Myanmar Artemisinin Monotherapy Replacement Malaria Project (AMTR) Independent Evaluation

Working Paper 2 – June 2014

Adding primaquine to the standard treatment of uncomplicated *P. falciparum* malaria – perceptions of various providers and options for implementation strategies

UKaid
from the British people

Myanmar Artemisinin Monotherapy Replacement Malaria Project (AMTR) Independent Evaluation

Is implemented by

Montrose

In partnership with

TROPICAL HEALTH

INNOVISION Consulting Private Limited
endless possibilities

ACKNOWLEDGEMENTS

The evaluation team would like to thank all those who have generously given their time, experiences and expertise in guiding this assessment. In particular, the staff of DFID and PSI in Yangon. The team would also like to specifically thank all individuals listed in this paper who were interviewed as part of the assessment.

This material has been funded by UKAid from the UK Department for International Development (DFID). The views expressed do not necessarily reflect those of HM Government

Table of Contents

ABSTRACT

An independent research team was tasked with evaluating the Artemisinin Monotherapy Replacement (AMTR) Project in Myanmar, funded by the UK Department for International Development (DFID), the Bill and Melinda Gates Foundation (BMGF), and Good Ventures, and implemented by Population Services International (PSI). In addition to their evaluation role, the team has also produced a series of working papers and case studies on areas of the project that provide valuable learning for project implementation, the internal stakeholders, and indeed the wider malaria community. This report is one in a series of papers, looking at the specific target area of malaria transmission reduction through use of the drug primaquine (PQ).

PQ is a malaria gametocidal, transmission-blocking drug that is currently included in Myanmar's National Malaria Treatment Guidelines, accompanying Quality-Assured Artemisinin Combination Therapy (QA-ACT) for treatment of *Plasmodium falciparum* (*P.falciparum*) malaria. Despite the national policy, which was amended to include the addition of PQ for *P. falciparum* in 2011, PQ is not used widely by medical practitioners. This is due, in part, to ineffective policy communication and also to the medical practitioners' fears that it induces haemolysis in patients, which is a risk if a patient has glucose-6-phosphate dehydrogenase (G6PD) deficiency. In malaria containment areas of Myanmar along the Thai border and in Kachin state, PQ is recommended to be given free of charge with ACT as part of active case management by volunteer malaria workers in high risk villages and to mobile malaria workers, especially targeting mobile and migrant populations. However, it is not necessarily being administered in the rest of the country and it is not currently available through pharmacists in the private sector. It is currently only distributed through the National Malaria Control Program.

The AMTR programme, which set out to remove Artemisinin Monotherapy (AMT) from the private market and replace it with QA-ACT, states in the log frame as its fourth output level indicator: the *"number of women and men who receive appropriate treatment to contain the spread of drug-resistant malaria through DFID funding."*[1] However, it is unclear whether in this context, the statement "appropriate treatment to contain…" refers to any QA-ACT, or only QA-ACT plus single dose of PQ. The latter can be considered as "stopping further spread," but is only present in the treatment guidelines in Myanmar and not yet implemented in the private sector by PSI. This output level indicator can be revised or removed, however the issue of PQ supply remains pertinent in halting the spread of malaria in Myanmar and therefore the arguments for and against supplying PQ widely are worth considering.

Studies[2] have shown that despite PQ having been recommended over the last 50 years as a malaria transmission-blocking drug, it is still not a perfect solution to the problem. It is one of the relatively inexpensive 8-aminoquinoline group of drugs (that also includes tafenoquine and bulaquine), but it can cause haemolysis in patients with G6PD

[1] Taken from PSI AMTR Project Log Frame

[2] See: Lawpoolsri, 2009; Smithuis, 2010; White, 2012; Graves, 2012; Recht, 2014

deficiency, which has a high prevalence in South and South East Asia[3]. This is a risk and an ethical dilemma that has to be weighed up when offering a drug which does not have an immediate health benefit to the recipient in curing *P. falciparum* malaria, but does have a public health benefit in preventing further transmission of the disease. This is an important consideration for a country that is in the pre-elimination of malaria stage. However, Myanmar is currently still in the control stage, dealing with the very immediate and urgent need to contain artemisinin resistance.

Stakeholder interviews[4] revealed that there is not a big lobby in support of widespread availability of PQ in Myanmar. Most health professionals acknowledge its role, but recognize the ethical barriers of having to test for G6PD deficiency and the public health nature of the drug versus the non-essential administration for individual treatment; practical barriers such as co-packaging; inability to supply blister packaging; different shelf-life of ACT and PQ; and making the drug available nationally in the private sector.

There is a call for further research before any final decision is taken. One review by White (2012)[5] has suggested that there is a possibility of offering a lower dose regimen of PQ, which still prevents transmission and is less dangerous with regard to G6PD. This is reiterated in the latest World Health Organisation (WHO) review of 8-aminoquinoline drugs[6]. However, further research is still needed to understand the extent of G6PD deficiency in Myanmar as there are still many unknowns. New products are in development – a G6PD Rapid Diagnostic Test (RDT) Kit[7]; and another transmission-blocking drug – tafenoquine, which although having the same properties as PQ, is considered a milder drug[8].

In conclusion, it is still considered too early for Myanmar to adopt PQ as the first line case management nationwide through the formal or informal private sector. It is responsible practice for containment, but supplying PQ through the private sector is fraught with practical difficulties, and more importantly, is also not an imperative for a country still in the control phase. Indeed, 'The Cochrane review'[9] states that the drug is ineffective in conditions of control whereby, "there is no reliable evidence that this will reduce transmission in a malaria-endemic community, where many people are infected but have no symptoms and are unlikely to be treated." Therefore, the issue should remain on the agenda and consensus sought for reducing the dosage to the safer 0.25 mg/kg dosage, administering on day one, exploring the options for RDT of G6PD, and indeed introducing the new milder drug when available. At the same time, training of health practitioners is needed to ensure that, as Myanmar moves toward pre-elimination and elimination, the malaria treatment policy is clearly articulated and included within a retraining programme to allay practitioner fears about the drug and ensure that it is used responsibly.

[3] Howes, 2012
[4] Conducted in field visit interviews, undertaken in Yangon, Nay Pyi Taw and Mandalay in February 2014
[5] White, 2012
[6] Recht, 2014
[7] Roca-Feltrer, 2012
[8] Review of Mass Drug Administration and Primaquine Use (Background Paper), UCSF Global Health Services, Jan 2014
[9] Graves, 2012

ACRONYMS AND ABBREVIATIONS

3MDG	3 Disease Fund & Millennium Development Goal (Principal Recipient of Global Fund)
ACT	Artemisinin Combination Therapy
AMT	Artemisinin Mono-Therapy
AMTR	Artemisinin Monotherapy Replacement
BHS	Basic Health Staff (contracted staff in public sector)
BMGF	Bill and Melinda Gates Foundation
CHW	Community Health Worker (same as VHW) – voluntary
DFID	Department for International Development
DOTs	Directly Observed Treatment
FDA	Food and Drug Administration
G6PD	Glucose 6-phosphate dehydrogenase
GMP	Good Manufacturing Practice
GPARC	Global Plan for Artemisinin Resistance Containment
MAM	Medical Action Myanmar
MARC	Myanmar Artemisinin Resistance Containment
MMA	Myanmar Medical Association (Private Medical Practitioners)
MMW	Mobile Malaria Workers
MoH	Ministry of Health
MPMEEA	Myanmar Pharmaceutical & Medical Equipment Entrepreneurs Association
NMCP	National Malaria Control Program
P. falciparum	Plasmodium falciparum
P. vivax	Plasmodium vivax
PQ	Primaquine
PSI	Population Services International
QA-ACT	Quality Assured Artemisinin Combination Therapy
QA/QC	Quality Assurance/Quality Control
RAI	Regional Artemisinin Initiative
RDT	Rapid Diagnostic Test
SCF	Save the Children Fund (Principal Recipient of Global Fund)
TSG	Technical Strategy Group (for Malaria in Myanmar)
UCSF	University of California and San Francisco
UNOPS	UN Operations (Principal Recipient of Global Fund)
VBDC	Vector Bourne Disease Control (MoH)
VHW	Volunteer Health Worker (same as CHW) – voluntary
VMW	Volunteer Malaria Worker - for MARC area only – voluntary
WHO	World Health Organisation

