MALARIA RESEARCH IN THE GREATER MEKONG SUBREGION: AN OVERVIEW

Abstract. The Greater Mekong Subregion (GMS) has low transmission of *Plasmodium falciparum* and *P. vivax* and is a prime region for malaria elimination based on evidence. The extent of GMS based research is unknown. Pub Med-identified research articles from the GMS were selected based on defined criteria and classified into 24 research areas. A research questionnaire was sent to WHO country offices, national malaria control programs (NMCPs), national research institutes and non governmental organizations (NGOs). Two thousand eight hundred ninety of 3,319 identified publications were included, dating from 1933 to June 2012; 1,485 (51.8%) of 2,890 since 2000. Ten research areas accounted for 2,264 (78.3%) publications: drug resistance 12.8% (*n*=371), entomology 11.42% (*n*=330), clinical trials 10.45% (*n*=302), pathophysiology 9.34% (*n*=270), epidemiology 8.96% (*n*=259), pharmacology 6.06% (*n*=175), parasite biology 5.19% (*n*=150), malaria control 4.88% (*n*=141), diagnosis/diagnostics 4.6% (*n*=133) and clinical studies 4.6% (*n*=133). Thailand produced most publications, 1,684 (58.27%), followed by Viet Nam (365, 12.63%), Cambodia (139, 4.81%), Myanmar (132, 4.57%), Yunnan Province, China (124, 4.3%) and Lao PDR (79, 2.73%). Other publications were multicountry, including ≥1 GMS country (*n*=269), or reviews (*n*=98). Publication numbers increased significantly over time. Eleven questionnaires were received. Principal research areas were treatment seeking behavior, knowledge, attitude and practice surveys, bed net use, access to treatment by migrants, and malaria diagnostics. Research in GMS is broad. Biomedical research dominates peer reviewed publications. NMCP and NGOs focus more on downstream malaria implementation issues. The challenge is to engage GMS research capacity to build quality evidence for malaria elimination.

Keywords: malaria, elimination, Mekong, Myanmar, Thailand, Yunnan, Lao PDR, Cambodia, Viet Nam

INTRODUCTION

Research, in all its forms, should inform us to do things better. Gathering quality evidence is a crucial element so that optimal decisions are made that are beneficial to populations and are economically feasible. National governments make decisions that affect primarily the territories they control. However, diseases know not such boundaries so regional approaches are necessary to undertake malaria control and research.

The Greater Mekong Subregion (GMS) lies in the heart of Southeast Asia, encompassing Lao PDR, Viet Nam, Myanmar, Thailand, Cambodia and Yunnan Province of China. Despite a decline in the malaria burden in the GMS, malaria remains one if its principal

health challenges (Delacollette *et al*, 2009; Cui *et al*, 2012). The GMS has mixed transmission of *Plasmodium falciparum* and *P. vivax* with varying ratios by country (WHO SEARO and WHO WPRO, 2010). *P. vivax* retains full sensitivity to chloroquine (CQ) in most parts of the GMS; focal areas of CQ resistance include the Thai Myanmar border and northeastern Cambodia (Guthmann *et al*, 2008, Rithea *et al,* 2013) (see Chapter 5).

By contrast, multidrug resistant *P. falciparum* is now a significant challenge made more pressing by the recent, additional development of artemisinin resistance that has been documented in multiple foci within the GMS, notably in western Cambodia, Thailand, Myanmar and Viet Nam (Dondorp *et al*, 2009; WHO, 2011; Phyo *et al*, 2012, Tran *et al,* 2012). This development is probably the single, biggest threat in a generation to effective malaria control because the artemisinins are the most potent antimalarial drugs and their widespread use has had a significant impact in reducing the global malaria burden (WHO, 2011). Research is currently on going to try to determine its genetic basis and assess if there are additional foci outside the GMS whilst efforts continue to be made at community level to contain its extent within the GMS, especially in western Cambodia, through the Artemisinin Resistance Containment Project (WHO and Global Partnership to Roll Back Malaria, 2011).

The WHO has identified other challenges faced by the GMS, including fake artesunate, substandard drugs, rational use of drugs, migrant populations and inadequate health care for remote, ethnic populations (WHO SEARO and WHO WPRO, 2010). GMS countries themselves have identified diverse challenges regarding malaria control and research such as fragmented and donor driven research agendas, limited research capacity, challenging treatment seeking behaviors and the changing ecology of anopheline mosquitoes.

Malaria research represents a spectrum of activities that is interconnected with so called upstream research at one end (*ie*, bench science) and downstream research (*ie*, field/community based research) at the other. Both types of research inform the other to generate new hypotheses and better ways to implement malaria control policy. Understanding the extent of research in the GMS and where it fits into the complex malaria research/control landscape is an essential step to improving malaria control. To date, there has not been an inventory of research specifically targeting the GMS. This lack of knowledge underlies the rationale for this review.

MATERIALS AND METHODS

For the published literature, Endnotev4 (Thompson Reuter, USA), was used to search Pub med, the National Library of Medicine and Web of Science databases using the country of interest plus anyone of the following terms: malaria, vivax, falciparum, antimalarial,

anemia, artesunate, chloroquine, mefloquine, halofantrine, piperaquine, pyronaridine, amodiaquine, lumefantrine, primaquine, glucose-6-phosphate dehydrogenase, entomological inoculation rate, and anopheles. The search was repeated using the word Mekong instead of the country name.

