

Technical Report: Analysis of Prescribing and Dispensing Practices and Adherence to Malaria Treatment in the Amazon Basin Countries

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About SPS

The Strengthening Pharmaceutical Systems (SPS) Program strives to build capacity within developing countries to effectively manage all aspects of pharmaceutical systems and services. SPS focuses on improving governance in the pharmaceutical sector, strengthening pharmaceutical management systems and financing mechanisms, containing antimicrobial resistance, and enhancing access to and appropriate use of medicines.

Summary

On July 28 – 30, 2009, the workshop for *improving prescribing and dispensing practices and adherence to malaria treatment* was held in Rio de Janeiro, Brazil. The results of the studies presented during the workshop will be the basis for institutionalizing the interventions currently under way and those that are undertaken in the coming years, and for orienting technical assistance activities.

Acknowledgments

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ABBREVIATIONS

AMI	Amazon Malaria Initiative
ACT	artemisinin-based combination therapy
MSH	Management Sciences for Health
PAHO	Pan American Health Organization
NMCP	National Malaria Control Program
RPM Plus	Rational Pharmaceutical Management Plus
SPS	Strengthening Pharmaceutical Systems
USAID	U.S. Agency for International Development

INTRODUCTION

The Amazon Region began to experience a re-emergence of malaria in the early 1990s, including the appearance of *Plasmodium falciparum* resistant to first line antimalarials. In response to the increased incidence and therapeutic failures, the U.S. Agency for International Development (USAID) launched the Amazon Malaria Initiative (AMI) in 2001. Its objective is to improve the control and treatment of malaria in the Amazon Basin countries: Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru and Suriname. Since then, with AMI support, these countries have changed their treatment policies to include more effective therapeutic combinations. Strengthening management of the drugs supply is essential for effective implementation of the new policies.

Management Sciences for Health (MSH), through its Rational Pharmaceutical Management (RPM) Plus and Strengthening Pharmaceutical Systems (SPS) Programs, has been AMI's technical partner since 2002, supporting management of the drug supply. With other partners of the initiative, it has helped to build the capacity of the national programs for malaria control in order to develop strategies aimed at improving the management of drugs and consumables. To date the activities have been concentrated on improving the acquisition processes and the supply chain of drugs and consumables. Practices for improving the use of the drugs have not been subject to in-depth analysis or the same level of effort.

On July 28 – 30, 2009 a workshop was held in Rio de Janeiro, Brazil, to analyze current practices for prescribing and dispensing antimalarials in the Region and their contribution to improving adherence to treatment. This report summarizes the methodology used during the event and the findings and conclusions, and the appendix includes the work plans presented by the participating countries to address the problems that were identified.

BACKGROUND¹

The problem of adherence was addressed under the AMI framework in 2004, with evaluations conducted in Bolivia, Colombia, Ecuador and Venezuela. These first studies were important for raising the malaria programs' interest in this subject. Problems were found involving incorrect use of antimalarials associated with poorly prepared prescriptions. The results of these studies are summarized in table 1.

Table 1. Adherence Studies Conducted by AMI/RAVREDA in 2004

Country	Place	Year	Species	Drug	Prescription Control	Evaluated	Adherence Failures	With Leftover Tablets	% Adherence Failures
Colombia	Tierralta	2004	P.vivax	CQ+PQ 14 d	No	38*	33	15	87.0
Ecuador	Milagro	2004	P.vivax	CQ+PQ 14 d	No	90	65	61	72.2
Ecuador	Milagro	2004	P.vivax	CQ+PQ 7 d	No	90	11	11	12.2
Ecuador	Huaquillas	2004	P.vivax	CQ+PQ 14 d	No	71	18	16	25.4
Ecuador	Esmeraldas	2004	P.vivax	CQ+PQ 14 d	No	65	34	17	52.3
Ecuador	Esmeraldas	2004	P.vivax	CQ+PQ 7 d	No	90	18	12	20.0
Venezuela	Tumeremo	2004	P.vivax	CQ+PQ 7 d	No	51	6		11.8
Venezuela	Tumeremo	2004	P.vivax	CQ+PQ 14 d	No	51	8		15.7
Venezuela	Atures	2004	P.vivax	CQ+PQ 7 d	No	60	20		33.3
Venezuela	Atures	2004	P.vivax	CQ+PQ 14 d	No	60	19		31.7

* 80 patients were included, of which 42 (52.2%) had errors in the prescription. The results are for 38 patients with correct prescriptions.

In 2005 a meeting was held in Caracas, Venezuela to discuss and establish a standardized methodology for analyzing patient adherence to treatment. Moreover, strategies were established for improving adherence by promoting best practices for prescribing and dispensing the malaria treatment.

After the Caracas meeting, additional studies were carried out in Brazil, Colombia and Ecuador (table 2). Although not all of them strictly followed the Caracas recommendation for prescription control, they all used the agreed-upon adherence classification.

¹ The notes in this section were taken from the research protocol developed by Paola Marchesini, prior to implementation of the adherence study conducted in Brazil in 2009.

Table 2. Adherence Studies 2005 – 2006

Country	Place	Year	Species	Drug	Prescription Control	Evaluated	Adherence failures			Probably adhering (number)
							Not adhering	Probably not adhering	% total adherence failures	
Brazil	Bragança - Augusto Correia	2005	P.vivax	CQ+PQ 7 d	no	94	4		4.0	90
	Colniza	2005	P.vivax	CQ+PQ 7 d	no	115	8		8.0	107
Colombia	Apartadó	2005	P.vivax	CQ+PQ 14 d	no	61	6	4	12.6	51
Ecuador	Esmeraldas, Sto Domingo, Milagro, Machala	2005	P.vivax	CQ+PQ 7 d	yes	101	20	20	39.8	61

A quick evaluation of management of the antimalarial supply carried out by MSH/SPS from October 2007 to May 2008² showed that the countries have implemented various interventions to improve the use of the drugs and promote adherence to treatment: written instructions, directly observed treatment, co-blister packages, among others. The immediate results of these practices and their effect on adherence to treatment have not been evaluated and discussed.

² Barillas, Edgar, Claudia Valdez and Silas Holland. 2008. *Situación de la gestión del suministro de medicamentos para el tratamiento de la malaria [sic] los países que comparten la Cuenca Amazónica*. Submitted to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health

METHODOLOGY

The workshop enjoyed the participation of 15 representatives of 6 (out of 7) countries that are part of the AMI initiative, 3 principal investigators in the adherence studies conducted by MSH/SPS, 3 PAHO/AMI liaison - advisors in the countries, and 6 MSH/SPS facilitator-consultants in the countries. The list of participants is found in appendix 1 of this document; the work agenda is found in appendix 2.

The meeting began with a review of concepts, frames of reference, and strategies for improving the use of drugs presented by David Lee, Deputy Director for the MSH Center for Pharmaceutical Management. His presentation offered the referents that were utilized later during the group work.

Claudia Valdez (MSH/SPS consultant) then presented the results of a review of literature on prescribing and dispensing practices and adherence to malaria treatment worldwide. A summary of the principal findings of this review of the literature is found in appendix 3 of this document. Her presentation allowed for a comparative analysis of practices in the region and those implemented on other continents. The need to document the regional experiences was mentioned, since, even though there is abundant information on this topic, the studies are generally not published in specialized scientific journals.

These two presentations laid the foundation for setting forth and discussing current practices in the countries and their effect on adherence to treatment. The presentations were divided into two blocks:

- a. **Presentation on current prescribing and dispensing practices and interventions for promoting adherence to treatment:** The presentations of each of the participating countries may be requested from MSH/SPS³. The conclusions are found in the next section of this document.
- b. **Presentation on the results of the studies of prescribing, dispensing and adherence to malaria treatment carried out by MSH/SPS:** In 2008/9, studies were carried out in Colombia, Peru, Ecuador and Brazil. The methodology and results of the studies were presented by the principal investigators and analyzed and discussed during the workshop. A summary of these studies is found in appendix 4 of this document. The findings, conclusions, and discussions during the workshop are summarized in the next section of this document.

After the presentations had been concluded, on the second day of activities, the participants, split into four work groups, analyzed the practices that had been presented, their advantages and disadvantages, and their applicability in the countries. After analysis of these practices at a session attended by all participants, work groups were organized by country to identify the interventions to be implemented upon return to the countries and the requirements for technical and financial assistance. The work plans are found in appendix 6 of this document.

³ Contact Angelica Perez (aperez@msh.org).

ANALYSIS AND DISCUSSION OF THE RESULTS

The presentations given by the country representatives and the principal investigators offered the elements necessary for the discussions in small groups and sessions attended by all participants. The findings specific to each country may be requested from MSH/SPS or consulted in appendix 5 of this document. The problems common to various countries and the interventions that merit a regional approach are included in the following sections:

1. **Drug shortage:** One requirement for analysis of prescribing and dispensing practices and practices that promote adherence to treatment is the availability of drugs in the health establishments. Inquiries were made about the drug shortage in the countries represented at the workshop. Three of the 6 countries represented said that, at that time, they were experiencing shortages of some of the drugs or makeups included in the program's therapeutic guidelines⁴: Colombia, Ecuador and Peru. The shortage was not yet reflected in interruptions of patient treatment, thanks to the implementation of emergency measures: loans among establishments, donations among countries, and breaking up of blister [packs] of Coartem® for high age bands, for the treatment of low-weight patients. The reasons put forth for this shortage are diverse: erroneous procedures for estimating requirements and delays in purchase and customs clearance.