1. INTRODUCTION

The Myanmar Artemisinin Resistance Containment (MARC) framework, developed in collaboration with the World Health Organisation (WHO) and in line with the Global Plan of Artemisinin Resistance Containment (GPARC), was endorsed by Myanmar's Ministry of Health in April 2011 and outlines immediate containment actions to be put in place to contain artemisinin resistance in Myanmar[10]. To date, resistance of *Plasmodium falciparum (P. falciparum)* has been confirmed in three states along the Thai-Myanmar border (Figure 1); containing this resistance is of upmost importance to prevent the further spread of resistance within Myanmar, as well as regionally and globally.

The goals of MARC are:

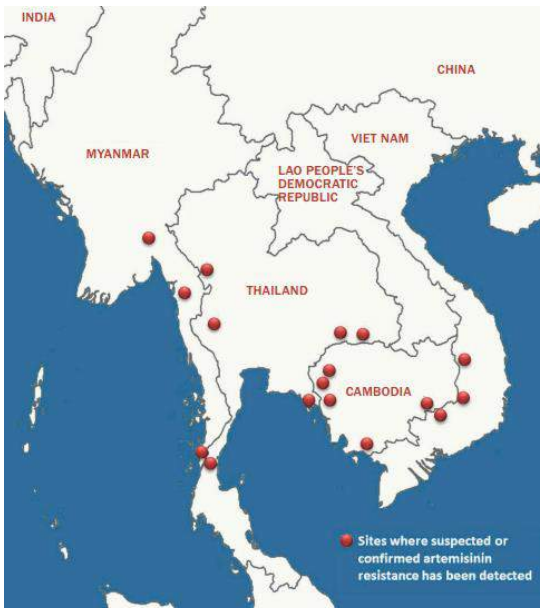
(i) To prevent, or at minimum, significantly delay the spread of artemisinin resistant parasites within the country and along its border; and

(ii) To reduce transmission, morbidity and mortality of *P. falciparum* malaria, with priority to areas threatened by resistance.[11]

Key activities include improving case management through community and private sector involvement, by providing subsidised Quality-Assured Artemisinin Combination Therapy (QA-ACT) and diagnosis, as well as banning oral artemisinin-based monotherapies.

The NGO, Population Services International (PSI) has received funding from UK Department for International Development (DFID), the Bill and Melinda Gates Foundation (BMGF) and Good Ventures, for the Artemisinin Monotherapy Replacement Malaria

Figure 1. Sites where suspected or confirmed artemisinin resistance has been detected as of 2012 (ERAR framework 2013-2015)



[10] Myanmar Artemisinin Resistance Containment Plan, 2011

[11] Myanmar Artemisinin Resistance Containment Plan, 2011

Project (AMTR). PSI has worked closely with private sector suppliers and providers throughout Myanmar to rapidly replace artemisinin monotherapy with highly subsidised QA-ACTs[12].

An independent research team was tasked with evaluating the AMTR Project in Myanmar, as well as with producing a series of working papers and case studies on areas of the project that provide valuable learning for project implementation, the internal stakeholders, and indeed the wider malaria community. This report is one in a series of papers, looking at the specific target area of malaria transmission reduction through use of the drug primaquine (PQ).

[12] Outlet Survey: Baseline Study The Republic of the Union of Myanmar 2012 Survey Report

2. BACKGROUND

P. falciparum gametocytes are sensitive to the drug primaquine (PQ). WHO recommends giving a single dose or short course of PQ alongside primary treatment for people with *P. falciparum* infection to reduce malaria transmission.[13]

In order to achieve local elimination or containment, which Myanmar is striving for, the full repertoire of malaria control activities must be applied. This includes: (i) vector control measures; and (ii) case management, where all infections, symptomatic or not, are targeted and treated with a complete course of a quality assured ACT in combination with a single, low dose of primaquine which is able to kill gametocytes and, thereby, prevent further transmission. Such ACT treatment – as long as there is compliance with the full course of treatment - will be able to kill even artemisinin resistant strains of *P. falciparum* as long as parasites are still sensitive to the partner drug within the ACT combination.

Further, *Plasmodium-vivax (P. vivax)* is becoming more prevalent in Myanmar. Treatment with chloroquine is the standard recommended therapy for malaria caused by *P. vivax* (as well as by *Plasmodium Malariae [P.malariae]*, and *Plasmodium. Ovale [P.ovale]*). In the areas of chloroquine sensitivity, a 3-day course of treatment kills most stages of all the non-*falciparum* species. However, chloroquine does not kill the liver stages (hypnozoites) of *P. vivax* or *P. ovale.* PQ is required as an additional drug given over 14 days.

[13] Single Dose Primaquine as a gametocytocide in Plasmodium falciparum malaria, WHO Global Malaria Programme, Updated WHO Policy Recommendation, Oct 2012

This has significant pertinence to the Artemisinin Monotherapy Replacement (AMTR) Project, since the fourth indicator at outcome level, taken from the DFID-Myanmar log-frame, requires a statement of the, "number of women and men who receive appropriate treatment to contain the spread of drug-resistant malaria through DFID funding"[14]. Part of the indicator requires a simple output measure of the number of QA-ACT sales in the PSI project area funded by DFID, and as such is easily measurable. However, the qualification regarding resistance containment makes the indicator un-measurable. It is therefore unclear whether in this context, the statement "appropriate treatment to contain…" refers to any QA-ACT, or only to QA-ACT plus single dose of PQ. The latter can be considered as "stopping further spread" but is only present in the treatment guidelines in Myanmar and not yet implemented in the private sector by PSI. Furthermore, to be determined as adequate treatment, it is essential to know whether the fever was a *P. falciparum* infection, *P. vivax* or no malaria at all, and this information is usually not available for routine data systems that provide the number of treatments sold or dispensed. As stated in the Inception Report, it is therefore important that this indicator be either revised or dropped. It is envisioned that this Working Paper will provide significant input into the discussion around this decision.

2.1. Hypothesis and Research Question

- Currently there is some controversy over the supply of PQ in the private sector. Although the Government of Myanmar's

[14] Taken from PSI AMTR Project Log Frame

Department of Health acknowledges and explicitly states that PQ should be included in public sector malaria treatment guidelines,[15] there is some reluctance to allow this provision in the unregulated private sector. PQ is not available as an over-the-counter drug. The purpose of this working paper is to examine the issues of supply of PQ in the private sector by questioning the various stakeholders about their concerns. Below are the research questions:What are the strategic options for PQ supply in Myanmar?

- What are the legal stipulations about PQ supply in the public and private sectors?
- Who are the main stakeholders in PQ supply, e.g. Myanmar Department of Health; Myanmar Department of Food and Drug Administration (DFDA); Myanmar Medical Association; PSI (and Sun Quality Health Franchisees); retailers etc?
- What are the main technical issues for consideration of PQ supply in Myanmar?
- What are the major barriers to PQ supply in the private sector and what are the necessary steps to overcome such barriers?
- How would PQ be packaged and supplied in the private sector?