Papers were selected if they met any one of the following criteria: (i) research was conducted within a Mekong country, (ii) patients or individuals were from a Mekong country or had acquired malaria from a Mekong country, (iii) samples or specimens were obtained from a Mekong country, (iv) a Mekong country was included in an important review article or epidemiological update/overview. From these data, the country or countries of origin were determined. Reviews were classified by their geographical scope as either by country, region or global. Research conducted on non-Mekong nationals was excluded with one exception – the AQUAMAT trial comparing artesunate with quinine for the treatment of severe, pediatric malaria (Dondorp *et al*, 2010). One important review on HIV in migrants in the GMS was also included because of the core issues involved (Bain, 1998).

A one arm, WHO *in vivo* test of drug efficacy was classed as a clinical study of resistance if the drug was registered or was otherwise commonly used. One arm studies which seemed to be more exploratory were classed under clinical studies. This almost certainly resulted in some overlap. Whilst malaria is the disease of interest in this review, other included diseases were the inherited blood disorders *eg*, glucose-6-phosphate dehydrogenase deficiency (G6PDd), anemia and other infectious diseases *eg*, fever surveys.

The type of research was classified into 24 main categories: resistance, entomology, clinical trials/clinical studies, pathophysiology, epidemiology, pharmacology (including studies with pharmacokinetics), parasite biology, malaria control, diagnostics, clinical case series/reports, malaria immunology (including vaccine work), hematology, malaria reviews, malaria treatment reviews, socio-economic research, malaria prophylaxis, other infectious diseases, research methodologies, drug discovery, mathematical models, migrants, donors, climate/environmental changes and malaria history/hypotheses. These research areas were further subdivided into more specific research areas and are detailed in Table 1. All classifications were done by the author Walter RJ Taylor.

National malaria control programs (NMCPs), ministries of health (MoH), national malaria institutes, WHO offices were contacted and requested to complete a questionnaire relating to their research activities. Further information was obtained from web sites as well as the clinicaltrials.gov web site. Data were entered into Microsoft XL and analyzed (descriptive statistics, chi-square for trend) with Stata v9 (Stata Corporation, College Station, TX).

RESULTS

Peer reviewed publications

Virtually all papers were identified from Pub Med. A total of 3,319 publications were obtained, dating from 1933 to June 2012; 429 did not meet the above defined criteria, leaving 2,890 publications. All but 2 papers had named authors. The number of published papers, classified on the basis of their main research area, is shown in Fig 1.

Time trend

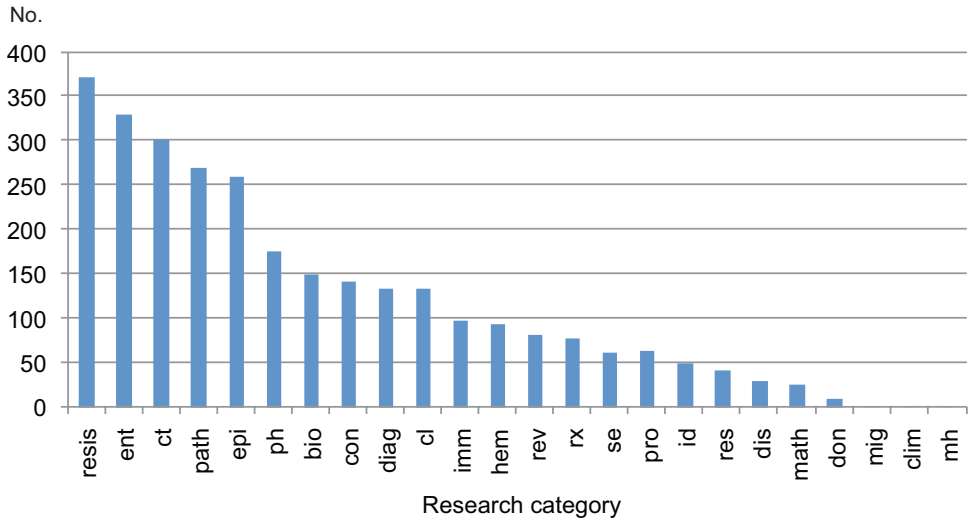
Over time, there has been an increase in the number of publications. Grouping by decades, the proportions of papers published ranged from 0.5% to 40.8%: 0.5% pre 1960, 4.33% in the 1960s (1960 to 1969), 5.99% (1970s), 9.52% (1980s), 28.24% (1990s) and 40.08% (2000-2009) (p<0.0000). Just over half of all publications, 51.38% (1,485/2,890), had been published since 2000. Examining the trend from 2000 but excluding 2012, there is also a significant increase (p=0.0016) in the proportions of published papers over time 2000 (Fig 2).

The main research areas are: drug resistance (resis) 12.84% (371/2,890), entomology (ent) 11.42% (n=330), clinical trials (ct) 10.45% (n=302), pathophysiology (path) 9.34% (n=270), epidemiology (epi) 8.96% (n=259), pharmacology (ph) 6.06% (n=175), parasite biology (bio) 5.19% (n=150), malaria control (con) 4.88% (n=141), diagnostics (diag) 4.6% (n=133) and clinical studies (cl) 4.6% (n=133). These ten research areas accounted for 2,264 (78.34%) publications.

Examining publications for these ten research areas from 2000 to 2011, there are no distinct trends over time *ie*, the proportions for a given research area in a given year vary widely (Fig 3, for clarity only 5 research areas are shown).

