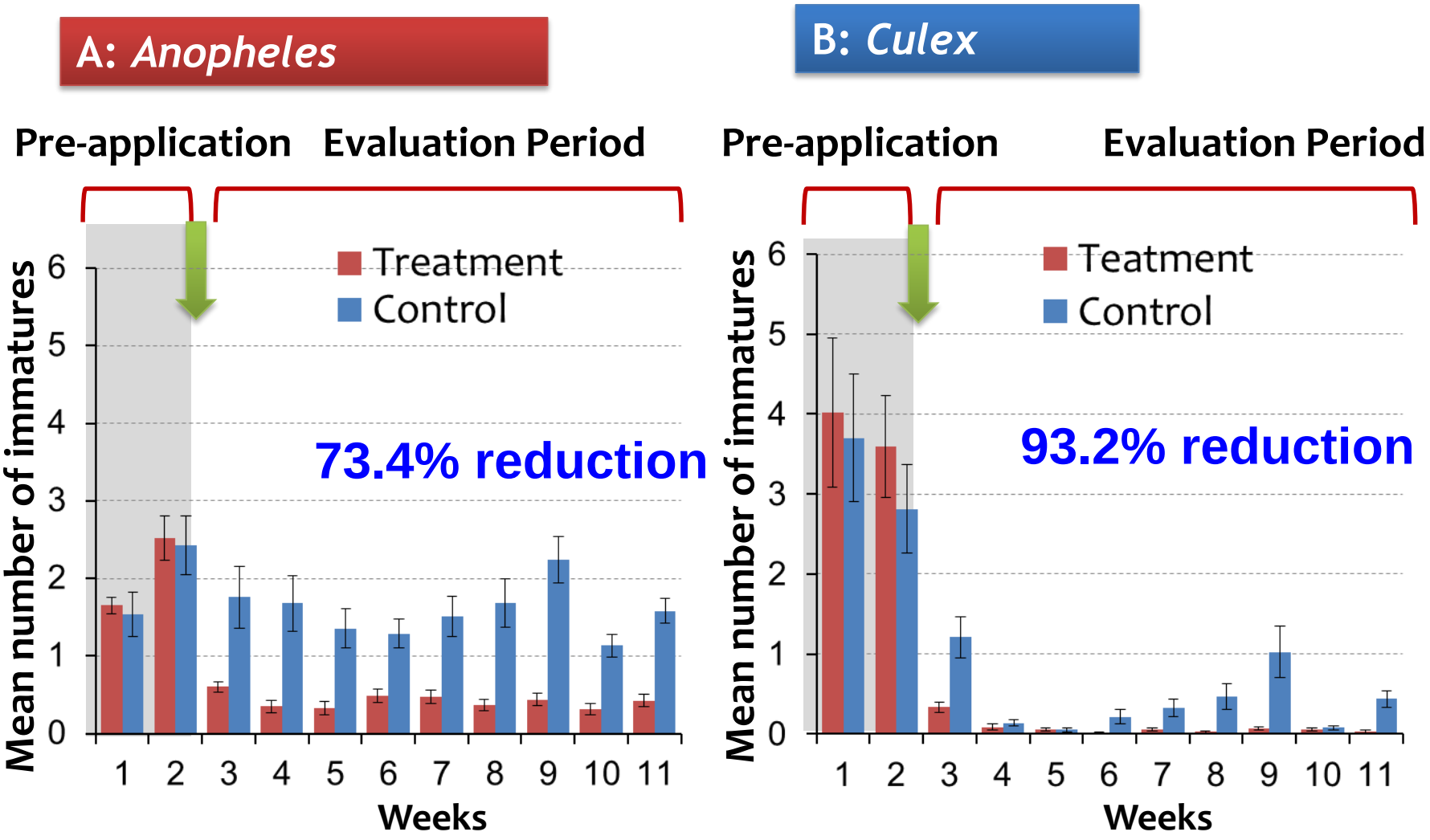
A: *Anopheles*



B: *Culex*



Long-lasting Larvicide Efficacy: 2016



Key Points

- Extensive environmental changes lead to major changes in vector species composition and survivorship of the mosquitoes
- High levels of resistance to insecticides (e.g., pyrethroid) in many vectors, and both *kdr* mutations and increased metabolism as the resistance mechanisms
- Larval control as additional tools for integrated vector management – long-lasting microbial insecticide as a cost-effective way

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  Jaranit Kaewkungwal
  Patchara Sriwichai
  Amnat Khamsiriwatchara
  Wanlapa Roobsong
  Wang Nguitragool
- **Myanmar Health Organization Network**
  Myat Phone Kyaw
- **University of California, Irvine**
  Daibin Zhong
- **China Medical University**
  Qi Fan, Yaming Cao
- **China Agricultural University**
  Baomin Wang
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  Jeeraphat Sirichaisinthop
- **Kunming Medical University, China**
  Zhaoqing Yang
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