2.2. Methodology

This working paper was informed by interviews with the primary stakeholders in-country. An interview guide was developed and interviews conducted with both national level stakeholders and also a small sample of lower level stakeholders such as retailers and private medical providers, to inform a full picture of the decision makers and the potential supply chain for PQ. These interviews were conducted in February 2014. Document and data sources were also reviewed and include papers regarding the supply of PQ in malaria control and elimination (see references for documents reviewed).

2.3. Timing

The independent evaluation team made the visit to Myanmar in early February 2014 to undertake the research for this paper.

[15] Myanmar National Drug Policy for Malaria: A Summary, July 7, 2012 VBDC, Myanmar

3. OVERVIEW

3.1. Primaquine – what it is and how it is used in malaria control?

Currently, in containment efforts to reduce the spread of *P. falciparum* malaria in Myanmar, PQ (described in Box 1) is the only malaria transmission blocking drug available, as stated in the WHO updated policy recommendation[16]:

"PQ potentially has a major role in reducing malaria transmission, especially in efforts to eliminate P. falciparum malaria. The population benefits of reducing malaria transmission by gametocytocidal drugs require that a very high proportion of patients receive these medicines." (WHO, 2012)

Mosquitoes become malaria infected when they ingest gametocyte stages of the parasite from the blood of a human host. *P. falciparum* gametocytes are sensitive to PQ. Gametocytes themselves do not cause any symptoms, so the administration of PQ does not directly benefit individuals. The benefits are felt on a Public Health front, preventing further malaria transmission within a population. However, PQ causes haemolysis in some people with glucose-6-phosphated dehydrogenase (G6PD) deficiency and so cannot be considered a completely safe Public Health option.

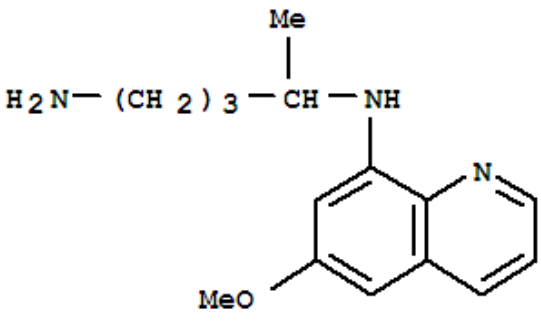
Due to the drug's major contraindication – the potential risk of haemolysis in patients who are G6PD deficient – PQ is underused when treating malaria. It is a member of the 8-aminoquinoline group of drugs that includes tafenoquine, bulaquine and pamaquine17. The 8-aminoquinolines have a rapid and powerful sterilising effect on mature gametocytes. The specific drug, PQ, was first synthesised in the 1940s. It is a relatively inexpensive drug and has been recommended in malaria treatment for over 70 years; however, it is still fraught with complications and contradictions both in its considered efficacy and in its practical administration for malaria treatment, or rather for malaria-transmission blocking.

Box 1: Chemical Structure of Primaquine (Source WHO, 2014 p 19)

Established: 1945

Pharmacokinetics: Elimination half-life in humans – 4-6 h; mean peak plasma concentration, 100–200 ng/ml 2–3 h after a 30-mg dose

Toxicity: Commonest side-effects are gastrointestinal, reduced when administered with food; haemolytic risk for G6PD-deficient individuals. Only 8-aminoquinoline widely used as anti-malarial agent.



[16] Single Dose Primaquine as a gametocytocide in Plasmodium falciparum malaria, WHO Global Malaria Programme, Updated WHO Policy Recommendation, Oct 2012

[17] Recht, 2014

Graves et al[18] found no reliable evidence that PQ reduces malaria transmission in malaria endemic areas where many people are infected but have no symptoms. However, White et al[19] proposed that in areas of low transmission, PQ is effective and went so far as to show that a single lower dose of PQ (0.25 mg/kg) is sufficient in reducing the infectiousness of malaria in conjunction with an ACT in *P. falciparum* cases and also at the same time further reducing the risk of haemolysis in a G6PD patient.

3.2. Use for treatment of *P. vivax*

PQ is mainly used to treat the *P. vivax* or *P. ovale* malaria. Once the parasite has been eliminated from the bloodstream, the remaining hypnozoites must be removed from the liver and this is done by administering a 14 day course of PQ (0.25mg base/kg/day for 14 days[20]). One reason for Myanmar medical practitioners' fear of administering primaquine is that it is used as a first line treatment in cases of *P. vivax*, where it is administered with chloroquine over 14 days. *P. vivax* treatment requires a much higher *total* dose than is required for *P. falciparum* malaria, which requires only a single dose. The higher dose for *P. vivax* is more likely to show up adverse reactions in people with G6PD deficiency, which is witnessed by medical practitioners (although this is very dependent on the type of G6PD deficiency.)

3.3 Contradictions – G6PD deficiency

The extent of the risks when administering PQ to populations with a potential G6PD deficiency is still being debated in academic circles. This working paper will highlight a few of the studies and their relevance to the situation in Myanmar.

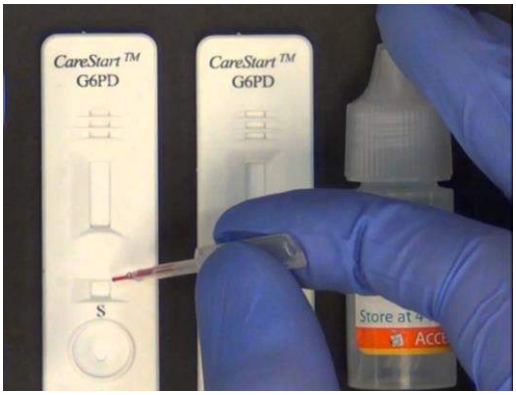
A geostatistical model-based map was developed[21] recognising that poor information is available about the distribution of individuals at risk of PQ-induced haemolysis. The programme team developed a continuous evidence-based prevalence map of G6PD deficiency and estimates of affected populations, together with a national index of relative haemolytic risk. They found that West Asian countries, where variants were most severe, had the highest relative risks from G6PD deficiency.

There is always a risk of haemolysis when PQ is given to G6PD-deficient individuals, but the extent of haemolysis depends on the dose and duration of exposure and the degree of deficiency[22].

There is no rapid test kit for G6PD currently available and White suggests[23] his findings are sufficient evidence of safety and efficacy to support wide scale deployment, without testing. It is worth noting that an inexpensive and heat-stable point-of-care diagnostic for screening G6PD deficiency (The CareStart G6PD Kit) is currently under development by AccessBio (USA) (see Box 2). It has been trialled in Cambodia[24]. More

[18] Graves, 2012
[19] White, 2012
[20] Guidelines for Diagnosis & Management of Malaria in Myanmar, WHO Myanmar, 2011
[21] Howes, 2012
[22] Recht, 2014
[23] White, 2012
[24] Roca-Feltrer, 2012

Box 2: The CareStart G6PD Kit is currently under development by AccessBio (USA)