Research output details

The detailed breakdown of studies within each research category is shown in Table 1. The most frequently published studies within given research areas were: one arm *in vivo* tests (36.93%), mosquito identification (29.36%), randomized controlled trials (46.18%), immunopathogenesis (49.26%), malaria epidemiology (54.05%), PK studies in patients (phases 2, 2b, 3 type studies), parasite genetics (53.33%), general aspects of malaria control 58 (41.13%), molecular diagnostics for identifying malaria species (39.1%), descriptive clinical studies (78.2%), basic immunology (78.13%), G6PD deficiency (45.16%), general malaria reviews (92.5%), treatment reviews of uncomplicated malaria (38.96%), costs of interventions (37.5%), prophylactic drug efficacy studies (72.58%), infectious



resis, resistance; ent, entomology; ct, clinical trials/clinical studies; path, pathophysiology; epi, epidemiology; ph, pharmacology (including studies with pharmacokinetics); bio, parasite biology; con, malaria control; diag, diagnostics; cl, clinical case series/reports; imm, malaria immunology (including vaccine work); hem, hematology; rev, malaria reviews; rx, malaria treatment reviews; se, socio-economic research; pro, malaria prophylaxis; id, other infectious diseases; res, research methodologies; dis, drug discovery; math, mathematical models; don, donors; mig, migrants; clim, climate/environmental changes and mh-malaria history/hypotheses.

Fig 1–The number of research publications for each of the main research categories from 1933 to June 2012.

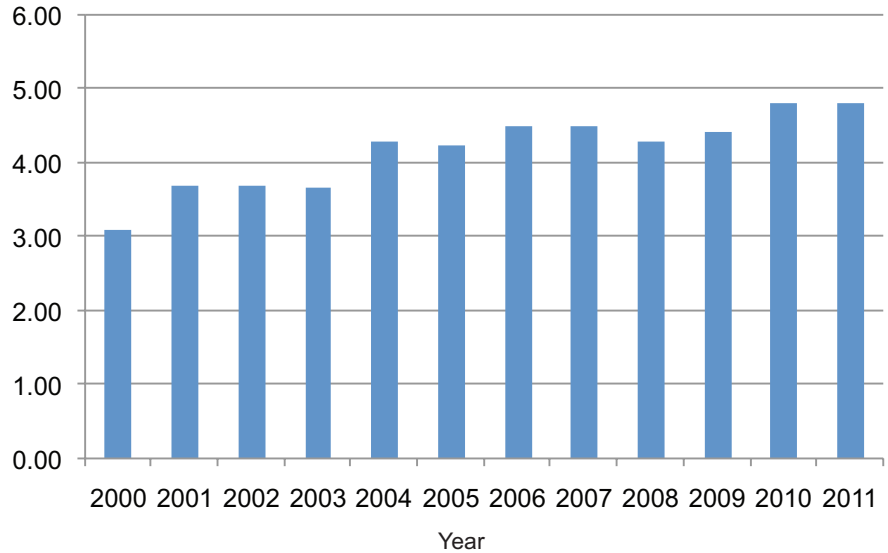


Fig 2–Published papers from 2000 to 2011 expressed as a proportion of the total number of papers published (*n*=2,890).

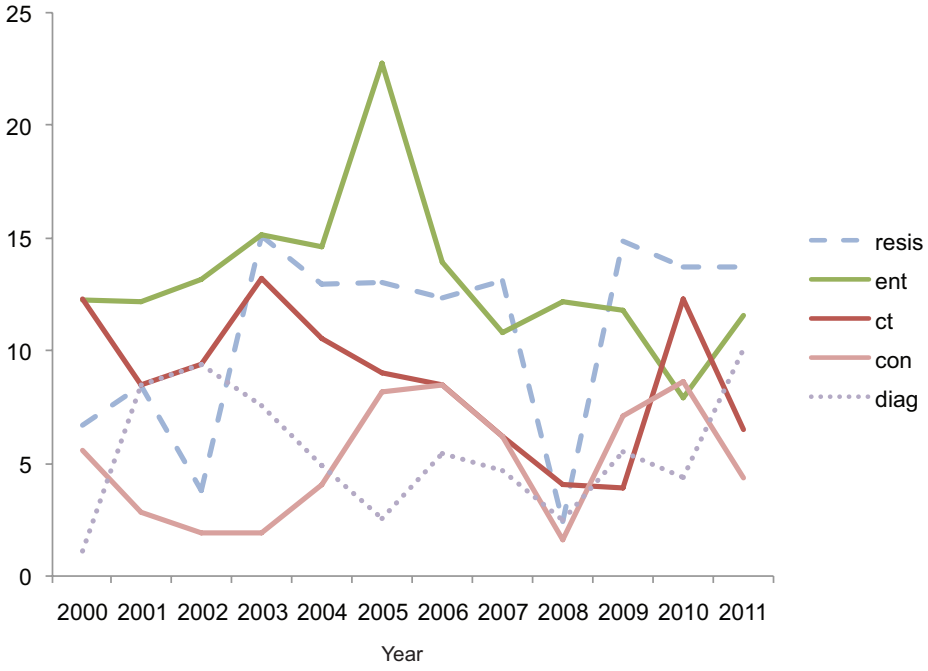


Fig 3–Time trends for five of the ten principal research categories: resistance, entomology, clinical trials, malaria control, and diagnostics, expressed as a proportion of the total number of publications for a given year.

disease reviews (53.06%), clinical and laboratory measuring techniques (68.29%), testing of potential antimalarial compounds, mostly plant derived new chemical entities (75.86%), and the application of mathematical models for malaria control and resistance (48%). The remaining research areas had few publications.