Problems regarding recent supply of drugs for special cases of malaria (malaria during pregnancy, second line, for serious cases) were discussed. Because of low current demand, as a consequence of the reduction in the number of cases, the pharmaceutical houses and representatives have lost interest in marketing them. MSH/SPS conducted a quick study to describe this problem in 2008⁵. The results were presented and discussed at a sub-regional workshop held in November 2008 in Guatemala. During the Rio de Janeiro meeting, emphasis was placed on the advisability of subregional joint purchases facilitated by the PAHO/WHO Strategic Fund.

2. **Lack of standardization and updating of therapeutic guidelines:** In some countries (such as Colombia), the national therapeutic guidelines are not standardized. Guidance for treatment comes from directives, visual aids, and handbooks supplied by the departmental programs, which the prescribers utilize at the malaria diagnosis and treatment centers. So, in Colombia, depending on the region, 7 or 14 day treatment plans are used for *P. vivax*. Also, several AMI countries will modify, in the coming months, the makeups of the drugs they currently use to include co-blisters, fixed-dose combinations, and/or pediatric makeups (Ecuador, Brazil, and Bolivia). This will necessarily require updating of the country's basic tables; revision, printing, and dissemination of updated versions of the therapeutic guidelines, and training of the personnel. During the

⁴ At the time of the workshop (July 28-30, 2009) problems involving shortages of Coartem® in Guayana were also documented. This means that 4 of the 6 AMI countries had shortage problems.

⁵ Briggs, J., and E. Barillas. 2009. *Informe de estudio sobre la disponibilidad de medicamentos para tratar "casos especiales" de malaria en Suramérica y Centroamérica*. Presented to the U.S. Agency for International Development by the Strengthening Pharmaceutical Systems (SPS) Program. Arlington, VA: Management Sciences for Health.

discussions it was noted that the diversification of makeups of the same product (multiple age or weight bands for pediatric patients, for example) present challenges vis-à-vis planning for needs, transport and inventory management. The shortage of various makeups of Coartem® is a recent example. Consequently, the introduction of new makeups should take the country's capacity for planning and logistics into consideration.

3. **Multiple treatment plans in the region:** During the meeting, the multiplicity of treatment plans in the AMI countries was evident. This diversity is not always based on resistance tests, adherence to treatment, or market studies. Benefits of the progressive standardization of treatment plans would be the potential for joint purchases to reduce prices, the exchange or donation of products among countries, and ongoing treatment of patients who move across borders. PAHO/WHO could facilitate a meeting of experts to establish therapeutic guidelines in the sub-region.
4. **Lack of standardization of prescribing and dispensing practices:** In some countries, particularly in the federal and/or decentralized countries (such as Brazil), prescribing and dispensing practices vary in each state or department. They should be standardized through national regulations which establish who prescribes, what document is provided, what information is provided, who dispenses, and how and where the patient takes the drugs. Few countries have standard procedures to regularize these practices (Suriname and Ecuador, for example). Others (Peru, for example) are considering developing training modules to standardize them.
5. **Significant improvements in adherence to treatment:** Generally, the studies presented (appendix 4) show a higher level of adherence to treatment than those for 2004 - 2006 (tables 1 and 2). This observation must be approached cautiously, because the studies, although they used similar methodologies and criteria to measure adherence, were conducted on different populations and, occasionally, for different therapeutic regimens. In any event, adherence to treatment was relatively high compared to [that found in] previous studies. The studies could not establish factors attributable to this change. For the moment, one can only hypothesize that the introduction of some measures, such as strictly supervised treatment and illustrated prescriptions, have had a positive effect on adherence to treatment.
6. **Insufficient following of official treatment guidelines:** Full adherence to treatment suggests effective treatment only if the treatment was prescribed in accordance with the national standards. The studies presented in tables 1 and 2 did not include the analysis of prescribing and dispensing practices. The studies conducted by MSH/SPS in 2008/9 (appendix 4) include the analysis of these practices. In three of the four countries studied by MSH/SPS in 2008/9, relatively low rates of non-correspondence were found between the national guidelines and the treatment actually prescribed. In Peru, on the other hand, a 40% error rate for prescriptions was found. This highlights the need to include these variables in future studies. At the operating level, the studies indicate the need to update and distribute revised versions of the therapeutic guidelines and train the personnel in their use. These interventions should be followed by oversight of the establishments to assess the provider's performance.

7. **Concentrated incidence in regions that are difficult to access and have irregular populations:** With the reduction of malaria cases in nearly all AMI countries, the incidence has been concentrated in places that are difficult to access (Suriname, Ecuador). This situation presents particular challenges for evaluating adherence to treatment and intervening with the problems that are identified. In Suriname, for example, the methodology will have to allow for a protracted study (because of the decreased number of cases) with high costs (because of travel to remote locations). The resulting interventions will certainly have to consider the irregular situation and high mobility of the population in the mining areas on the border with Brazil, the existence of contraband drugs, and the need to communicate in Portuguese.
8. **Late attention to treatment:** The study conducted in Colombia showed that approximately one third of patients seek care at a public establishment later than the 4th day after the onset of symptoms. The study shows that 48% of patients believe that treatment is not free at public establishments. Although the delayed seeking of care cannot be attributed solely to this finding, this can be a contributing factor. With USAID MSH/SPS funds, a demonstration communication campaign to increase early care-seeking is being financed. Late care-seeking does not seem to have a direct effect on adherence, but it does have an effect on the final results of treatment. This information is not systematically compiled in the AMI studies, and that deserves to be considered in future work.
9. **Introduction of new practices for improving adherence to treatment:** As a result of the exchange of experiences and the information included in the studies (appendix 4), the countries' representatives developed work plans (appendix 5) which include specific tasks and identification of responsible parties. The plans include activities that comprehensively address the problems of supplying drugs in the light of the evidence of supply problems in several countries. They also took into consideration interventions that address adherence to treatment in a more specific way. Several countries will introduce new makeups of drugs, others will use illustrated prescriptions similar to those currently used by Ecuador or checklists to improve the prescriber's performance, and some will strengthen supervised treatment, particularly in low-incidence areas. Peru, for example, submitted a proposal in which it considers high and low transmission zones and parasite species for the selective introduction of interventions intended to improve prescribing by the health services and adherence to treatment in the population (table 3), but its implementation depends on demonstrating its cost-effectiveness in each zone.

Table 3. Strategy Suggested by the Delegation from Peru to Improve Adherence to Treatment

Scenario	High transmission		Low transmission	
	<i>P. falciparum</i>	<i>P. vivax</i>	<i>P. falciparum</i>	<i>P. vivax</i>
Coblister /Fixed Dose	Yes	When Available	Yes	When available
Illustrated Prescription	Yes	Yes	Yes	Yes
Supervised Treatment	Only at-risk groups (children under 5, pregnant women, older adults)	Only at-risk groups (children under 5, pregnant women, older adults)	Universal	Universal

COMMITMENTS UNDERTAKEN BY THE AMI PARTNERS

1. **Support operational research to determine effect of interventions:** As a result of the event, several countries included innovative interventions for improving adherence to treatment in their work plans. MSH/SPS, with USAID funds, offered the technical assistance that might be required to document the effect of the interventions, particularly those that could be applicable in other countries of the region.
2. **Support for the introduction of new makeups:** The previous section mentions that several countries are in the process of introducing new makeups of drugs currently in use (co-blisters, pediatric makeups). This will entail the revision of therapeutic tables, identification of suppliers, updating of guidelines, and additional considerations for planning for needs and distributing to the outlying areas. MSH/SPS can support, in accordance with the countries' demands, the process of introducing these products.
3. **Explore the best mechanisms for acquiring drugs for “special cases:”** PAHO/WHO, through the Strategic Fund, will explore the situation of the regional and international market for the drugs required in the treatment of “special cases” of malaria. Based on this analysis, it will present alternatives so that the AMI countries may acquire these drugs.
4. **Support studies of adherence to malaria treatment:** In its work plan, Suriname proposed the implementation of a study of adherence to treatment in the mining region on the border with Brazil. The representatives of that country indicated that they have resources from the International [Monetary] Fund to finance this study. Given the geographic complexity of the region and the irregular situation of the population that lives there, the study will probably be complicated and costly. MSH/SPS offered technical assistance for review of the study protocol.
5. **Publication of standardized procedures for prescribing and dispensing and practices that promote adherence:** As a result of the meeting, some countries will revise the procedures for prescribing and dispensing antimalarials and will introduce new practices for promoting adherence to treatment. If necessary, MSH/SPS, with USAID funds, can support the revision [*Translator:* or “review”] and validation of the procedures and training of the personnel.
6. **Systematization of unpublished studies:** Several of the studies of adherence to treatment supported by AMI (results of which were included in tables 1 and 2) were not published and disseminated. The analysis of the effect of interventions implemented in the future will require properly systematized results of previous studies. MSH/SPS, with USAID funds, offered technical assistance for systematization of the studies previously carried out in the AMI countries.
7. **Evaluation of social mobilization campaign in Colombia:** MSH/SPS, with support from COHAN, is implementing a social communication campaign in Colombia the purpose of which is to promote early care for malaria cases and adherence to treatment. The evaluation

of the impact of this campaign will be shared with the country's health authorities and AMI counterparts and partners.