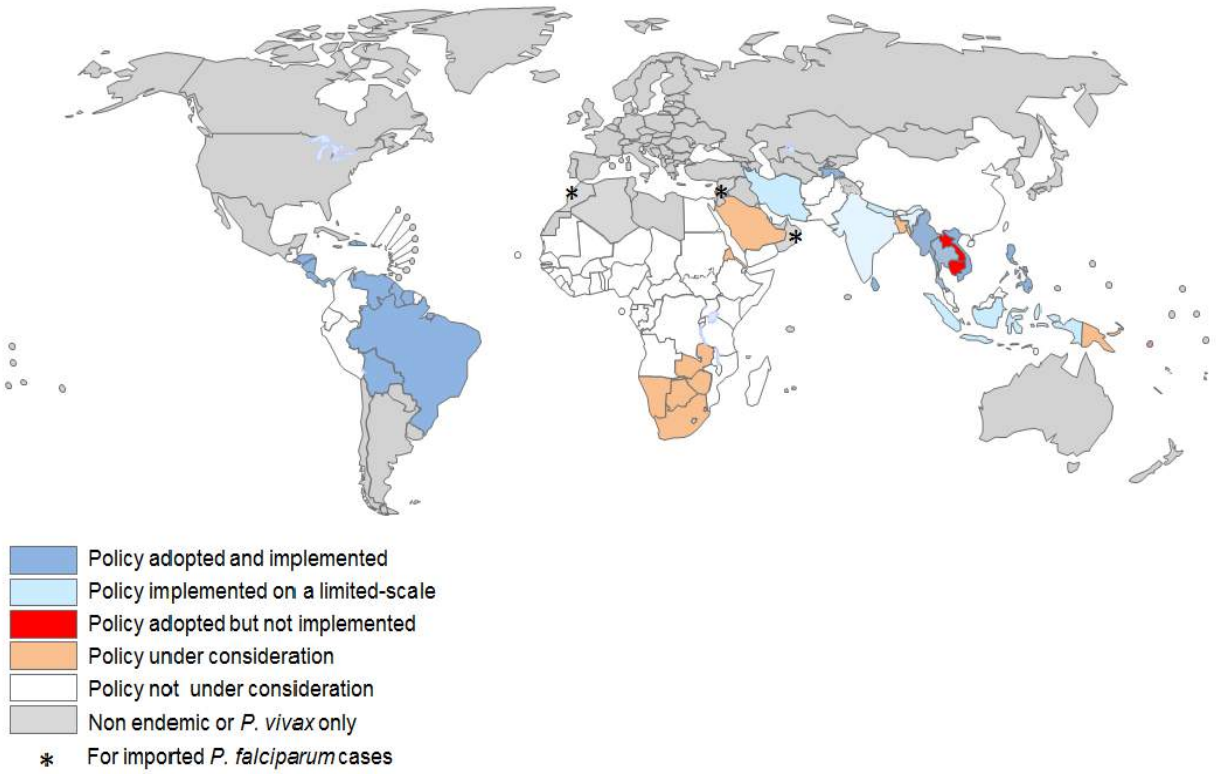


recently, a review of Mass Drug Administration & PQ Use[25] concluded that the lower dose 0.25/kg has a very low risk of haemolysis among subjects with mild or moderate G6PD deficiency and found that PQ regimens were accompanied by safety monitoring in populations that underwent MPPT (15mg of PQ daily for 14 days), including in populations that were G6PD deficient.

Further contraindications are that PQ should not be given to pregnant women or children under 1 year.

Although most published articles call for further research, it appears that amongst academic circles, the use of low dose PQ is accepted as efficacious to reduce infectiousness and indeed is now stated so in the updated WHO Policy[26].

Figure 3: The global distribution of country policies regarding deployment of primaquine as a single dose gametocytocide



[25] Review of Mass Drug Administration and Primaquine Use (Background Paper), UCSF Global Health Services, Jan 2014

[26] Single Dose Primaquine as a gametocytocide in Plasmodium falciparum malaria, WHO Global Malaria Programme, Updated WHO Policy Recommendation, Oct 2012

3.3. Use in different countries in the region

Malaria Treatment Policies vary in the Greater Mekong Sub-region and other parts of Asia (Figure 2). Despite WHO guidelines, the timing and dosage of PQ for *P. falciparum* is left up to the discretion of each country malaria program (see Tables 1-3).

Table 1: Use of Primaquine in different countries in the region

Country	Adult Dosage	Timing of Administration
Myanmar	45 mg (6 x 7.5 mg tablets)	3rd day
Thailand	30 mg (2 x 15 mg tablets)	3rd day
Vietnam	30mg (2 x 15 mg tablets)	3rd day
Sri Lanka	45 mg (3 x 15 mg tablets)	3rd day [reports of 1st day also]
India	45 mg (3 x 15 mg tablets)	2nd day
Cambodia	None *(15 mg tested in 2013)*	None
China	None	None
Lao PDR	None	None

Table 2: Primaquine regimens commonly used for P. vivax

Daily Dose mg base/kg	Adult Dose*	Duration	Total Adult Dose	Recommendations
0.25	15 mg	1 per day x 14 days	210 mg base	A higher dose of 0.5 mg/kg is used in some countries incl. Melanesia
0.75	45 mg	1 per week x 8 weeks	360 mg base	Recommended by WHO in mild to moderate G6PD deficiency

N.B. Neither to be used in known or severe G6PD deficiency *based on 60kg adult

Table 3: Primaquine regimens commonly used for P. falciparum

Daily Dose mg base/kg	Adult Dose*	Duration	Total Adult Dose	Recommendations
0.75	45mg	1 day	45mg base	WHO, 2010: Require G6PD test. Some countries decided to use 0.5 mg base/kg or give PQ on multiple (Central America) or various days (1 to 4)
0.25mg	15mg	1 day	15mg base	WHO, 2012: For elimination areas or those threatened by artemisinin resistance. Day 1 recommended but there is no evidence on which day is better.

*based on 60kg adult

4. USE OF PRIMAQUINE IN MYANMAR

4.1 Primaquine and the malaria treatment regimen for *P. falciparum*

In Myanmar, in practice, the use of PQ is very low. The latest MARC survey shows virtually no awareness of PQ as a malaria treatment drug[27], despite it being recommended as a malaria treatment since 2008 (see Figure 4). There is a strategic difference between malaria control and containment and this is not clearly articulated in Myanmar, particularly where PQ is concerned.

As Smithuis[28] pointed out, there is not a big lobby for supply of PQ in the private sector. However, he believes it does have a role in Targeted Malaria Elimination (TME), a MARC strategy where whole villages are treated three times in one month. Further confusion is evidenced, when reviewing the Myanmar Guidelines for Diagnosis & Management of Malaria in Myanmar (2008)[29] - Annex 1: Drug Schedules:

PQ dosage for P. vivax malaria
A course of chloroquine (as for treatment of P. vivax malaria) is to be followed by PQ at 15 mg daily for 14 days. (PQ at 0.25 mg per kg daily for 14 days after standard chloroquine course in case of children over one year).
Note: *Side effects include abdominal pain (common if taken on an empty stomach), intravascular haemolysis (particularly in patients with G6PD deficiency).*

PQ dosage for falciparum malaria
PQ 0.75 mg /kg stat is given to interrupt infectivity of malaria to Anopheles. Contraindications: It is contraindicated in pregnancy. Anti-relapse treatment with PQ can be given after delivery. In patients with G6PD deficiency, PQ should be given at 45 mg weekly for 8 weeks.

Note: *It is contraindicated in severe G6PD deficiency.*

The updated Drug Policy (2011)[30] did not make the situation any clearer:

A guideline for diagnosis and management of Malaria in Myanmar 2011 was developed for those involved in deploying malaria treatment.

In January 2011, minor modifications were made in the national treatment guidelines; i.e., 1) PQ single is prescribed for all confirmed falciparum cases; 2) PQ (8 week single dose) is prescribed for all P.vivax cases by village health volunteers.

This statement does not state the revised 0.25 mg/kg dosage (or adult 15 mg dosage). The policy is not clearly stated in the published literature.

There are two sizes of tablet most commonly used: the 7.5mg and the 15mg tablet. Both formulation sizes have been available in Myanmar, further complicating training for correctly administering the drug. Currently the 7.5mg tablet is procured in tubs of 1000 tablets e.g. UNOPS procurement in 2013 was 562 tubs[31]. This 7.5mg tablet form is also easier to administer to children.