Research output by country

For convenience, relevant studies from China (*n*=37) where the region could not be determined were included in the studies from Yunnan Province. Publications involving one Mekong country totaled 2,523 of 2,890 (87.3%). The distribution of papers from individual countries was Thailand 1,684/2,890 (58.27%), Viet Nam 365 (12.63%), Cambodia 139 (4.81%), Myanmar 132 (4.57%), Yunnan Province, China 124 (4.3%) and Lao PDR 79 (2.73%). Papers from: (i) two or more Mekong countries numbered 96 (3.32%), (ii) at least one Mekong country and at least one country from SE Asia 63 (2.18%), and (iii) at least one Mekong country and a country from other regions 110 (3.81%). There were 98 (3.39%) review papers with global themes that were written by authors based in the Mekong region. Countries outside of the Mekong region came from all continents.

Several, ground breaking studies involving Mekong countries that have led to significant changes in malaria drug policy have been the multicenter trials that lead to the global WHO recommendation to use artemisinin based combinations (ACTs) for drug resistant *P*. *falciparum*, establishing the superiority of intravenous artesunate over quinine for the treatment of severe malaria in adults and children, analysis of data showing that Day 14 was inadequate for determining clinical resistance to antimalarial drugs, including the short half life artemisinins, and the simple, field adapted Day 3 parasite positivity rate as a surrogate marker of possible artemisinin resistance (Adjuik *et al*, 2004; Stepniewska *et al*, 2004; Dondorp *et al*, 2005, 2010; Stepniewska *et al*, 2010). Multicenter trials involving Mekong countries have also lead to the registration of several ACTs (Ashley *et al*, 2006; Mayxay *et al*, 2010; Poravuth *et al*, 2011; Rueangweerayut *et al*, 2012).

Questionnaires

A total of 11 questionnaires were returned from 9 institutions: (i) 5 NGOs: Population Services International (PSI, separate replies for Myanmar, Cambodia and Lao PDR), Family Health International (FHI) 360, University Research Co (URC), Partners for Development (PFD), Malaria Consortium (MC, covering all GMS except Yunnan Province), Global Health Access Program (GHAP), and (ii) two government research institutions: the National Institute for Malaria, Parasitology and Entomology (NIMPE) in Viet Nam, and the Center for Malaria, Parasitology and Entomology (CMPE) in Lao PDR, and (iii) the Bureau of Vector Borne Diseases (BVBD) program in Thailand.

Areas of research that are covered (Table 2) by all or most of the NGOs/institutions are treatment seeking behavior, knowledge, attitude and practice surveys (KAP), bed net use, access to treatment by migrants, and malaria diagnostics *eg*, mostly evaluating rapid diagnostic tests (RDTs). Research areas covered by about half of the NGOs/institutions are surveillance for artemisinin resistance/Day 3 parasite positivity, migration patterns, monitoring and evaluation of activities, non-bed-net personal protection, use of the private sector and quality of diagnosis and treatment.

Very little research is conducted in most areas of vector control, randomized control trials, epidemiology of *P. vivax* and G6PD deficiency, molecular, *in vivo*, and *in vitro* resistance monitoring and data systems and policy making. None of the NGOs/institutions are conducting work on drug dose optimization, primaquine for radical cure of *P*. *vivax*, cost effectiveness of integrated infectious disease surveillance and treatment and prevention strategies, willingness to pay and work and income stability. However, GHAP is implementing a data system to inform their policy making.

Two NGOs reported conducting other research. PSI in Myanmar is working on surveys

Table 1
Breakdown of the main research categories.