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ANNEX 2. MEETING AGENDA

Day/ Time	Activity	Responsible party/ Comments
Day 1 08:30 – 09:00	Registration	
09:00–09:30	Welcome and introduction to the workshop	Representative of the host country's National Malaria Program
9:30 – 10:00	Introduction of participants	
10:00 – 10:30	Workshop objectives and methodology	Edgar Barillas (MSH/SPS)
10:30 – 11:00	Break	
11:00 – 11:30	Strategies for improving the use of drugs: conceptual framework	David Lee (MSH/SPS): Presentation on importance of rational use. Factors that contribute to rational use. Best practices in prescribing and dispensing
11:30 – 12:00	Worldwide experiences for promoting adherence	Claudia Valdez (MSH/SPS): Results of studies conducted in other countries. Conclusions derived from experiences outside of the Region.
12:00 – 13:15	Practices for prescribing and dispensing antimalarials in AMI countries Bolivia Brazil Guyana Colombia	Each country presents, in 15 minutes, the current prescribing and dispensing practices (see model for presentation appendix 1.2)
13:15 – 14:15	Lunch	
14:15 – 15:00	Continued: Practices for prescribing and dispensing antimalarials in AMI countries Ecuador Peru Suriname	Each country presents, in 15 minutes, the current prescribing and dispensing practices (see model for presentation appendix 1.2)
15:00 – 17:00	Presentation of studies of the effect of practices for promoting adherence to treatment a) Brazil b) Peru c) Ecuador d) Colombia	Presentation of case studies and research in selected countries. The presentations will follow the guide in appendix 1.3 Each presentation will be followed by a question and comment period
Day 2 08:30 – 10:00	Work groups: Evaluation of practices for improving adherence (work guide 1 – in appendix-)	Work groups will analyze in depth the illustrative practices and interventions presented during the meeting
10:00 – 10:30	Break	
10:30 – 11:00	Work groups continued: Evaluation of practices for improving adherence (work guide 1 – in appendix-)	Work groups will analyze in depth the illustrative practices and interventions presented during the meeting

Analysis of Prescribing and Dispensing Practices and Adherence to Malaria Treatment in the Amazon Basin Countries

Day/ Time	Activity	Responsible party/ Comments
11:00 – 13:00	Work group presentations	
13:00 – 14:00	Lunch	
14:00 – 17:00	Work groups by country: National guidelines for promoting adherence to malaria treatment (work guide 2 –in appendix-)	Following work guide 2, the countries develop guidelines for the implementation of practices that promote rational use and adherence to treatment
Day 3 08:30 – 10:00	Presentation and discussion of proposals by country	
10:30 – 11:00	Follow-up commitments for finalization and validation of the proposal	Establish follow-up commitments and work agenda for the coming months
11:00 – 11:30	Workshop evaluation	
11:30 – 12:00	Final remarks and closing	

ANNEX 3. REVIEW OF DOCUMENTATION ON WORLDWIDE EXPERIENCES WITH ADHERENCE TO ANTIMALARIALS

MSH /SPS
Rio de Janeiro, Brazil
July 28-30, 2009

I. Context

The definition of adherence is based on the patients' receiving drugs in the correct doses, for the necessary length of time, and instructions for their proper administration. Adherence contributes to the patient's recovery and prevents the development of resistance⁶⁻⁷. The rational use of drugs is an important factor in the management of supply; consequently, it is necessary to describe the strategies for promoting the initiation of, adherence to, and compliance with treatment (e.g., the use of combination drugs in fixed doses, pharmaceutical forms administered just once a day, blister packaging, education and peer support, duration of treatment, among others)⁸.

Factors associated with good prescribing, dispensing and patient education are recognized as essential elements for good adherence to malaria treatment⁹. Consequently, the efficacy of prescribing and dispensing practices for the development of strategies for control and rational use of malaria drugs has been the subject of several evaluative studies.

Patient adherence is an important factor in determining the therapeutic response to antimalarials when a high number of treatments are taken at home without medical supervision. With the introduction of new, effective but costly antimalarials, there is concern that the high level of efficacy observed in many clinical trials may not translate into their effective use in a normal context.¹⁰

Under the framework of the Amazon Malaria Initiative (AMI), situational analyses have been developed that have made it possible to document problems with access to and use of drugs. Practices have been promoted to improve adherence to treatment, protocols have been developed and implemented for study of the use of drugs and adherence to treatment, and support has been provided for national initiatives to improve prescribing and dispensing practices.

⁶ **Gomes M, Wayling S, Pang L.** Interventions to improve the use of antimalarials in south-east Asia: an overview. *Bull World Health Organ* 1998; 76 (Suppl 1): 9-19.

⁷ **Fungladda W, et al.** Compliance with artesunate and quinine + tetracycline treatment of uncomplicated falciparum malaria in Thailand. *Bulletin of the World Health Organization*, 1998, 76 (Suppl. 1): 59-66

⁸ **Girón, N.** Informe Fondo Regional para Suministros Estratégicos de Salud de la OPS/OMS. July 2005.

⁹ **Qingjun Li, et al.** The effect of drug packaging on patient's compliance with treatment for *Plasmodium vivax* malaria in China. *Bulletin of the World Health Organization*, 1998, 76 (Suppl. 1): 21-27

¹⁰ **Yeung S.** How do patients use antimalarial drugs? A review of the evidence. *Trop Med Int Health*. 2005 Feb;10(2):121-38

With this review, we want to disseminate information about interventions that could help improve prescribing, dispensing, and adherence to malaria treatment. Some of these have been effective and properly confirmed using rigorous designs and methods. Others, which still need to be studied with more rigorous methods, suggest benefits or support findings of studies of proven effectiveness.

II. Factors affecting adherence. Causes and consequences of low adherence.

The international literature amply describes the factors associated with low adherence to treatment with antimalarials, which include: those related to ***patient-regimen, health services, socioeconomic and cultural***¹¹⁻¹²⁻¹³. Experts have concluded that “The patient’s behavior is the most critical link between the prescribed regimen and the results of the treatment”¹⁴. Consequently, correct prescribing and dispensing are critical factors for adherence to malaria treatment.

The structural aspects of the health systems include the training of prescribers, limited geographic access of health services, deficient management of the systems for supply of consumables, information inappropriate to the patients’ level of education, packages or bottles that are unfriendly and devoid of information. Another cause is the failure of the health professional to provide the patient with information about the disease and therapy with antimalarials. Studies have shown that language is a barrier to adherence when the prescribing doctors do not communicate in the patient’s local language, making it difficult for the patient to understand¹⁵. Consequently, it is important ***to strengthen the prescriber-patient relationship and develop educational interventions based on the characteristics of the affected population***¹⁶.

A study conducted in Peru in 2001 demonstrated that there are factors which have a positive or negative effect on adherence to therapy with antimalarials. Factors with positive effects include awareness of the disease, confidence in the effectiveness of drugs, knowledge about the disease and the risk of complications, drugs that are easily administered for a short period of time, free, supervised treatment, and the participation of health outreach workers¹⁷. Those with negative effects include rapid recovery from

¹¹ **Llanos-Zavalaga F, Cotrina A, Campana P.** Factores Asociados a la adherencia al tratamiento de Malaria en Piura y Tumbes-Peru. Revista Médica Experimental, Vol. 18, 3-4. 2001.

¹² Yopez MC, Zambrano D, Carrasco F. **The factors associated with non compliance with antimalarial treatment in Ecuadorian patients.** Rev Cubana Med Trop 2000, 52:81-89.

¹³ Gomes M, et al. **Inteventions [sic] to improve the use of antimalárials [sic] in South-East Asia: an overview.** Bulletin of the World Health Organization, 1998, 76 (Suppl. 1): 9 -18

¹⁴ **Llanos-Zavalaga F, Cotrina A, Campana P.** Factores Asociados a la adherencia al tratamiento de Malaria en Piura y Tumbes-Peru. Revista Médica Experimental, Vol. 18, 3-4. 2001.

¹⁵ Dahab M, Charalambous S, Hamilton R, Fielding K, Kielmann K, Churchyard G J, Grant A D “That is why I stopped the ART”: patients’ and providers’ perspectives on barriers to and enablers of HIV treatment adherence in a South African workplace programme BMC Public Health 2008 Feb 18; 8:63

¹⁶ **Llanos-Zavalaga F, Cotrina A, Campana P.** Factores Asociados a la adherencia al tratamiento de Malaria en Piura y Tumbes-Peru. Revista Médica Experimental, Vol. 18, 3-4. 2001.

¹⁷ **Llanos-Zavalaga F, Cotrina A, Campana P.** Factores Asociados a la adherencia al tratamiento de Malaria en Piura y Tumbes-Peru. Revista Médica Experimental, Vol. 18, 3-4. 2001.

symptoms, adverse effects, the presence of a migrant population, predominance of agricultural activity, poor accessibility, poor quality of care, and self-medication.

Confidence in the treatment was described as another factor for adherence, and it is determined by the perception of the effectiveness and quality of the drugs; this, in turn, is connected with popular cause-effect models (remedy-cure), without understanding of the slow-acting nature of some of them, which causes a lack of confidence in the therapy received and results in poor adherence.¹⁸

Migration or recurrent movement for reasons of work and commerce has also been described in the international literature as a factor which contributes to poor adherence to treatment. The distance between the establishment and the patient's home is an obstacle to accessing health services; moreover, the times when medical care is available are not the most appropriate, considering their work schedules. This relationship between accessibility and adherence has been described in malaria¹⁹. In China²⁰, the poor quality of care and failure of the health care providers to furnish information is a cause of poor adherence to malaria treatment.

III. Successful interventions: Prescribing, dispensing and adherence to treatment with antimalarials.

Available evidence on adherence to antimalarials published in the international literature was reviewed. Some 26 research studies, 1 systematic review, and 3 documents that merely described experiences and lessons learned were identified. These were developed in various countries of Africa, Asia, and Latin America and the Caribbean.