[27] Myanmar Artemisinin Containment (MARC) Survey Report, 2012
[28] Taken from interview with Frank Smithuis, MAM in Yangon, February 2014
[29] ibid
[30] National Malaria Control Programme Summary of Malaria Treatment Policy, 2012
[31] Taken from interview with UNOPS staff in Yangon, February 2014

4.1. Regulatory aspects

During the data collection in February 2013, a visit was made to the DFDA in Nay Pyi Taw to ascertain the current regulatory practice for PQ supply in the country. Two manufacturers were listed as supplying Myanmar currently with PQ: Jayson Pharmaceuticals Pvt Ltd (India) and Macleods Pharmaceuticals Ltd (India). The DFDA stated the PQ is a "prescription-only" drug and as such is not available in the private retail sector. Only a licensed medical doctor can prescribe PQ. As far as the DFDA were concerned, the main problem with PQ being supplied over-the-counter is the safety issue of blood dysplasia and haemolysis, although it was stated that this was more of a problem with the *P. vivax* treatment over 14 days than a single *P. falciparum* treatment. The DFDA brought up the issue of packaging a single dose PQ with an ACT. They stated that if there is sufficient liaison with the supplier, they could not foresee a problem of including, for example, a single dose of PQ into a pre-packaged formulation with ACT. The expiry date on the pack would, of course, be expected to match the earliest expiry date of the two products (see example blister pack illustration, Figure 3).

WHO representatives[32] have stated that sugar coating affects the absorption of the drug PQ; it can prevent the side-effect of irritation in the stomach as the tablets dissolve in the intestines and not the stomach. Currently, the formulation used in Myanmar is not sugar-coated.

Presently only 3 international manufacturers of PQ with WHO pre-qualification were identified from WHO pre-qualification lists:

- Remedica – Cyprus
- Sanofi/Valeant Pharmaceuticals – Canada
- IPCA – India

4.2. Provision and perspective of stakeholders

Currently, the main source of provision of PQ is through the NMCP – who then distribute to:

i. Public Sector hospitals;
ii. Village Health Workers / Voluntary Malaria Workers – are trained to tell patients to look out for dark urine (as a symptom of G6PD deficiency after taking primaquine); and
iii. Private Sector Medical Practitioners through MMA, PSI.

[32] Taken from interview with WHO-Myanmar Malaria Advisors, in Yangon, February 2014

These perceptions are detailed in Table 4 below:

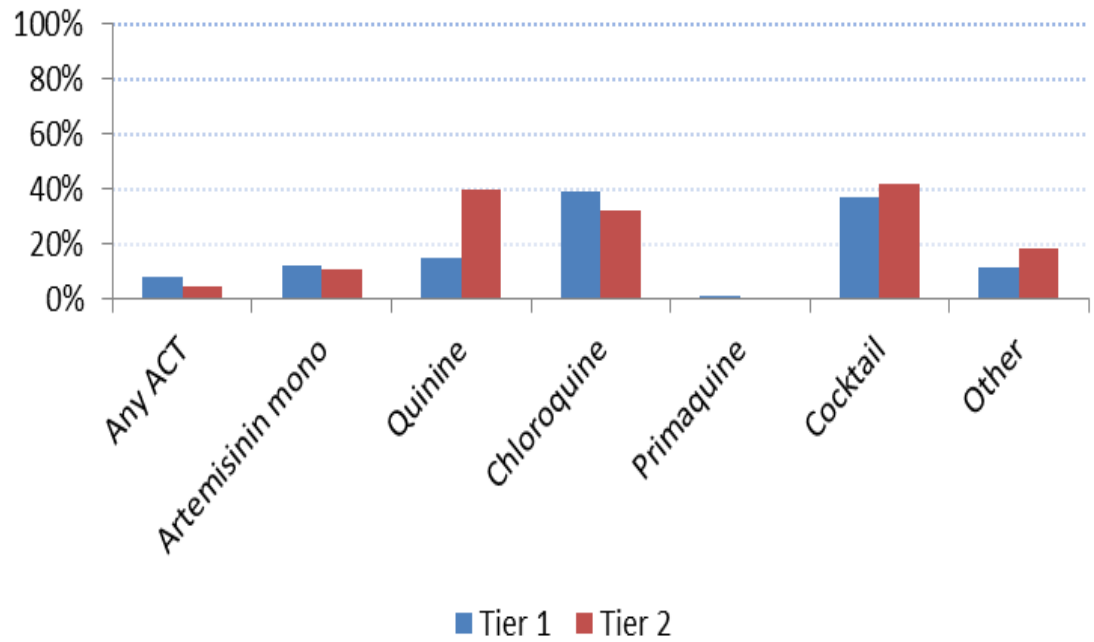
Table 4: Stakeholder Perceptions[33]

Stakeholder	General Perception	View on Private Sector Supply
VBDC	- Generally in favour of PQ use, but recognise that practitioners' fear consequences of high G6PD deficiency and so do not use widely. - Policy in place for VHWs and VMWs to administer PQ for *P. falciparum.* They receive the drug in bulk (large tubs) and administer individual tablets according to weight of patient. - Under a new funding programme RAI (Regional Artemisinin Initiative, in Kayah by SCF/Merlin funded by UNOPS) – there will be an attempt to follow Directly Observed Treatment protocols (DOTs) for PQ administration on day 3 of *P. falciparum* treatment. Day 3 has been chosen over day 1, because it is believed that the highest priority is to treat the *P. falciparum* with ACT and the public health priority is secondary to prevent the spread. It has been found that the 3 day treatment of ACT is not always adhered to by patients whose symptoms start to fade after one or two days. Hence the trial of DOTs, which will also include PQ.	Not clearly stated – this would have to form part of wider discussion with PSI etc.
FDA	- Generally the FDA do not see any problem with approving PQ for sale in the private sector if it has been approved at government level – they stated that they will follow guidance from WHO/VBDC/NMCP as to best course of action and make internal approvals as necessary. The FDA will be guided by policy.	Approve - in principal if recommended by VBDC and Ministry of Health (MoH).
Implementing agencies/NGOs	- Have adopted PQ supply for administering amongst VMWs and other volunteers giving RDT and ACT treatment for *P. falciparum* MAM's Smithuis is conducting research into efficacy.	Approve - in principal if recommended by VBDC and MoH.
Private Medical Practitioners	- MMA stated that PQ is not available on the open market in Myanmar - it has to be obtained through NMCP. - It is only in the MARC areas that PQ is being given. - Not all GPs are being trained to prescribe it. - Ethics of giving a drug for public health reasons rather for the good of the individual patient is also an issue for many. - There has been an issue in procurement of PQ – 3MDG supplied it in 15mg tablets. UNOPS supply in 7.5mg tablets, which is more expensive. This therefore required a complicated re-education process to ensure that the correct number of tablets was given. - Believe it is more economical to purchase the 15mg tablet, but it cannot be cut or broken and so cannot adjust for patients of different weight. - MMA stated that PQ is understood by private medical doctors but not widely given. Some openly state that it is not necessary. Some state that they will follow guidance of MoH if test facilities are available for G6PD.	Approve
Multilateral Agencies	- 3MDG stated that the National Treatment Guidelines are being revised to state that the required *P. falciparum* treatment is ACT, plus PQ on day 1.	Not clearly stated – this would have to form part of wider discussion with MoH, PSI etc.