Research category	No. (%)	Research category	No. (%)	Research category	No. (%)	Research category	No. (%)	Research category	No. (%)
Resistance *n*=371		Larvicidals	2 (0.61)	red cell rheology		Bioequivalence	6 (3.43)	Access	3 (2.13)
In vivo	137 (36.93)	Viral coinfection	2 (0.61)	Clinical	97 (35.93)	Assessing adherence	3 (1.7)	Migrants	3 (2.13)
In vitro	97 (26.15)	Physiology	2 (0.61)	Histopathology	25 (9.26)	Drug mechanism of	1 (0.57)	Adherence	2 (1.42)
Molecular	38 (10.14)	Trapping	1 (0.31)	Host genetics	6 (2.22)	action		interventions	
Epidemiology	35 (9.43)	Gene flow	1 (0.31)	Nonroutine biochemistry	3 (1.11)	Pharmacogenetics	1 (0.57)	Early warning system	2 (1.42)
Molecular *in vitro*	15 (4.04)	GIS	1 (0.31)	Red cell invasion	3 (1.11)			Political aspects	2 (1.42)
In vitro in vivo	14 (3.77)	Insecticide analysis	1 (0.31)	Review	3 (1.11)	**Parasite biology *n*=150**		Looking after bednets	2 (1.42)
Molecular *in vivo*	13 (3.5)					Parasite genetics	80 (53.33)	Combined fever	2 (1.42)
in vivo vivax	6 (1.62)	**Clinical trials *n*=302**		**Epidemiology *n*=259**		Parasite proteomics	27 (18)	malaria surveillance	
Risk factors	6 (1.62)	RCT	139 (46.18)	Malaria	140 (54.05)	Animals -	12 (8)	Research policy gap	2 (1.42)
Mechanism	3 (0.81)	Phase 2	68 (22.59)	Genetic diversity	40 (15.4)	induced infections		Refugees	1 (0.71)
Gametocytes *in vitro*	2 (0.54)	Tolerability / toxicity	31 (10.3)	Fever	14 (5.41)	Parasitemia &	15 (10)	Mass drug administration	1 (0.71)
Vivo+*vitro*+molecular	2 (0.54)	Adjunct treatments	23 (7.64)	Molecular resistance	26 (10.04)	life cycle		Data sharing	1 (0.71)
Reversal	1 (0.27)	Primaquine-relapse	14 (4.65)	markers		Parasitemia	5 (3.33)	Human rights	1 (0.71)
Animal models	1 (0.27)	Primaquine-	8 (2.66)	Temperospacial & GIS	14 (5.41)	biomarkers		Primary health care	1 (0.71)
Pseudoresistance	1 (0.27)	gametocytocide		Serological surveys	9 (3.47)	Relapse molecular	5 (3.33)	Fever management	1 (0.71)
		Primaquine toxicity	5 (1.66)	Migrants	5 (1.93)	biology		Pregnancy	1 (0.71)
Entomology *n*=330		Effectiveness/	5 (1.66)	Host genetics	3 (1.16)	Gametocyte clearance	3 (2)	Drug supply	1 (0.71)
Species identification	96 (29.36)	adherence		Morbidity/mortal	3 (1.16)	Cell lines	2 (1.33)	Effect of development	1 (0.71)
insecticide testing	66 (20.18)	Efficacy-	3 (1.0)	Infectious disease	2 (0.77)	Drug effects on	1 (0.67)	Improved nutrition	1 (0.71)
Species epidemiology	48 (14.68)	induced malaria		surveillance		oxidant capacity			
Transmissibility	31 (9.48)	Gametocyte	1 (0.33)	Mapping	2 (0.77)			**Clinical studies *n*=133**	
Net/hammock studies	19 (5.81)	carriage & SP		Gametocyte carriage	1 (0.39)	**Malaria control *n*=141**		Descriptive	104 (78.2)
Mosquito behavior	13 (3.98)	Tafenoquine-	1 (0.33)			General aspects	58 (41.13)	*P. knowlesi*	10 (7.52)
Infect species	10 (3.06)	gametocytocide		**Pharmacology and PK *n*=175**		Drug quality	13 (9.22)	Postpartum malaria	7 (5.26)
Breeding sites	8 (2.45)	Antisequestration	1 (0.33)	PK studies in patients	65 (37.14)	Effectiveness	12 (8.51)	Scores & prognosis	5 (3.75)
Control	7 (2.14)	efficacy		Phase I	34 (19.43)	monitoring		Infants	5 (3.76)
EIR	5 (1.53)	Study design	1 (0.33)	PK PD	18 (10.29)	Health promotion	7 (4.96)	Neurological	1 (0.75)
Morphology	5 (1.53)	Consent	1 (0.33)	Assay methodology	14 (8.0)	Village health workers	7 (4.96)	examination	
Review	4 (1.22)			Review	10 (5.71)	Drug policy	6 (4.26)	Decision making	1 (0.75)
Salivary gland studies	3 (0.92)	**Pathophysiology *n*=270**		PK interaction	8 (4.57)	Health system review	5 (3.55)		
Insecticide toxicity	2 (0.61)	Immunopathogenesis/	133 (49.26)	Animal studies	8 (4.57)	Private sector	5 (3.55)		

Table 1 (Continued).

Research category	No. (%)	Research category	No. (%)	Research category	No. (%)	Research category	No. (%)	Research category	No. (%)
Diagnostics *n*=133		IHBs & malaria	17 (18.28)	Pharmacodynamics	5 (6.49)	Urbanization	1 (1.56)	Life cycle/blood stage	11 (44)
Molecular techniques	52 (39.1)	protection		*P. vivax*	2 (2.6)	Social cultural aspects	1 (1.56)	Health system	2 (25)
Rapid diagnostic tests	33 (24.81)	Thalassemia	9 (9.68)	IPT	1 (1.3)			dynamics	
Antibody based tests	8 (6.02)	Anemia	7 (7.52)	Drug toxicity	1 (1.3)	**Other diseases and malaria *n*=49**		Intrahost artemisinin	1 (4)
Review	7 (5.26)	Treatment trials	5 (5.38)	Elimination	1 (1.3)	Review	26 (53.06)	resistance	
Acridine orange stain	6 (4.51)	Review	4 (4.3)	Adherence	1 (1.3)	Epidemiology	21 (42.86)	Gametocyte carriage	1 (4)
Microscopy	6 (4.51)	IHB epidemiology	4 (4.3)			Community	1 (2.04)		
Detecting cryptic	5 (3.76)	G6PD diagnostics	2 (2.15)	**Drug prophylaxis *n*=62**		based surveillance		**Donors/funding *n*=8**	
parasites		G6PD: *in vitro*	1 (1.08)	Efficacy	45 (72.58)	Wound infection	1 (2.04)	Postpone funds	4 (50)
Radioactive techniques	4 (3.01)	hemolysis		Review	7 (11.29)			Health system	2 (25)
High technologies	4 (3.01)	Artemisinin &	1 (1.08)	PK	5 (8.06)	**Research methodology *n*=41**		Review	2 (25)
RDT storage/stability	3 (2.26)	thalassemia		Tolerability	3 (4.84)	Clinical/laboratory	28 (68.29)		
Clinical diagnosis	2 (1.5)	Hemoglobin-	1 (1.08)	Preclinical	2 (3.23)	techniques		**Migrants *n*=3**	
Buffy coat	1 (0.75)	hematocrit				Review	7 (14.63)	Treatment	1 (33.33)
Bone marrow	1 (0.75)			**Socio economics *n*=60**		Relapse animal models	4 (9.76)	Health effects	1 (33.33)
User knowledge	1 (0.75)	**Reviews *n*=80**		Economics	24 (37.5)	Mobile technology	1 (2.44)	HIV	1 (33.33)
		General reviews	74 (92.5)	(control, diagnosis)		Web tools	1 (2.44)		
Immunology *n*=96		Radiology	2 (2.5)	Treatment seeking	12 (18.75)			**Climate/environment *n*=2**	
Basic immunology	75 (78.13)	Relapse	2 (2.5)	behavior		**Drug discovery *n*=29**		Effect malaria	2 (100)
Review	11 (11.46)	*P. knowlesi*	2 (2.5)	KAP	9 (14.06)	New chemical	22 (75.86)	epidemiology	
Vaccine trials-all phases	6 (6.25)			Migrants	5 (7.81)	entities			
Animal work	4 (4.17)	**Treatment reviews *n*=77**		Consumer aspects	4 (6.25)	Rev (news item)	7 (24.14)	**Medical history *n*=1**	
		Uncomplicated malaria	30 (38.96)	Advocacy	3 (4.69)			Anemia	1 (100)
Hematology *n*=93		Broad review	24 (31.17)	Vector control	2 (3.13)	**Modeling *n*=25**			
G6PD	42 (45.16)	Severe malaria	12 (15.58)	Social class	1 (1.56)	Control & resistance	12 (48)		