The research studies are classified by type of design into 2 major groups: a) Studies with a rigorous design, such as: randomized-controlled, quasi-experimental trials, randomized-comparative and randomized-open studies; b) Studies without rigorous designs: Surveys, interviews, clinical/observational follow-up.

Five categories of interventions were defined: associated with prescribing, associated with dispensing, associated with patient education in the community, and associated with the health systems. The studies were grouped by the different types of interventions with respect to adherence that they were evaluating. (See appendix 1: summary table of studies and documents):

1. Prescription: Adherence associated with therapeutic regimens

¹⁸ **Kroeger A, Mancheno M, Ruiz W, Estrella E.** Malaria y leishmaniasis cutánea en el Ecuador. Centro Latinoamericano del Instituto de Higiene Tropical y Salud Pública, Heidelberg University. Heidelberg; 1993.

¹⁹ **Shwe T, Lwin M, Aung S.** Influence of blister packaging on the efficacy of artesunate + mefloquine over artesunate alone in community based treatment of non severe Falciparum malaria in Myanmar. Bull World Health Organ 1998; 76 (Suppl 1): 35-41.

²⁰ **Qingjun Li, et al.** The effect of drug packaging on patients' compliance with treatment for Plasmodium vivax malaria in China. Bulletin of the World Health Organization, 1998, 76 (Suppl. 1): 21-27

a. CQ+PQ prescribed in health establishments (short treatment).

A review was conducted of four studies aimed at learning whether the dose of CQ+PQ in 14, 7, and 5 day courses had a direct effect on the level of adherence of patients with P. Vivax malaria. The method utilized in two (2) was observational follow-up; two used structured questionnaire interviews before and after treatment. For measuring the level of adherence, a complying patient was defined as one who took the prescribed number of pills every day for the specified number of days, with the established interval, and at the precise time. This information was collected through interviews.

Three (3) of these studies showed high levels of adherence; 58% with the short (7 day) course of CQ+PQ (Yépez M, 2004), up to 82% with a 5-day course (Reilly 2002). Whereas the level of adherence for the 14-day course was 23.8% (Khantikul N, 2009).

In one of the studies, conducted in a rural area of Venezuela, the level of adherence to the 7-day course of CQ+PQ was compared with [the level of adherence to the 14 day] course of CQ+PQ. The results were: 76.3% CQ+PQ for 7 days vs. 70.5% with CQ+PQ for 14 days (Castillo E, 2004).

This suggests to us that the short CQ+PQ treatment may be a factor that contributes to a higher level of adherence to malaria treatment. Even so, information about the level of adherence to short treatment vs. traditional regimens is scarce. Other associated factors were knowledge about malaria and access to a correct, clear prescription for the drugs.

But the use of short, easily-administered courses of treatment as determinants of good adherence to treatment has been reported for chemoprophylaxis²¹⁻²² and treatment of Falciparum malaria²³⁻²⁴.

b. Artemisinin-based combination therapy (ACT) prescribed in health establishments.

A review was conducted of 3 studies on adherence under treatment with ACT in cases of uncomplicated P. Falciparum malaria. The method utilized in all the studies was clinical follow-up, interviews before and after treatment in the home. Measurement of the patients' level of adherence was determined by means of the level of the drugs in the bloodstream, pill counting, and interviews about dose, days and frequency.

²¹ Wilairatana P, Krudsood S, Chokejindachai W, Bussaratid V, Silachamroon U, Viriyavejakul P, et al. A clinical trial of combination of artesunate and mefloquine in the treatment of acute uncomplicated falciparum malaria: a short and practical regimen. Southeast Asian J Trop Med Public Health 1998; 29(4): 696-701.

²² Abraham C, Clift S, Grabowski P. Cognitive predictors of adherence to malaria prophylaxis regimens on return from a malarious region: a prospective study. Soc Sci Med 1999; 48(11): 1641-54.

²³ Fungladda W, Honrado ER, Thimasarn K, Kitayaporn D, Karbwang J, Kamolratanakul P, et al. Compliance with artesunate and quinine + tetracycline treatment for uncomplicated falciparum malaria in Thailand. Bull World Health Organ 1998; 76 (Suppl 1): 59-66.

²⁴ Wilairatana P, Krudsood S, Chokejindachai W, Bussaratid V, Silachamroon U, Viriyavejakul P, et al. A clinical trial of combination of artesunate and mefloquine in the treatment of acute uncomplicated falciparum malaria: a short and practical regimen. Southeast Asian J Trop Med Public Health 1998; 29(4): 696-701.

The levels of adherence were high with ACT; they were 80% in 3 day courses of treatment with MAS [artesunate-mefloquine combination therapy] (Yeung 2004), 87% for 2 day courses of treatment with MAS (Na-Bangchang 1997), and 90% for 5 day courses of treatment with Coartem[®] (Fogg 2003). These results suggest to us that FDC and ingestion over a short time period may be factors that help improve the level of adherence to malaria treatment.

The combination of fixed doses of Artesunate (AS), combining two drugs in one pill instead of two, ingestion over a short number of days, and simple oral or written information could significantly facilitate adherence to treatment, in particular for very poor, illiterate populations.

Artemisinin compounds, being developed as a fixed-dose combination to meet the urgent need for new malaria treatments in the developing world, where multidrug resistance is contributing to a growing health crisis. More than 90 percent of malaria cases and the vast majority of deaths occur in Sub-Saharan Africa, where *P. falciparum* malaria is the most common kind. Currently, the World Health Organization (WHO) Global Malaria Program recommends that national malaria control programs use ACT for treatment of uncomplicated malaria in the public sector.

2. Prescribing: Adherence associated with patient education by the prescriber in health establishments

In a quasi-experimental study conducted in Ghana, it was demonstrated that: clear information, simple language used with patients by the prescriber, and better labeling of the drugs for home treatment of malaria contributed to an increase in adherence, in all the clinics evaluated, from 42% to 91% (Agyepong IA, Ansah, 2002).

Another study, which employed interviews of service users in rural areas of Gambia, showed that the introduction of a pictogram, intended for the illiterate population, which does not understand the use of age or weight in dispensing drugs, can be utilized as a substitute for written information provided to the patient. This strategy increased adherence from 51% to 73% (Okonwo, 2001).

3. Dispensing: Adherence associated with dispensing strategies

a. DOTS/Supervision

Four studies on the effectiveness of the dispensing strategy of supervised malaria treatment with ACT were reviewed. Three of the studies were randomized-controlled and randomized-comparative, and one was qualitative-transversal. Patients' level of adherence was determined by means of the level of the drugs in the bloodstream.

In two of the studies, conducted in Bangladesh (Rahman MM, 2008) and Myanmar (Smithuis F, 2006), supervised and unsupervised treatment with ACT was compared. The results showed 93% adherence without supervision. The efficacy of the unsupervised treatment, in the context of regular use, was the same as its efficacy for supervised patients, which is an indication of good adherence without supervision, when factors [of] correct prescribing, FDC, and a small number of days are involved. Adherence was independent of level of education.

In the study conducted in Ghana, supervised administration of the treatment is considered by the patients and dispensers to be essential for adherence to treatment. Those who were supervised had an adherence rate of 90.3% and those who were not supervised had an adherence rate of 80% (Oduro AR, 2008).

In a qualitative transversal study conducted in Peru, it was reported that the outreach workers recognize their value in guaranteeing compliance with supervised treatment, and some providers are not confident about where the drugs will end up if they are delivered without supervision. The absence of supervision in malaria is a determining factor of inadequate treatment and severe malaria. Supervision may be carried out at the health center, in the locality, in the patient's home, or even at the workplace.

We can conclude, with the studies carried out in Myanmar and Bangladesh, that there are factors associated with good unsupervised adherence, such as correct prescribing, FDC makeups of ACT, and ingestion for a small number of days. The study conducted in Peru was not developed using a rigorous design. Even so, it corroborates and supports the finding of the Ghana study, which concluded that adherence to treatment is close to 90% supervised as opposed to 84% unsupervised, and that unsupervised treatment at home probably contributes to poor compliance with the treatment.

b. Dispensing by community distributors: Home management of malaria (HMM)

The strategy of dispensing through community distributors was described by means of a large-scale multi-centric study carried out in Sub-Saharan Africa in 2008. Level of adherence was measured by interviewing the patients' care-givers about the number of doses administered, number of days for which the treatment was administered, and the promptness of [beginning] treatment after the onset of symptoms.

It showed that treatment with ACT dispensed by community distributors achieved an average of 94% adherence to treatment in the three countries (Ajayi IO, 2008).

This study provides encouraging data about positive results in persons treated with ACT in the context of Home Management of Malaria (HMM), and it adds to the base of evidence on HMM as a public health strategy and on expanding the use of ACT in the community. Consequently, the use of ACT in the community has been recommended as a means of increasing access to effective antimalarials for high-risk groups living in underserved areas, especially Sub-Saharan Africa. This strategy has been shown to be feasible and acceptable to the community. Even so, the methods utilized in this intervention were not rigorous enough to yield firm conclusions.

c. Pre-packaged/Blister

Four studies that evaluated the effectiveness of pre-packaged/blister packs vs. traditional wrappers were reviewed. Two (3) [sic] of the studies were randomized-controlled and one was based on a survey. Measurement of patients' level of adherence was based on patient interviews and cards.

In three (3) of the studies, which used control groups, the results were 94.5% pre-packaged + printed information vs. 76.5% not pre-packaged and no information (Lauwo JA, 2006), 82% pre-packaged/blister packs vs. 60.5% with traditional wrappers (Yeboah-Antwi, 2001), and 83% traditional wrappers vs. 97% pre-packaged/blister packs (Quinjun L *et al.*, 1998). All demonstrate that treatment in pre-packaged wrappers + printed information is a factor that increases adherence to malaria treatment in comparison with non-pre-packaged wrappers and without information.