[33] Taken from stakeholder interviews, in Yangon, Nay Pyi Taw and Mandalay, February 2014

Pharmacists /Drug Shops/Retailers	- PQ is not known as drug for *P. falciparum*. It is not sold by wholesale pharmacists – even in large wholesale tubs of 1000 single tablets. Procurement appears to be through NMCP and not the private market (according to MMA).	Approve
Pharmaceutical distributors	- MPMEEA believe there are very few manufactures of PQ with WHO prequalification; the different expiry date or shelf-life of the 2 drugs ACT and PQ was stated as an issue if packaging together; adherence to treatment would be adversely affected if the 2 drugs were given separately; they did not believe that PQ would be a problem for the FDA as an over-the-counter drug. Blister packaging in Myanmar has not been possible to date, but will be possible in Myanmar at the end of 2014, as a private factory with an approved GMP (Good Manufacturing Procedures) status is being built.	Approve
General Public (see Figure 4)	- Very low awareness in MARC areas. - This could be a function of the fact that very few medical practitioners give PQ.	Unable to ascertain

Figure 4: Knowledge of antimalarial drugs by Tier (MARC Survey Report)



The minimum dose of 0.25 mg/kg is not being given in Myanmar – rather the 0.75mg/kg and it is given on day 3, rather than day 1. There was some debate within Myanmar staff at both WHO-Myanmar and UNOPS[34] about the increased efficacy of transmission blocking on day 1, rather than day 3, as currently practiced. This however, could be amended according to the recent Technical Strategy Group Meeting minutes, to Day 1:[35]

"Regarding revision of National Treatment guidelines - it was proposed that the TSG core group review and revise it and present it to the TSG. The first point is timing of PQ prescription. For practical reason in implementing directly observed therapy (DOT) in RAI project the TSG agreed to administer PQ with ACT e.g. artemether-lumefantrine on the first day of treatment for all P. falciparum infections. It was agreed that falciparum will be observed when taking the first dose of ACT along with PQ and on the last day (not last dose) of ACT. The second point, it was also agreed to include standby treatment to special groups such as migrants without performing diagnosis and prescribing PQ. It was also decided that volunteers should also administer PQ"[36]

[34] Taken from interview with WHO-Myanmar and UNOPS Malaria Advisors, in Yangon, February 2014

[35] Technical & Strategy Group (TSG) Meeting (17th Feb 2014 in Yangon)

[36] Technical & Strategy Group (TSG) Meeting Minutes (17th Feb 2014 in Yangon)

5. INCLUSION IN AMTR PROJECT

5.1. Current AMTR programme in private sector

As already stated, the inclusion of primaquine in the AMTR programme has significance, particularly as the AMTR programme will be evaluated against indicators that include containing the spread of drug-resistant malaria.

Currently, there are no plans to introduce primaquine into the AMTR programme by PSI. In interviews[37] many practical difficulties in incorporating primaquine into the AMTR programme were discussed. These are summarised in Table 5.

5.2. Risks

Many of the risks presented have been countered. The main ethical issue of using a drug for Public Health grounds (to halt the spread of malaria), that could cause harm (if G6PD deficiency is present) appears to have been accommodated in Myanmar, as far as the containment program is concerned, since they are administering PQ without testing for G6PD deficiency. The main issue for PQ in Myanmar is not in advocating its use, since it is currently recommended in the National Malaria Treatment Guidelines; rather, the problem for malaria containment is in the correct administration of the drug. In the public sector this is advocated and indeed administered by volunteers, despite the issue of G6PD deficiency. As stated, currently there is not a clear picture of how well PQ is being administered by medical practitioners, despite being recommended.

The general consensus from stakeholder interviews is that PQ is still not fully trusted and so not as widely used as required. The question remains whether there is sufficient imperative, time, budget, and ability to include a single low dose of primaquine in the Padonmar approved pre-packaged QA-ACT (that PSI has been responsible for supplying to the private sector distributors to replace monotherapy). To date, the RDT kit implementation has been delayed and is still to be fully implemented nationwide at time of writing. It is essential that this component of the project is fully implemented in order to correctly diagnose *P. falciparum*, if present.

Although the project is due to end in September 2014, it may receive an eighteen month no-cost extension and thereby, give an opportunity to potentially test the inclusion of PQ.

However, with the QA-ACT being distributed nationwide in the private sector through one or two national distributors, this makes the Public Health imperative of administering PQ less strong, since there is no evidence that PQ is effective in malaria 'control' conditions. The whole country is still in a 'control' phase, it is only in the MARC areas that 'containment' is the goal.

[37] Taken with Chris White, PSI, and other stakeholders in Yangon, February 2014

Table 5: Practical issues of introducing primaquine

Issue	Discussion/Result
Project Time Constraint	- The AMTR project is nearing its end date (Sep 2014). However, an 18 month, no-cost extension is possible, which may give an opportunity to explore this issue in greater detail.
Product Registration	- Current distributors are not registered to import PQ and supply it in the private sector – it may take some months to get FDA approvals.
WHO Pre-qualification	- There are few pre-qualified manufacturers of PQ; this may make small procurements problematic.
Dosage	- The issue of dosage 0.75mg /kg (adult dose: 45mg) vs 0.25 mg / per kg (adult dose: 15mg) is still unresolved. It is not determined whether Myanmar should adopt the safer, smaller dosage or continue supplying the 0.75 mg dose.
Blister Packaging	- Packaging will require considerable redesign to include additional tablets (possibly 6 PQ). Currently, the blister for the QA ACT is supplied by the manufacturer and PSI then simply fits this into a cardboard cover pack. - PQ is not currently supplied in blister packaging – this would be costly and difficult to do in Myanmar – and therefore possible but not economical. - However, there are reports of a GMP factory to be built at end of 2014 which may be able to accommodate this.
Co-Packaging of 2 separate drugs	- Co-packaging of two drugs, from two different manufacturers will also be practically difficult. The main issue is that of expiry - the different shelf-life for ACT and PQ. The closer expiry date of the two drugs would have to be used, but this presents a potential problem in wastage of the other drug.
Adherence to full treatment	- Products available in the private sector, offer very little opportunity to ensure adherence to treatment regimen.
Dealing with contra-indications (G6PD)	- The potential side-effects of the drug and G6PD deficiency symptoms would have to be very clearly articulated and referral recommended if symptoms present. This would require a significant investment in product detailing and ensuring referral mechanisms are understood.
Ethics of Public Health intervention	- The ethical issue of including this drug, which has no beneficial effect on the individual patient, but is included for public health grounds, is more difficult to position in an over-the-counter retail drug.
Monitoring product sales/supply	- Monitoring where the product is sold will be difficult with the inclusion of an additional distributor - the second distributor to be used in the AMTR program uses agents rather than their own sales force, which means that the final retail outlets will not be monitored with the same rigour. - Therefore product detailing will not be as rigorous and this is important for a product which requires further retailer education.

Graves et al[38] pointed out in the Cochrane review paper, that in higher endemic situations only a small proportion of cases would be treated and the effect of PQ on infection would therefore be very small. There is no evidence that PQ is effective in control situations, and currently, WHO recommends that its use should be limited to elimination or drug resistance settings. Therefore, it may be too soon to include PQ in the private market. The next phase of MARC surveys will shed more light on how significant the private sector retail market is for malaria treatment, particularly after the increased public sector and VMW efforts have increased in the MARC area. The main difficulty is that it is assumed that it is the high risk mobile populations that may be accessing malaria treatment through the informal private sector and therefore this important population group, which is likely to be responsible for the spread of malaria because of their mobile lifestyle, could be missed.

In addition, Graves et al[39] pointed out "since PQ is acting as a monotherapy against gametocytes, there is a risk of the parasite developing resistance to the drug." Therefore, the wide use of PQ would certainly require that the drug's efficacy is monitored over time.