Table 2

Questionnaire results.

Research activities	Institutions / Countries	Lao PDR	PSI Myanmar	Cambodia	FHI360 Cambodia	URC Cambodia	PFD Cambodia	MC GMS[b]	BVBD Thailand	NIMPE Vietnam	CMPE Laos	GHAP Thailand	Total
Vector control	Vector biology & climate change	0[a]	0	0	0	0	0	0	1	0	0	0	1
	Mosquito vectors & transmission	0	0	0	0	1	0	0	1	1	0	0	3
	Vector resistance	0	0	0	0	0	0	0	1	1	1	0	3
	Non LLITN personal protection	1	0	0	0	0	1	1	1	1	0	0	5
	Long lasting ITNs	0	0	0	0	0	0	0	1	1	1	0	3
Case management	Diagnosis/diagnostics	1	0	1	1	1	0	0	1	1	1	0	7
	Randomized controlled trials	0	0	0	0	0	0	1	1	1	0	0	3
	Drug optimization studies	0	0	0	0	0	0	0	0	0	0	0	0
P. vivax, G6PD	*P. vivax* epidemiology	0	0	0	0	0	0	0	1	1	0	0	2
deficiency & drug	G6PD epidemiology	0	0	0	0	0	0	1	0	1	0	0	2
resistance	Primaquine for radical cure	0	0	0	0	0	0	0	0	0	0	0	0
	Artemisinin resistance surveillance	0	0	0	0	1	1	1	1	1	0	1	6
	Day 3 parasite positivity	0	0	0	1	1	1	0	1	1	0	1	6
	Extended therapeutic efficacy studies	0	0	0	0	0	0	0	1	0	0	0	1
	Mapping resistance molecular markers	0	0	0	0	0	1	0	0	0	0	1	2
	In vitro drug sensitivity testing	0	0	0	0	1	0	0	1	1	0	0	3
Mobile populations	Strategies for malaria prevention	0	0	0	0	0	1	1	1	0	0	1	4
	Accessing to care & treatment	0	0	0	1	1	1	1	1	1	1	1	8
	Migration patterns	0	0	0	1	1	1	1	0	0	1	1	6
Heath systems	Data systems & policy making	0	0	0	0	0	0	1	1	0	0	0	2
	Cost effectiveness of ID surveillance	0	0	0	0	0	0	0	0	0	0	0	0
Private sector	Role of the private sector	0	1	1	0	1	0	0	0	0	1	0	4
	Patient use of private sector	1	1	1	0	0	0	0	0	0	1	1	5
	Quality of diagnosis & treatment	0	1	0	1	1	0	0	1	1	0	0	5
Monitoring & Evaluation		0	1	0	0	1	1	1	1	0	0	1	6
Social aspects	Treatment seeking behavior	1	1	1	1	1	1	1	1	1	1	1	11
	KAP surveys	1	1	1	1	1	1	1	1	1	1	1	11
	Bed net use at home	1	1	1	0	1	1	1	0	1	1	1	9
Economics	Willingness to pay	0	0	0	0	0	0	0	0	0	0	0	0
	Work & income stability	0	0	0	0	0	0	0	0	0	0	0	0
	Cost effectiveness treatment & prevention	0	0	0	0	0	0	0	0	0	0	0	0

[a]0=no 1=yes; [b]except Yunnan Province

of the supply chain of antimalarial drugs and RDTs and malaria outlets. URC in Cambodia is working on bed net acceptability/bed net preference and KAP surveys among high school children, assessing the relapse pattern of *P. vivax*, and the effectiveness of insect repellents.

Three NGOs reported on projects that had had a major impact on policy in Cambodia. The PSI ACT watch project focused on the availability and cost of ACTs as well as treatment seeking behavior. Data from this project helped policy makers ensure that quality and affordable ACTs were available and to recommend ways of improving patient - provider interactions. FHI360 piloted a novel system of loaning bednets in Pailin, western Cambodia; its success has led to its adoption by the Centre National de Malariologie (CNM) and expansion into other provinces. By the systematic monitoring of Day 3 positivity of *P. falciparum*, URC can alert CNM policy makers early of the possible emergence of pending artemisinin resistance. In 2009 in Lao PDR, a survey to stratify malaria risk translated into the development of a new National Strategic Plan 2011-2015. In Thailand, project work led to the devolving of malaria control.