However, the study carried out using patient surveys reported 96.3% adherence with the use of pre-packaged (Kolaczinski JH, 2006). This corroborates and supports the findings of the previous studies.

The pre-packaged or blister packs were considered helpful because they keep the drugs clean and dry, can eliminate contamination of the product, and reduce costs by 50% (Yeboah-Antwi. K *et al.*, 2001).

The information provided inside the package was of limited use, since the majority of those surveyed were illiterate. The pre-packaged, along with printed and oral information about the disease, and instructions on effects of the drugs, contribute to adherence to treatment with antimalarials. The results show that the patients' pre-packaged/blister packs significantly improved compliance in comparison with the traditional means of dispensing antimalarials (paper wrapper); the number of days made no difference in terms of compliance with treatment when the drug was in blister packs.

A team from the University of Auckland, New Zealand conducted a systematic review of randomized trials to quantify whether the FDC makeups and the pre-packaged doses

improved adherence. It showed that the accumulated evidence indicates that the FDC and pre-packaged doses tend to improve adherence in diverse settings²⁵.

4. Education: Adherence associated with community education (IEC)

Two studies were reviewed on educational strategies and materials at the community level distributed by community educators (IEC). One of the studies was conducted using a randomized-comparative design and one used an in-home survey. Measurement of the patients' level of adherence in both was determined through interviews.

Adherence was 39% for educational materials consisting of posters + videos, in comparison with 15% for posters alone. The study, based on in-home surveys, reported that the educational materials with graphics included on the instructions for the treatment dose + pre-packaged [drugs] have 75% adherence, compared to 4% prior to the intervention. The latter, which was not developed under a rigorous design, corroborates and supports the findings of the previous study. It was demonstrated that health education campaigns can improve peoples' attitudes, as was shown in Cambodia, where the use of audiovisual media significantly increased adherence to malaria treatment²⁶.

The majority of users recognize that the presence of health outreach workers is another determining factor for good adherence to treatment. Supervision of treatment by health outreach workers reduces distance and minimizes waiting time for care, since care is delivered within the community.

5. Systems: Adherence associated with improvement of the health systems

In Asia the benefits of intervening in sociocultural factors in order to improve adherence to antimalarials have been described²⁷. The experiences of Ethiopia and Tanzania emphasize the importance of creating a decentralized community-oriented program with appropriate human resources and information systems for delivering cost-effective, universal coverage. The anti-malaria "best practices" were those that occurred at the community level using active community participation and the appropriate human resources²⁸.

Conclusion

Numerous interventions have been described, some focusing on the service provider or prescriber, knowledge or quality of the information received by the patient, and others on the type of packaging, delivery of the correct dose, dispensing through community structures, and educational materials that respond to a need of the population.

²⁵ **Connor J, Rafter N, Rodger A.** Mejoran la observancia las combinaciones a dosis fijas y las tomas pre-envasadas? Revision Sistemática. University of Auckland, New Zealand. WHO Bulletin 2004.

²⁶ **Denis MB.** Improving compliance with quinine + tetracycline for treatment of malaria: Evaluation of health education interventions in Cambodian Villages. Bull World Health Organ 1998; 76 (Suppl 1): 59-66.

²⁷ **Gomes M, Wayling S, Pang L.** Interventions to improve the use of antimalarials in south-east Asia: an overview. Bull World Health Organ 1998; 76 (Suppl 1): 9-19.

²⁸ PAHO/WHO. ¿Es posible extender los sistemas de salud Basados en la Atención Primaria de Salud? Lecciones aprendidas de la extensión de los programas verticales. Washington, D.C.: PAHO, © 2007.

Pre-packaged drugs accompanied by illustrated instructions, supervised short treatment, correct prescribing, FDC of ACT, and a small number of days, as well as information in simple language provided by the prescriber and the utilization of audiovisual media or materials (videos, posters, pictograms) in the community have been evaluated with methods that demonstrate their effectiveness as interventions which improve prescribing, dispensing and adherence to treatment with antimalarials. Interventions with less rigorous designs support the aforementioned results. While others lack sufficient evidence and information to support their effectiveness as interventions that significantly improve adherence to antimalarials [sic]. The methods utilized in some were not subject to methodological designs that would enable us to draw conclusions.

Knowing some of the interventions that have been evaluated and others whose effectiveness has not yet been demonstrated gives us the opportunity to intervene and evaluate the initiatives that have developed in our countries and promote research in this field.

ANNEX 4. BRAZIL

Study on the adherence to treatment for *P. vivax* malaria with 25 mg/kg of chloroquine for 3 days and 0.50 mg/kg of primaquine per day for 7 days for malaria patients in the cities of Goianésia, State of Pará, and Manaus, State of Amazonas

Investigator: Paola Marchesini

Abstract

In 2005, in a meeting in Caracas, Venezuela, for the purpose of discussing and defining a standardized methodology for the analysis of patient adherence to antimalarial treatment, RAVREDA/AMI developed a protocol to help malaria programs in conducting studies on adherence in a standardized manner. This study was conducted in Goianésia, Pará, and Manaus, Amazonas, in accordance with these guidelines.

There was a total of 26 patients with adherence failure in Goianésia (non-adherent + probable non-adherent), representing 18.8% of the total. Of these, 6.1% (7 non-adherents) had blisters with pills and 13.8% reported non-adherence (19 probable non-adherents). In Manaus there was a total of 31 patients who failed to adhere, representing 18.8% of the total, of which 6.1% (10) had blisters with pills and 12.72% (21) reported non-adherence. The study evidenced problems in adhering to the treatment (primaquine) related to various factors that vary from the instructions given by the dispensers and actually not understood by patients to the presentation of the medications.

Background

The adherence problem was initially addressed in 2004 under the auspices of AMI, through assessments conducted in Bolivia, Colombia, Ecuador, and Venezuela. These initial studies were important to spark the interest of malaria control programs in this subject. They identified problems of improper usage of antimalarial drugs associated with improper instructions.

In 2005, a meeting was held in Caracas, Venezuela, under the auspices of RAVREDA, to discuss and define a standardized methodology for analyzing patient adherence to treatment. Thus, a protocol was developed to help malaria programs in conducting adherence studies in a standardized manner.

In Brazil, two studies were conducted in 2005 to assess adherence to the treatment scheme recommended by the Ministry of Health for *P. vivax*, 7 days of Chloroquine + Primaquine, in the cities of Colniza, state of Mato Grosso, and Augusto Correia, in the state of Pará. The quality of prescription was not controlled. Adherence was verified through home visits on the eighth day and interviews with patients. In Augusto Correia, 94 patients were assessed,

and pills were found in 4 (4%) cases, which were classified as non-adherents. The remaining patients (96%) were considered to be probable adherents. In Colniza, of the 115 patients included in the assessment, 8 (7%) were considered to be non-adherents, and 107 (93%), probable adherents. This study was conducted in 2009 in the states of Amazonas (Manaus) and Pará (Goianésia) for the purpose of assessing patient adherence to the treatment scheme for vivax malaria with 7 days of chloroquine+primaquine in the health centers' routine care; and identifying factors that determine low treatment adherence and adverse events associated with the treatment of vivax malaria.

Methodology

The methodology used was defined by the Amazon Network for the Surveillance of Antimalarial Drug Resistance - Amazon Malaria Initiative (RAVREDA/AMI) for adherence studies. This work was proposed by the Strengthening Pharmaceutical Systems Project of Management Sciences for Health (MSH), in accordance with RAVREDA/AMI and the Brazilian Ministry of Health's National Malaria Control Program.

It is a transversal study designed to quantify adherence by conducting home interviews and verifying how many pills were remaining. The study was conducted with patients seen in 5 health centers in the city of Goianésia and 11 health centers in the city of Manaus, in the states of Pará and Amazonas, respectively, in coordination with national and local authorities. The availability of medication in accordance with the official recommendations in the Ministry of Health's Malaria Treatment Manual was ensured. In D7, i.e. one day after the completion of treatment, patients were located in their homes where the proportion of adherent and non-adherent patients was established through a structured interview and the verification of pills remaining.

The size of the sample was determined by using an expected 15% proportion of low adherence, a 95% confidence range, and a 5% level of significance. In Goianésia, it included 275 cases of malaria per month on average. Therefore, 114 patients should have been included. Considering the loss of approximately 15%, due to failure to locate the patient, the total sample included 131 patients. In Manaus, there was an average of 962 cases of malaria per month. Therefore, 163 patients should have been included. Considering a loss of approximately 15%, due to failure to locate the patient, a total of 188 patients should have been included. Consent and a signature were requested from all patients or guardians.

Classification of Adherence Assessment

- Non-adherent: pills remaining.
- Probable non-adherent: blister missing or empty and interview revealing that the patient took the medications at the incorrect time or in the incorrect quantity.
- Probable adherent: blister missing or empty and interview revealing that the patient took the medications at the correct time and in the correct quantity.

Distribution of Results

The Ministry of Health will determine how the results will be distributed among health authorities and other actors in the system. In addition, the results are part of RAVREDA/AMI and their distribution must in compliance with the agreements signed with network partners.

Results

The results for both studies will be presented separately. The first refers to city of Goianésia, state of Pará, and the second to the city of Manaus, state of Amazonas.