In contrast, to further call into question the wide scale adoption of PQ, a recent paper[40] aimed to model transmission blocking and malaria elimination. The model attempts to calculate the probability of malaria elimination in countries throughout the world, taking into account the quantitative relationships between patient treatment seeking behaviour, treatment coverage, and the effects of curative therapies that also block *P. falciparum* transmission. According to this particular model, there are significant portions of Myanmar (as well as Cambodia, Southern Laos, and Southern Thailand) where malaria elimination is not likely. It was found that there was little difference in the benefits of ACTs versus ACTs+PQ in terms of transmission reductions, and further, that "because untreated individuals are so much more infectious than treated individuals, leaving even a few individuals untreated drastically reduces the effectiveness of a control program". The model calculates that with high coverage levels (91%) of treatment "with ACTs, the addition of the gametocytocidal agent primaquine affords no major gains in transmission reduction." Therefore this suggests that it is more important to treat effectively with ACTs in large numbers than to add to the complexity by including PQ in the treatment regimen.

[38] Graves, 2012
[39] ibid
[40] Johnston, 2014

6. WAY FORWARD

6.1. Research requirements

At present, PQ is the only transmission-blocking drug available, and tafenoquine and bulaquine are the only other candidates in development. PQ causes variable haemolysis in G6PD deficient people and is therefore not recommended for those with severe deficiency of this enzyme. Most patients are, however, not aware of their deficiency status. Thus, although WHO recommends the use of PQ for *P. falciparum* malaria, particularly in low-transmission settings and in the context of pre-elimination or elimination programmes, more widespread use to prevent transmission is limited. In addition, PQ is contraindicated for pregnant women and infants in the first months of life. As tafenoquine is in the same chemical class as primaquine, similar limitations would apply if it were eventually licensed and recommended for use. It is believed that the side-effects of haemolysis from this drug are less severe than with PQ. It is currently undergoing phase 4 clinical trials in the Australian Army[41].

Prospective studies should be conducted to confirm the safety of a single dose of PQ 0.25 mg base/kg as a gametocidal regimen together with ACT in individuals with G6PD deficiency, and to assess transmission blocking activity dose–response relationships in different geographic areas, particularly in the context of artemisinin resistant *falciparum* malaria[42]. Although there appears to have been a recent consensus on the safety of the lower dose,[43] there is still a need for additional studies because the evidence here was not graded for quality, and indeed Uthman et al[44] recommend a protocol to enable systematic review of prospective studies to assess the safety of 8-aminoquinolines.

> *"The gametocytocidal effect of PQ requires only a single dose, and a review of dose–response relations suggests that, when given with ACT, a single dose of 0.25 mg of base/kg (adult dose, 15 mg) has maximum effects. Current evidence suggests that this dose is unlikely to result in dangerous haemolysis, even in people with severe G6PD deficiency[45]."*

Studies summarised in this review suggest that a lower dose (0.25 mg/kg) may be equally effective and safer. This lower single dose has therefore been recommended in the context of containment or elimination. It is considered safe even in patients with severe variants of G6PD deficiency, and so individual G6PD testing is not necessary for those who receive this dose[46].
Ironically, the impact of PQ on malaria transmission reduction has not yet been proven, despite its having been recommended over the last 50 years.

6.2. Options

Table 6 shows five options that are available to be discussed among the stakeholders in Myanmar.

[41] Global Plan for Artemisinin Resistance Containment, Roll Back Malaria, WHO, 2011
[42] White, 2012
[43] Recht, 2014; and Single Dose Primaquine as a gametocytocide in Plasmodium falciparum malaria, WHO Global Malaria Programme, Updated WHO Policy Recommendation, Oct 2012
[44] Uthman, 2014
[45] Recht, 2014
[46] ibid

Table 6: Options to discuss with stakeholders in Myanmar

Option	Discussion
No Private sector Supply	- Continue on current path. - Do not supply primaquine in the private sector. - Limit primaquine to a public health intervention amongst high risk groups – target risk populations closely with VMWs and MMWs. - Monitor mobile populations (who may be using private sector for malaria treatment)
Co-package with Padonmar product	- Include with pre-packaged ACT in private sector for a limited period - as *P. falciparum* is declining in MARC areas. - See previous list of practical difficulties which would then need addressing.
New Product Development	- Consider introduction of the G6PD test kit and potential for the new milder drug, tafenoquine.
Further Research	- Research transmission blocking using the low dose and effect on G6PD in Myanmar.
Education Programme for Medical Practitioners	- Undertake a campaign to educate medical practitioners about the national malaria treatment guidelines, to ensure that malaria control and malaria containment strategies are clearly articulated and thus the role of primaquine in malaria containment and elimination is clearly understood.

6.3. Conclusions

This paper intends to provide a working document from which to open the debate about the use of PQ in Myanmar for malaria (*P. falciparum*) containment via the private sector. The arguments for and against PQ have been summarised but are somewhat moot, since the drug has been adopted in Myanmar and is being administered as a transmission blocker in the public and voluntary sector in the MARC areas. It is apparent that despite this, there is not a clear articulation of the national policy and treatment guidelines that is well understood and implemented in the country (Figure 5 shows the stages of malaria control, suggesting that Myanmar is still in the control phase nationally and containment in the limited MARC region, and therefore 'Case Management' requirement).

The key issue that warrants further discussion is whether there is a strong belief that PQ should be supplied alongside the QA-ACT nationwide in the private sector. This brings up many practical programmatic complications; it also brings up the ethical issue of using a drug which has been found ineffective at the earlier malaria control phase of interventions. It therefore may simply be that it is too early to introduce PQ into the private sector retail channels throughout Myanmar. If this is the final decision that is taken, it leaves the great threat that the spread of the disease is not being contained in the most at risk group which should be the priority target group i.e. mobile and migrant populations in hard to reach areas of the country.

The following quotation sums up the primary issue with using a drug, PQ, which is still not ideal in its transmission blocking properties:

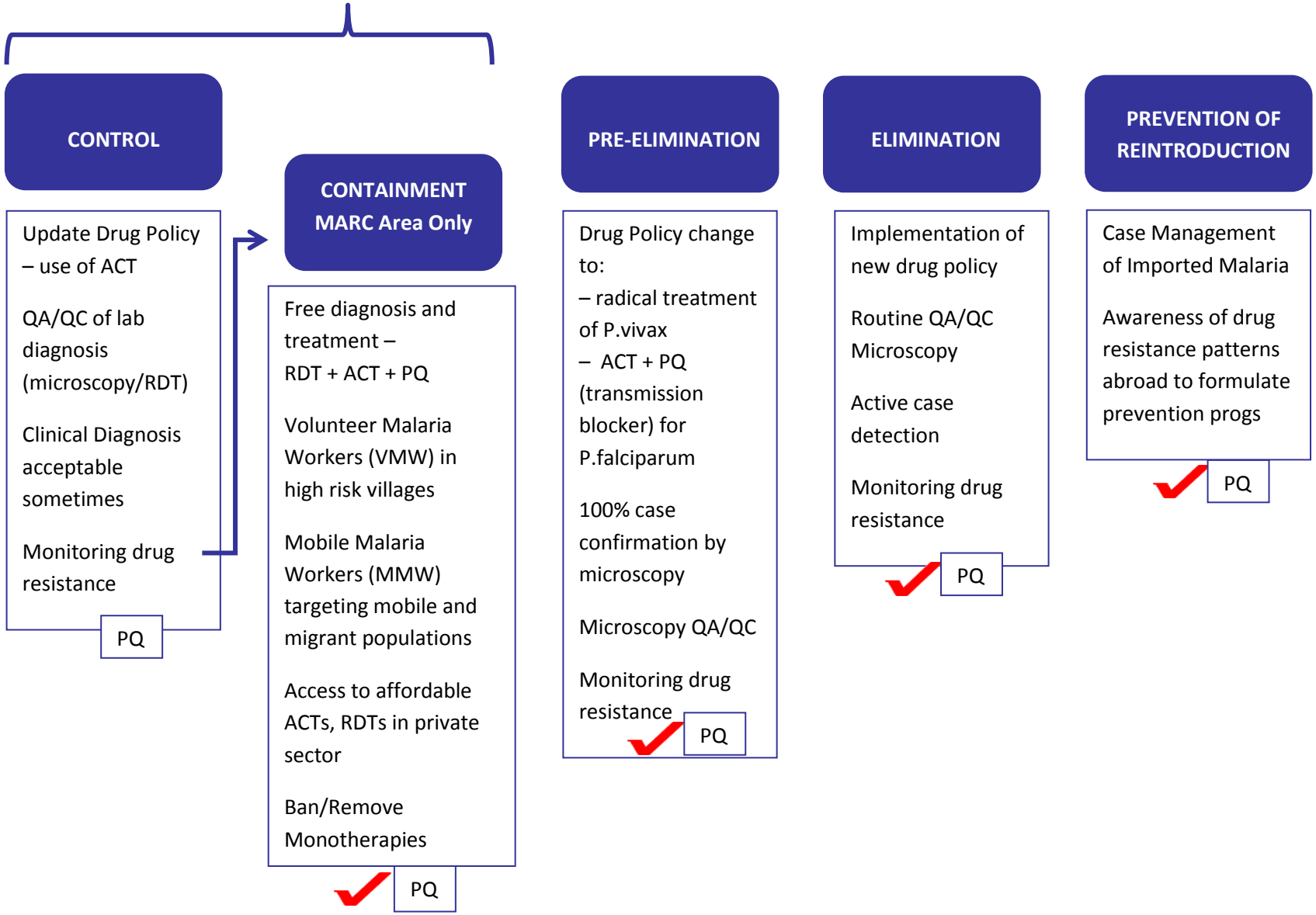
In 1957 Wallace Peters wrote[47], "Development of an 8-aminoquinoline...should be attempted as this would be an invaluable weapon against malaria if properly applied". More than 50 years later, the dream of a safe, long-acting drug that eliminates malaria infection by killing liver stages and that blocks transmission by killing gametocytes remains both unfulfilled and a top priority….The only known antimalarial drugs that kill dormant liver stages and gametocytes are the 8-aminoquinolines PQ and tafenoquine. Both of these drugs have a serious flaw for a drug that would be used to eliminate infection and block transmission in people who are not themselves acutely sick with malaria—they cause hemolysis (destruction of red blood cells leading to anemia) in individuals with G6PD deficiency, a red cell polymorphism that is common in tropical populations because it is associated with some degree of protection against malaria illness. Any drug used for malaria elimination in people who are not sick must have a low risk-to-benefit ratio akin to the low risk-to-benefit ratios of routine immunizations.

The paucity of information about pharmacokinetics, pharmacodynamics, and rational dosing of drugs represents a critical knowledge gap that needs to be addressed in order to use current drugs in conjunction with other tools to reduce malaria transmission, as well as to provide rationally designed treatment strategies. The other top priority is the development of robust and sensitive field diagnostics to guide drug interventions and to detect carriage of gametocytes that are infectious to mosquitoes[48]

[47] Peters W (1957) A malaria survey in the Western District of Papua. P N G Med J 2: 25–38.

[48] A Research Agenda for Malaria Eradication: Drugs**.** The malERA Consultative Group on Drugs. PLoS Med. Jan 2011; 8(1): e1000402. Published online Jan 25, 2011.

Figure 5: Phases of malaria control for Myanmar – case management and inclusion of PQ



7. REFERENCES

1. A Research Agenda for Malaria Eradication: Drugs**.** The malERA Consultative Group on Drugs. PLoS Med. Jan 2011; 8(1): e1000402. Published online Jan 25, 2011
2. Agenda Technical Strategy Group Meeting, Myanmar, February 2014
3. Baird, K. et al, Primaquine Therapy for Malaria. CID Oxford Journal, Nov 2004
4. Bassat, Q. The Use of Artemether-Lumefantrine for the Treatment of Uncomplicated *Plasmodium vivax* Malaria. PLOS Medicine, Dec 2011
5. Burgoine, K. et al, The Reality of Using Primaquine, Malaria Journal, 2010
6. Emergency Response to Artemisinin Resistance in the Greater Mekong Sub Region: Regional Framework for Action, WHO 2013-15
7. Global Plan for Artemisinin Resistance Containment, Roll Back Malaria, WHO, 2011
8. Graves, P.M. et al. Primaquine for reducing Plasmodium falciparum transmission. Cochrane Database Syst Review, Sep. 2012
9. Guidelines for Diagnosis & Management of Malaria in Myanmar, WHO Myanmar, 2011
10. Hill, D. et al, Primaquine: Report from CDC Expert Meeting On Malaria Chemoprophylaxis I, American Journal of Tropical Medicine, 2006
11. Howes, R.E. et al, G6PD Deficiency Prevalence and Estimates of Affected Populations in Malaria Endemic Countries: A Geostatistical Model-Based Map, PLOS Medicine, Nov 2012
12. India National Drug Policy on Malaria, 2013 Directorate of National Vector Bourne Disease Control Programme
13. Johnston, G.L. et al, Modeling Within-Host Effects of Drugs on Plasmodium falciparum Transmission and Prospects for Malaria Elimination. PLOS Computational Biology, Jan 2014
14. Lawpoolsri, S. et al, Optimally timing primaquine treatment to reduce *Plasmodium falciparum* transmission in low endemicity Thai-Myanmar border populations. Malaria Journal, Jul 2009
15. Malaria Control in the Greater Mekong Sub-region: An Overview of the Current Response and its Limitations, Southeast Asian Journal of Tropical Medicine and Public health, Vol 44, 2013
16. Myanmar Artemisinin Containment (MARC) Survey Report, 2012
17. Myanmar Artemisinin Resistance Containment (MARC) Survey: Malaria Diagnosis and Treatment, 2012
18. Myanmar National Drug Policy for Malaria: A Summary, July 7, 2012 VBDC, Myanmar
19. National Malaria Control Programme Summary of Malaria Treatment Policy, 2012
20. Recht, J. et al, Safety of 8-Aminoquinoline Antimalarial Medicines, WHO, 2014

21. Review of Mass Drug Administration and Primaquine Use (Background Paper), UCSF Global Health Services, Jan 2014
22. Roca-Feltrer, A. et al. A field trial to evaluate the performance of a point-of-care diagnostic for screening G6PD deficiency in a falciparum and vivax malaria endemic area of Western Cambodia, Malaria Consortium 2012

23. Single Dose Primaquine as a gametocytocide in Plasmodium falciparum malaria, WHO Global Malaria Programme, Updated WHO Policy Recommendation, Oct 2012

24. Smithuis, F. et al, Effectiveness of five artemisinin combination regimens with or without primaquine in uncomplicated falciparum malaria: an open-label randomised trial, The Lancet, Vol 10, Oct 2010

25. Uthman, O.A. et al, Safety of 8-aminoquinolines given people with G6PD deficiency: protocol for systematic review of prospective studies. BMJ Open, May 2014

26. White, N.J. et al, Rationale for recommending a lower dose of primaquine as a Plasmodium falciparum gametocytocide in populations where G6PD deficiency is common. Malaria Journal, 2012

27. WHO Evidence Review Group: The Safety and Effectiveness of Single Dose Primaquine as a P. falciparum gametocytocide. WHO Malaria Policy Advisory Committee Meeting Report, Sep 2012