Most responded with suggestions for research to strengthen policy and practice. The most extensive list came from the National Malaria Programme in Lao PDR (CMPE) and WHO, and is presented almost verbatim: (i) Maintaining village based diagnosis and treatment in high risk areas with Combo RDT for diagnosis and radical treatment with primaquine for Pv infections; (ii) Integration of surveillance and response activities within national surveillance systems; (iii) Expanding and integration of village health worker (VHW) scope of work (*ie*, including other diseases – acute respiratory infections, diarrheal disease, etc) and harmonizing incentive mechanisms among various stakeholders; (iv) Adopting effective proactive strategies for addressing external risk factors like deforestation, plantation, mining and hydro dam and road development projects; (v) Health systems strengthening – human resource development, incentives, capacity building at provincial/district levels, integration of service delivery and surveillance and response; (vi) Impact of rapid development on malaria: plantations, hydro dams, road construction, mining; (vii) Epidemiology of malaria among mobile workers in development projects (mining, rubber plantation, dam construction, etc); (viii) An investigation of determinants of continued malaria transmission in villages with high ITN coverage and access to early diagnosis and treatment; (ix) Mapping of G6PD deficiency in Lao PDR, field-based testing and clinical trials for safe dosage of primaquine; (x) Entomological mapping, study of vector behavior, insecticide resistance monitoring; (xi) Strengthen supply management at all levels monitoring stocks, including through SMS text messaging; (xii) Feasibility studies for suitable malaria prevention methods for forest goers; (xiii) Health Facility survey on Access and Rational Use of Medicines; (xiv) Evaluation knowledge of community on medicine use; (xv) Survey on

Good Pharmacy Practices, and (xvi) Price Monitoring Control Survey.

All respondents except PSI Myanmar have strong collaborations with partners be they MoHs/Malaria Control Programs, the WHO, academia and other NGOs. All respondents also reported that they strive to publish their work either on their web site or in peer review journals. Nine respondents reported they had a back log of work awaiting publication.

Web sites of national malaria institutes

There are several institutions in the Mekong that are dedicated to malaria research. There were no web sites for CMPE in Lao PDR or the Malaria Control Program in Myanmar. Two sites with a reasonable amount of information in English are the Yunnan Institute for Parasitic Diseases (www.yipd.org) and the National Malaria Center in Cambodia (www.CNM.gov). Both institutions conduct academic and operational research, notably, therapeutic efficacy studies, malaria surveillance, bed net effectiveness, *in vitro* drug sensitivity testing and molecular mapping of drug resistant *P. falciparum*. The YIPD has a broader range of studies that include malaria mapping, relapse patterns of *P. vivax*, and mosquito vector studies. NIMPE Hanoi has a good web site in Vietnamese with limited English. However, it collaborates closely with the Institute of Tropical Medicine in Antwerp which has an extensive web site (www.itg.be). The Thai Ministry of Public Health has a comprehensive summary of its malaria activities but this does not include a research agenda (http://eng.moph.go.th/SpecificHealth/malaria/malaria.htm). The Thai Bureau of Vector Borne Diseases web site appears comprehensive and is in Thai only. The web site for the Myanmar MOH is well presented with brief summaries of research activities. Because of the challenges with these web sites, no attempt was made to evaluate them.

DISCUSSION

Eliminating malaria is a public health challenge but is believed to be achievable in areas of low malaria transmission like the GMS. Ultimately, global malaria elimination is a stated ambition of the WHO. Optimal strategy recommendations by NMCPs or the WHO should be based on quality evidence that has enough weight to be convincing. Obtaining that evidence defines what we mean by research but research does not stop there. Once recommendations are being implemented, the results should be documented and evaluated critically to determine whether they work outside of the research setting and to inform policy makers of the need to change or test new strategies. In addition, NMCPs need to know if they are hitting their targets by monitoring and evaluation (M&E).

This overview has shown that research in the GMS is rich and extends across many areas. As expected, most of the research output is biomedical in nature. The ten main

research areas accounted for just under 80% of the total research output. Some of these areas are highly relevant for public health policy, notably drug and insecticide resistance, bed net studies, phase III type clinical trials, malaria control, malaria epidemiology and diagnostics, especially RDTs. Other research areas like pharmacokinetics are essential to confirm or otherwise optimal drug dosing in different population subgroups and parasite biology and pathophysiology aim to increase our understanding of malaria. Knowledge of G6PDd in this region is important because primaquine, whose main toxicity is acute intravascular hemolysis in G6PD deficient patients, is recommended by the WHO for transmission blocking and for antirelapse treatment of liver hypnozoites (WHO, 2010). It is considered a very valuable drug for malaria control (http://www.who.int/entity/malaria/pq_updated_policy_recomendation_en_102012.pdf) (White, 2013).

A small number of publications have dealt with non malaria infections (Phongmany *et al*, 2006; McGready *et al*, 2010). As malaria declines, non malaria fevers will increase in importance and will require appropriate clinical and laboratory management. Accordingly, research to evaluate easy to use RDTs for diagnosis and surveillance will need to be done, treatment algorithms developed and training given.

Some research areas are distinctly underrepresented by the published literature; these include socioeconomics, modeling, migrants (see further details in Chapter 4), and the effects of climate change on malaria. Migrants have been identified as one of the most vulnerable populations in the GMS and potentially important spreaders of artemisinin resistance. Mathematical modeling is a tool that could have a major impact on malaria control, especially artemisinin resistance and the effect of primaquine as a transmission blocking drug (Maude *et al*, 2009, 2010).