Goianésia

- Of the 138 patients interviewed, 101 were male and 37 were female, of which 119 were the patients themselves and 19 were guardians (16 mothers and 3 fathers).
- The interviewed patients were identified through the following health centers, in the city of Goianésia, in the urban area (Nucleus of Endemics) and in settlements (remaining centers):

Table 6.1.1: Distribution of patients included in the study per healthcare unit where they were identified for the interviews

Healthcare Unit	Number	%
Nucleus of Endemics	91	65,9
P.N Rouxinol	37	26,8
P.N.Urutu	5	3,6
P.N Ararandeuá	3	2,2
P.N.Santa Paula	2	1,4
Total	138	100,0

- Patients were 6 months to 74 years old, distributed by age group as indicated in the table. The comparison with the number of positive blades logged at the SIVEP during the month of June 2009 is also presented. Although the proportions are different, the age groups with the highest number of cases are represented in the study.

Table 6.1.2: Distribution by age group, patients included in the study and patients from the city of Goianésia with positive blades/SIVEP in June 2009

Age Groups	STUDY		SIVEP	
	Number	%	Number	%
< 1	2	1,4	6	2,3
1 a 4	10	7,2	18	6,8
5 a 9	6	4,3	24	9,1
10 a 14	6	4,3	23	8,7
15 a 19	8	5,8	21	8,0
20 a 29	44	31,9	68	25,9
30 a 39	35	25,4	47	17,9
40 a 49	21	15,2	39	14,8
50 a 59	4	2,9	13	4,9
60 a 69	1	0,7	4	1,5
70 a 79	1	0,7	0	0,0
Total	138	100,0	263	100,0

- No patient was examined by a doctor and only one mentioned having been weighed on a scale. Of all patients, only 11 received information regarding the illness. 128 patients believed that the illness could be cured, 8 did not know. 92.8% of the interviewed patients reported that they had not been informed about the possibility of side effects from the medications
- 77.5% (107) of patients said that malaria is acquired through a mosquito bite, 15.5% (20) said that it was through contaminated water, and 8% (11) said otherwise. Of the 107 patients who pointed to the mosquito as the source of their malaria, 17 mentioned that the illness could also be acquired otherwise, and 1 was not too sure whether the mosquito really is the source of transmission. The other forms of acquiring malaria mentioned by patients were: contaminated water, garbage, river bank, bad weather, rise and fall of waters.
- The distribution of interviewees (or guardians) according to the type of instruction provided (written or verbal) and whether or not they understood what was said/written is indicated in the table below:

Table 6.1.3: Distribution of interviewees according to the type of instruction provided and their understanding

Instruction	Understood	More or less	Did not understand	No information	Total
Written	19	1	NA	NA	20
Verbal	112	3	1	2	118
Total	131	4	1	2	138

- All patients received free medication, as recommended by the Ministry of Health, at the time of diagnosis. However, 6 adult patients received primaquine 5 mg instead of 15 mg. They had to take 6 pills of child primaquine per day to complete the correct dose.

- 39 patients referred to some kind of reaction/side effect from the medication: 16 mentioned that they had had a reaction, 18 that they had had two reactions/effects, and 5 that they had had three reactions/effects. The effects mentioned are listed in the table below, in the order that they were “mentioned”.

Table 6.1.4: List of side effects mentioned by patients included in the study

Effect	Frequency
Headache	9
Nausea	8
Dizziness	8
Fever/Chills	7
Allergy/Itchiness/Skin Irritation	6
Swollen Liver/Liver Inflammation	4
Stomach Inflammation/Gastritis/Stomach Ache	4
Vomiting	4
Ill Feeling /Discomfort	3
Diarrhea	2
Weakness/Lack Of Energy	2
Sweat	2
Fainting	1
Body Ache	1
Insomnia	1

- According to the classification, patients who had blisters with pills were classified as NON-ADHERENTS, corresponding to $7/138 = 5.1\%$ of the total number of interviewed patients.
- Patients who reported that they had not taken the medication according to the instruction received (probable non-adherents) totaled 19, representing $19/138 = 13.8\%$ of total patients.
- The total number of non-adherent + probable non-adherent patients was 26, representing **18.8%**.
- Of the 26 non-adherent + probable non-adherent patients, 19 were men and 7 were women. 22 patients who did not adhere/probably did not adhere to the treatment were 15 years old or older. Of these, 18 were 15-39 years old. Three patients were 4 years old or younger.

Table 6.1.5: Patients who did not adhere/probably did not adhere to the treatment, per age group.

Age Groups	Number	%
<1-4	3	11.5
5-9	0	0
10-14	1	3.8
15-19	4	15.4
20-29	8	39.8
30-39	6	23.1
40-49	2	7.7
50-59	2	7.7
60-69	0	0
70-79	0	0
Total	26	100

- Of the 26 non-adherent + probable non-adherent patients, 24 received verbal instructions and reported that they had understood the instructions. Of the 2 who received written instructions, 1 mentioned that he had understood and the other that he had understood them more or less. Of the 20 interviewed patients who received written instructions, 2 failed to adhere (10%) to the treatment and 24/118 of those who received verbal instructions (20%) did not adhere/probably did not adhere to the treatment.
- The causes indicated by the interviewees for not adhering to the entire treatment were the following:

Table 6.1.6: List of causes mentioned by patients for non-adherence/probable non-adherence to treatment.

Causes for non-adherence	Frequency
Forgot some doses	8
Did not explain	6
Got confused/did not know how to take	4
Did not received all the medications	2
Drank alcohol/beer and did not take	1
Accelerated the treatment	1
Felt ill	1
"It was only these"	1
Lost the medication	1
The medication caused a lot of nausea/vomiting	1

- The blister containing pills (all of them, primaquine) was produced by 7 patients: 4 blisters with 2 pills, 2 blisters with 4 pills, and one with 6 pills. Of these patients, 3 reported that they had forgotten to take one dose, one that he forgot to take 2 doses, one discarded some doses and another reported that he had received child primaquine and that he would have had to take 6 pills per day but indicated that he had not received the entire treatment. One of the patients who reported that they had forgotten said that he had not taken the medication because it made him ill. Of the 6 patients who received child primaquine instead of adult primaquine, 5 failed to adhere.

Table 6.1.7: Distribution of interviewed patients according to whether or not they experienced reactions and whether or not they adhered to the treatment

Reaction	Adherence		Total
	No	Yes	
Yes	10	29	Yes
No	16	83	No
Total	26	112	Total

6.2. Manaus:

- The initially calculated sample included 188 patients. 165 patients were interviewed, of which 98 were male and 67 female, and 100 were the patients themselves and 65 their guardians.
- The interviewed patients were identified in the following health centers (Table 6.2.1), in the city of Manaus, in the western and eastern zones of the city, which is an urban area.

Table 6.2.1: Distribution of patients included in the study per healthcare unit where they were identified for the interviews.

Healthcare Unit	Number	%
CAMPOS SALES	44	26.7
LINDALVA DAMASCENO	34	20.6
JOAO PAULO II	26	15.8
BO KM 10	21	12.7
PLATAO ARAUJO	10	6.1
MAMA NA EGUA	8	4.8
BASE O JOCUM	7	4.2
BELA VISTA	7	4.2
GRANDE VITORIA	5	3.0
BO SANTA INES	2	1.2
UBS ALFREDO CAMPOS	1	0.6
Total	165	100.0

- The patients were 6 months to 78 years old, distributed by age group as indicated in the table below. The comparison with the number of positive blades logged at SIVEP during the month of June 2009 is also presented.

Table 6.2.2: Distribution by age group, patients included in the study and patients from the city of Manaus with positive blades/SIVEP in June 2009

Age Groups	STUDY		SIVEP	
	Number	%		Number
< 1	1	0.6	< 1	1
1-4	15	9.1	1-4	15
5-9	24	14.5	5-9	24
10-14	18	10.9	10-14	18
15-19	23	13.9	15-19	23
20-29	33	20.0	20-29	33
30-39	28	17.0	30-39	28
40-49	12	7.3	40-49	12
50-59	7	4.2	50-59	7
60-69	2	1.2	60-69	2
70-79	2	1.2	70-79	2
80+	0	0.0	80+	0
Total	165	100.0	Total	165

- One patient was examined by a doctor and only one mentioned having been weighed on a scale. Of all patients, 42 received information regarding the illness. 89.1% (147) of patients said that malaria is acquired through a mosquito bite, 4.2% (7) said that it was through contaminated water, and 5.5% (9) said otherwise. Of the patients who said otherwise, 8 did not know how to explain, and 2 patients who said that it was through a mosquito also reported that it could be through garbage and contaminated water. 129 patients (78.2%) believe that the illness can be cured, 25 do not know, and 10 believe that it cannot be cured.
- 138 of interviewees received written and 25 received verbal instructions regarding how to take the medications (2 received no information). The distribution of interviewees (or guardians) according to the type of instruction provided (written or verbal) and whether or not they understood what was said/written is indicated in the table below:

Table 6.2.3: Distribution of interviewees according to the type of instruction provided and their understanding

Type of instructions	Understood				Total
	Yes	No	mais ou menos	S.I.	
Written	132	1	3	2	138
Verbal	22	0	3	0	25
Total	154	1	6	2	163

- 87.3% of the interviewed patients reported that they had not been informed about the possibility of side effects from the medications. 94 patients mentioned at least one reaction/side effect from the medication, 51 mentioned two reactions/effects, 20 mentioned three reactions/effects, and 4 persons reported that they had had 4 types of reaction. The effects mentioned are listed in the table below, in the order that they were “mentioned”.

Table 6.2.4: List of side effects mentioned by patients included in the study

Effect	Frequency
Dizziness	24
Nausea	21
Itchiness	17
Headache	14
Weakness	12
Stomach ache	11
Dryness in mouth	10
Vomiting	9
Dry mouth	6
Tingling	5
Mouth sores	4
Body allergy	4
Chills	4
Body ache	4
Diarrhea	3
Discomfort	3
Prickling	2
Colic	2
Fever	1
Insomnia	1
Palpitation	1
Body stinging	1

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Effect	Frequency
Body sores	1
Low pressure	1
Breathlessness	1
Yellow mouth	1
Purple mouth	1
Blisters	1
Darkening of vision	1
Dulling of vision	1
Loss of appetite	1
Drowsiness	1

- According to the classification of failure to adhere, 10/165 = **6.1%** were classified as non-adherents because they had blisters with pills, with 1-5 pills remaining.
- A total of 21 patients reported that they had not taken the medications correctly, representing 21/165 = **12.72 %** of all interviewed patients.
- Non-adherents + probable non-adherents in Manaus, in this study, totaled **18.83%** (31).
- The causes indicated by these patients for non-adherence were:

Table 6.2.5: List of causes for non-adherence

Causes for Non-Adherence	Frequency
Forgot	10
Missed some doses	3
Ill feeling	2
Drank beer/alcohol and thought that it would be bad	2
Medication caused a lot of nausea/vomiting	1
Asthma attack	1
Reported that he took the medications as described	1
Did an LVC on the fifth day, with negative result, and stopped taking	1
Took incorrectly (two doses of Prim on the first day)	1
Total	22

- Of the 31 patients who did not adhere, 22 were men and 9 were women. 19 patients (61.3%) who did not adhere/probably did not adhere to the treatment were 19 years old or younger.

Table 6.2.6: Patients who did not adhere/probably did not adhere to the treatment, per age group

Age Groups	STUDY	
	Number	
< 1	0	< 1
1-4	3	1-4
5-9	6	5-9
10-14	4	10-14
15-19	6	15-19
20-29	3	20-29
30-39	4	30-39
40-49	3	40-49
50-59	0	50-59
60-69	1	60-69
70-79	1	70-79
80+	0	80+
Total	31	Total

- Of the 31 non-adherent + probable non-adherent patients, 26 received written and 5 received verbal instructions.
- For the 12 interviewed guardians, the patients were 13 years old or younger.

Interviewee	Number	%
Patient	19	61.30%
Guardian	12	38.70%
Total	31	100.00%

- 24/26 who received written instructions reported that they had understood the instructions and 4/5 who received verbal instructions understood what was said
- The blisters with pills (all primaquine) was produced by 10 patients: 4 blisters with 2 pills, 3 blisters with 4 pills, 1 blister with 1 pill, 1 blister with 5, and one blister with 3 pills.
- 17 patients who failed to adhere experienced reactions to the medication

7. Discussion

The studies were conducted under routine healthcare conditions, which allows a partial extrapolation of the results to situations where the same care strategy is used. However, as social and cultural aspects also determine adherence, the results cannot be inferred for populations with significant differences in these aspects. However, the results of the studies are important indicators of adherence and, when the various intervening factors are considered, they may and should be used as an alert and guidance for strategies.

The presence of the investigation team and the study itself may affect the behavior of the patient and the healthcare unit team. Contacting patients to register their home address in more detail and the suggestion of a home visit may influence their adherence.

Several factors may be related to non-adherence to the treatment for malaria, such as the age, gender, marital status, color and socio-economic status of person with the illness; their priorities, perceptions, motivations, and level of knowledge regarding the illness. They may also be related to the seriousness of the illness, the attenuation of effects, the complexity of the treatment regime, and uncomfortable side effects from the medication. Further, to the acceptance or denial of the illness, religious or cultural beliefs, and the costs involved in executing the treatment regime; factors related to barriers to understanding, such as cognitive and hearing difficulties, and problems related to the healthcare service and team.

The value found for non-adherence/probable non-adherence may still be understated due to the possible introduction of selection biases when patients are identified for a visit for their inclusion. Patients who are available for a visit and interview may cooperate more and be more willing to follow the healthcare staff recommendations than patients who refuse to receive visits or to respond to the healthcare team's questionnaire and inform the home address in detail. The patient selection bias may also occur in this sense during the request/acceptance of informed consent. Errors in the presentation of questions during the interview may introduce bias or the patient may choose not to acknowledge the "error" or non-compliance with the recommendations. That is, even patients who did not reveal that they took the medication incorrectly may in fact not have adhered to the treatment, i.e. the failure to adhere may be even higher.

The results of these studies revealed a larger number of non-adherents + probable non-adherents to the treatment of *P. vivax* malaria in comparison to studies conducted previously with the same protocol in Mato Grosso and Pará. However, it cannot be said that adherence declined between these two points in time. The result must be analyzed with all the aforementioned factors in mind.

Even if the results of the adherence studies cannot be extrapolated, i.e., they represent the location and time where and when they were conducted, we must pay attention to the results. Approximately 19% in Manaus and Goianésia are significant values when we consider the importance of correct treatment to reduce morbidity and interrupt transmission. It is important to analyze the factors related to non-adherence in order to promote better adherence to treatment.

Gender and age: In none of the studies was gender statistically significant to adherence or non-adherence to treatment.

However, by age group, some groups in both studies were under or over-represented when compared to Sivep's data. In Goianésia, the 5 to 19 year-old age groups were apparently under-represented and the 20 to 39 year-old age groups were over-represented in the study. In Manaus, the 20 to 39 year-old groups are similarly proportioned in the study and by Sivep. However, the 5 to 9 year-old group in the study is practically double the proportion found in Sivep. In Goianésia, interviewers conducted the interviews after working hours, which may have led to a higher proportion of patients from the productive groups (workers), while in Manaus, they were conducted during the day, i.e. during work hours, which may have led to finding more underage patients, when guardians are at home caring for the children. The sampling losses should be analyzed in any attempt to confirm this hypothesis.

Written or verbal instructions: Whether instructions were provided verbally or in written form did not influence their understanding as reported by the interviewed patients in any of the two studies. The proportion of written instructions is much higher in Manaus than Goianésia. However, the value of non-adherence/probable non-adherence in both cities is practically the same. Another factor that may be considered is that, despite the instructions, the prescriber/dispenser must always place much emphasis on the importance of completing the treatment and, based on what was reported by the interviewed patients, a minority received guidance regarding the illness, reactions, etc.

The hope is that written instructions will improve adherence. However, this was not confirmed in these studies. This may be explained in part by how the information is written. Perhaps pictograms may be easier for the population to understand. A majority of the patients who failed to adhere to treatment said that they had understood the instructions. If this is true, does non-adherence become a patient choice? If they choose not to adhere, do they know how important it is to complete the treatment? Is malaria a "banal" illness for this population? Have they truly understood the instructions on how to take the medications?

Even if a majority of patients who did not adhere/probably did not adhere reported that they understood the instructions, when we observe the causes mentioned for non-adherence or probable non-adherence (Table 6.1.1), we can see that the justifications are related to a "lack of understanding" of the instructions or a lack of understanding of the importance of completing the treatment (forgotten doses, confusion as to what doses were taken, acceleration of doses).

Knowledge regarding the illness: In general, despite the fact that these cities are in the endemic area of malaria, i.e. where the illness is relatively common, knowledge regarding the illness (mode of transmission, what to do to cure it, for example) demonstrates lack of knowledge regarding the illness. In addition, a great majority of patients reported that they did not receive guidance regarding the illness when medication was dispensed. Thus, informing the population about how the illness is transmitted, how to avoid it, the importance of treating it correctly as a way to reduce morbidity and transmission (measured individually and collectively) must be a part of the service provided to the population.

Lack of information about side effects from the medications may also have contributed in part to non-adherence. In Goianésia, 38.5% of non-adherent patients experienced reactions to the medications while 25.9% of those who completed the treatment (probable adherents) experienced reactions. This was not observed in Manaus.

Treatment scheme: The adherence to chloroquine was total, as reported by patients. Perhaps this was due to the duration of treatment (3 days) and the reduction of effects. Non-adherence/probable non-adherence occurred solely with primaquine. This result is expected based on the literature – long treatments tend to be less respected/completed.

Despite the reports from some patients, as to lack of medication, no supply problems were recorded at these locations. However, even if no lack of supply that would lead to an incomplete treatment scheme occurred, child primaquine was used by some patients as a replacement for adult primaquine. Therefore, an important factor that should be mentioned as a probable cause of non-adherence is the substitution of child for adult primaquine pills.

8. Recommendations

Some simple practices may be introduced to improve adherence to treatment: a check list for the dispenser, with all the steps that must be followed to provide guidance for the patient, a pictogram for the patient, with instructions on how to take the medication, emphasizing to dispensers the importance of explaining to the patient what is malaria, the importance of completing the treatment, the possibility of reactions, what to do to try to avoid the illness. In places where community healthcare agents are available, some malaria treatment patients could receive home visits as a way to reinforce the importance of adherence.

Monitoring case management and the systematic and standardized supervision of health centers is fundamentally important to ensure correct dispensing and avoid supply shortages. Other countries' studies of the Amazon region found adherence failure results that were similar to those found in these studies, revealing a serious problem in the control of *P. vivax*. The co-blister may be an essential strategy to resolve the problem.

It may be useful to study adherence in comparison to socio-economic status, educational level, marital status, occupation, having previously contracted malaria (and how many times) so that strategies to increase adherence may be developed according to the factors that lead to failure in adherence.