Two research reviews similar to one presented herein have been published, one a global overview (Lewison and Srivastava, 2008), the other an overview of the 11 Asian Pacific countries of the Asia Pacific Malaria Elimination Network (APMEN, www.apmen.org) that are all committed to eliminating malaria (Andersen *et al*, 2011).

The global review classified research into two broad categories, namely, clinical and basic science and was subdivided into ten research areas relating to malaria control such as mosquitoes, their habitats, bed nets, vaccine work, and the commonly used antimalarial drugs. Lewison and Srivastava (2008) speculated that research would reduce the malaria burden because effective control measures were more likely to be adopted by control programs. This would be worth moritoring in the GMS.

Two findings of note were the high research output from Thailand and the predominance of research by non-malarious industrialized countries. This GMS review also found that

Thailand produced the most papers, ~ 60%, and is accounted for by its large number of research institutions as well as being the home for two important research collaborations between Mahidol and Oxford Universities, and the Armed Forces Research Institute of Medical Science (AFRIMS) which is a collaboration between the Royal Thai and US Armies.

The APMEN review had 10 research categories covering a broad spectrum of research but also classified research output based on malaria species. In common with the global review, malaria research did not keep up with other research areas and Thailand produced the highest number of papers. One finding was the increase of *P. vivax* publications relative to *P. falciparum*, a welcome trend given the neglect of vivax research and the challenges posed in trying to eliminate *P. vivax* (Price *et al*, 2007).

This GMS review has attempted to shed light on work done by NMCPs and NGOs. Not surprisingly, the research output in terms of peer reviewed papers is low. The administered questionnaire met with some success in terms of a response and has provided a reasonable amount of information on their research activities and project work.

Much of the work of the NGOs is field/community based and done in partnership with the country NMCPs. Doubtless, reports are written but access to them, if not web sited, is difficult. Furthermore, it is crucial to put reports on web sites and to update web sites on a regular basis. This review did not detail the quality of the accessed web sites but most of them only provided superficial information. Improving web site information is one area of future work for the NMCPs and NGOs.

Work by NMCPs and NGOs can potentially raise many research questions of a practical nature and answers to these questions will inform future work and strategy development. They could also conduct more biomedical research but this would need a degree of further training and enhanced capacity in such areas like protocol development, good clinical and laboratory practices and scientific writing.

A comprehensive report on operational research in the GMS has been written by the Malaria Consortium, “Report of the Greater Mekong Sub-region Malaria Operational Research Symposium.” The report details current research activities, knowledge gaps and research needs. Research needs are numerous and broad and include containing artemisinin resistance, malaria control in migrants, G6PDd mapping, studies of primaquine safety, vector ecology and bionomics, training for private pharmacies, molecular mapping for drug resistance, *in vitro* culture for *P. vivax*, evaluating the effectiveness of insecticide treated materials, and capacity building. Interestingly, malaria in pregnancy was not listed as a separate research area. This long list of research needs illustrates the research challenges faced by the GMS.

Limitations

This overview, by virtue of having easy access to peer reviewed articles, is heavily biased towards the scientific literature. The system of classification used was based on personal judgment in conjunction with information from Pub Med. The broad areas of classification were straight forward but the subdivisions were more problematic especially when papers covered several research areas or research areas with similar themes. Malaria in pregnancy was not listed as a separate subject area but was coded for during classification; there were 72 pregnancy related publications.

The classifications used by the global and APMEN research reviews were similar but had fewer subdivisions (Lewison and Srivastava, 2008; Andersen *et al*, 2011). Use of a search algorithm by Andersen *et al* (2011) is salutary. Discussions within the malaria research community would be helpful to have one system of classification that harmonizes with Pub Med and other key search engines. A uniform system for classifying broader areas of research would also be helpful for researchers and those in NMCPs. Currently there is much confusion. A system to define operational, implementation and health systems research has been proposed by Remme *et al* (2010). This GMS review did not attempt to classify research along the lines suggested by Remme *et al* (2010) nor were attempts made to assign studies to institutions or ascertain funding sources. Such data would be useful to give us a more comprehensive picture.

Where to go from here?

Many of the important research gaps have been identified as well as issues of concern for NMCPs and NGOs; the long list of research needs from CMPE/WHO Lao PDR is very informative and reflects a substantial need. Clearly a lot needs to be done to set priorities, write proposals, seek funds, develop protocols, execute quality work, record and analyze data and feedback the data to NMCPs, the WHO, NGOs and the regional and wider research community.

There are now many organizations in the Mekong region dedicated to malaria control and research. Good coordination and keeping abreast of who is doing what are crucial to optimize the use of resources for projects of the highest public health benefit. In addition, closer cooperation is needed between control and research so that the research policy gap can be bridged – a familiar theme (Garner *et al*, 1998; Woelk *et al*, 2009). Some research is initiated by NMCPs themselves and this needs to be further encouraged and supported. Capacities vary across the Mekong and training is, thus, essential. The Asian Collaborative Training Network for Malaria (http://www.actmalaria.net) is Mekong based and provides training in such areas as malaria surveillance and epidemic management,

malaria microscopy, operational research, drug policy development and mid-level field management/operations.

Coordinating malaria research and setting priorities in the GMS is a tremendous challenge that would require an adequately resourced organization working with all the relevant partners.

Concluding remarks

The GMS has pressing research challenges, not least of which are the determinants of artemisinin resistance, how best to contain it and tacker the issue of primaquine safety. Finding optimal solutions will require a concerted effort over several years in a coordinated fashion and must involve academia, NMCPs, NGOs and the WHO. The research capacity of this region certainly varies but the research activities cover a very broad range of activities so obtaining robust evidence for implementing optimal strategies is possible.

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