ANNEX 5. INDICATORS, VARIABLES, AND RESULTS

GOIANÉSIA

Indicator	Variables	Results
% of patients included in the study who received a written prescription	Numerator: Patients included in the study with written prescription Denominator: Total number of patients included in the study	20/138= 14.5%
% of patients diagnosed with malaria who completed the treatment * in accordance with the national recommendation *Probable adherents	Numerator: probable adherent patients Denominator: total number of patients included in the study	112/138= 81.2%
% of patients diagnosed with malaria who did not complete the treatment * in accordance with the national recommendation	Numerator: non-adherent/probable non-adherent patients Denominator: total number of patients included in the study	26/138= 18.8%
% of patients diagnosed with malaria who did not complete the treatment * in accordance with the national recommendation Non-adherents: produced blister	Numerator: non-adherent patients Denominator: total number of patients included in the study	7/138 = 5.1%
% of patients diagnosed with malaria who did not complete the treatment * in accordance with the national recommendation Probable non-adherents	Numerator: probable non-adherent patients Denominator: total number of patients included in the study	19/138 = 13.8%
% of patients included in the study who received all prescribed medications (medications and doses)	Numerator: Patients included in the study who received all the medications Denominator: Total number of patients included in the study	All patients received the medications. However, 6 had child primaquine instead of adult primaquine
% of patients included in the study who reportedly understood the written/verbal instructions	Numerator: Patients included in the study who understood the instructions Denominator: Total number of patients included in the study	Questionnaire 131/138= 94.9%
Causes of non-adherence	List of causes of non-adherence	In the text
% of patients who reported side effects	Numerator: Patients included in the study who reported side effects Denominator: Total number of patients included in the study	Questionnaire 39/138= 28.3%

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MANAUS

Indicator	Variables	Results
% of patients included in the study who received a written prescription	Numerator: Patients included in the study with written prescription Denominator: Total number of patients included in the study	138/165= 83.6%
% of patients diagnosed with malaria who completed the treatment * in accordance with the national recommendation *Probable adherents	Numerator: probable adherent patients Denominator: total number of patients included in the study	134/165= 81.2
% of patients diagnosed with malaria who did not complete the treatment * in accordance with the national recommendation	Numerator: non-adherent/probable non-adherent patients Denominator: total number of patients included in the study	31/165= 18.8%
% of patients diagnosed with malaria who did not complete the treatment * in accordance with the national recommendation Non-adherents: produced blister	Numerator: non-adherent patients Denominator: total number of patients included in the study	10/165 = 6.1%
% of patients diagnosed with malaria who did not complete the treatment * in accordance with the national recommendation Probable non-adherents	Numerator: probable non-adherent patients Denominator: total number of patients included in the study	21/165 = 12.72%
% of patients included in the study who received all prescribed medications (medications and doses)	Numerator: Patients included in the study who received all the medications Denominator: Total number of patients included in the study	100%
% of patients included in the study who reportedly understood the written/verbal instructions	Numerator: Patients included in the study who understood the instructions Denominator: Total number of patients included in the study	Questionnaire 154/165= 93.3%
Causes of non-adherence	List of causes of non-adherence	In the text
% of patients who reported side effects	Numerator: Patients included in the study who reported side effects Denominator: Total number of patients included in the study	Questionnaire 94/165= 56.9%

ANNEX 6. WORK PLANS PRESENTED BY THE PARTICIPATING COUNTRIES

Annex 6.1 Bolivia

Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones) and ending date	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
Updating of the weight/age guide for treatment and prescribing of antimalarials	Step 1 Revise guide, Step 2 design a new model Step 3 validate the guide, Step 4 print new guide	December 2009 Guide validated	AMI/RAVREDA	Magdalena Jiménez, Arletta Añez, Juan Carlos Arraya
Continue integration of management of antimalarials into the SNUS*	Printing of "IIMM [<i>Translator: probably Monthly Report of Movement of Drugs and Supplies</i>]," "CPT [<i>Translator: probably Consolidated Quarterly Order for Drugs and Supplies</i>]" forms, Use Card, train personnel in [forms] completion at the network head level, installation system personnel	Management of antimalarials integrated into SNUS by late 2011	Regional pharmacy headquarters	Almicar Rada, Juan Carlos Arraya
Coordination with the drugs unit for implementation of the information system	Promote coordination meeting between the drugs unit and the malaria program	September 2009, Meeting sponsored	PAHO/WHO	Arletta Añez
Revise age/weight tables for treatment	Establish the malaria technical/pharmacological committee for review of treatment tables, design new table, validate, print	December 2009 table validated	PAHO/WHO	Arletta Añez
Administer treatment by mouth insofar as possible	Develop malaria program instructions on administration by mouth insofar as possible	October 2009, instructions sent to the regions and discussed at the malaria assessment meeting	Malaria program	Juan Carlos Arraya

Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones) and ending date	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
Investigate availability of co-blister on the market	Request PAHO WDC	November 2009 availability of co blister on the market investigated	PAHO/WHO	Arletta Añez
Implementation [of] illustrated prescription pad	Design new prescription / receipt pad	New prescription pad designed October 2009	AMI/RAVREDA	Magdalena Jiménez, Roxana Herrera
Improve storage practices	Design of "good storage practices" posters	"Good storage practices" posters November 2009	AMI/RAVREDA	Magdalena Jiménez

Annex 6.2 Brazil

Name of the practice/intervention	Description of steps required for the introduction/extension of the intervention	Products (goals) and conclusion date	Required resources (materials/technical assistance)	Person in charge of implementation
Prescription in the form of a pictogram (printed information)	1.Pictogram drawing for treatment of vivax. 2.Field-testing of the instrument 3.Training of prescribing staff .	1 By March 2010 2. April 2010 3. May-July 2010	1. Technical Assistance 2. Technical staff and materials for field-testing 3. Material for large-scale implementation and training resources	DAIANE, PAOLA, ELZA
Check list for prescriber routine	1. Prepare check list 2. Field-test 3. Train prescribers	1. By March 2010 2. April 2010 3. May-July 2010	1. Technical Assistance 2. Technical staff and materials for field-testing 3. Material for large-scale implementation and training resources	DAIANE, PAOLA, ELZA
Supervision of diagnostic centers	1. Script for implementation monitoring/duplication by states 2. Monitoring and Assessment	1.By December 2009 2. Assessment July 2010	1. Technical Assistance and travel to monitor the implementation in the cities of each State. 2. Travel resources for those involved in the supervision action to attend a general assessment and preliminary results meeting	DAIANE, PAOLA, ELZA
Appropriate presentation of medications/scheme for P. vivax (co-blister)	1. Under development by Farmanguinhos	1. Co-blister with Chloroquine and Primaquine according to age groups and weight, by 2012		Farmanguinhos
Continuing education for those responsible for R&D	Prepare recommendations for the States to maintain the Continuing Education Program for all who are responsible for R&D, with the support of PNCM	1. November 2009	State resources	
Assessment of strategies that are being used by states/cities to improve adherence	Promote discussion with involved areas at PNCM's national assessment meeting	Nov-09	PNCM (Technical Assistance), PECM resources	PNCM and local management

Name of the practice/intervention	Description of steps required for the introduction/extension of the intervention	Products (goals) and conclusion date	Required resources (materials/technical assistance)	Person in charge of implementation
Adherence studies	1.. Analysis of results 2. Presentation of results 3. Discussion of strategies to increase adherence based on evidence 4. Preparation of implementation plan and 5. Implementation of strategies	1. August 2009 2. and 3. November 2009 4. and 5. By July 2010	MSH, PNCM, PECM	DAIANE, PAOLA, ELZA

Annex 6.3 Colombia

Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones)	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
Adjust technical document [on] National Drug Policy, developed under the framework of RAVREDA AMI, and manage its official publication	Development of terms of reference for contracting of consultant Call for bids and contracting of consultant	Technical document [on] National policy on antimalarials completed and published 8/20/09 to 10/19/09	Consultant, resources for publication	Julio Padilla, MPS, José Pablo Escobar PAHO/WHO, Edgar Barillas MSH and Lesly Bustamante COHAN
Review technical reports of research on adherence to malaria treatment conducted under the framework of the RAVREDA AMI project in the departments of Córdoba, Cauca and Antioquia, prepare and manage their publication	Development of terms of reference for contracting of consultant Call for bids and contracting of consultant	Scientific article(s) ready and management of publication completed 8/20/09 to 11/19/09	Consultant, resources for publication	Julio Padilla, MPS, José Pablo Escobar PAHO/WHO, Edgar Barillas MSH
Finish updating guide on malaria care and prepare official publication	Hold workshop for final review and adjustment	Guide updated and management of publication completed 9/1–30 2009	Consultant MPS - PAHO/WHO agreement	Contractor MPS - PAHO/WHO agreement
Review technical report of research on the use and availability of antimalarials at the central level and [in] the departments of Antioquia, Nariño and Córdoba, conducted under the framework of the RAVREDA AMI project, prepare and manage its publication	Development of terms of reference for contracting of consultant Call for bids and contracting of consultant	Scientific article ready and management of publication completed 8/20/09 to 11/19/09	Consultant, resources for publication	Julio Padilla, MPS, José Pablo Escobar PAHO/WHO, Edgar Barillas MSH
Prepare and manage publication of technical documents: supervision of the network of posts for diagnosis and treatment and information system for the	Development of terms of reference for contracting of consultant Call for bids and contracting of consultant	Technical documents ready and management of publication completed 8/20/09 to 10/19/09	Consultant, resources for publication	Julio Padilla, MPS, José Pablo Escobar PAHO/WHO, Edgar Barillas MSH

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Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones)	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
management of antimalarials and diagnostic consumables of the national malaria prevention and control program, and manage their official publication				
Prepare and manage publication of research on prescribing and dispensing practices and adherence to malaria treatment in the departments of Nariño and Chocó and communication campaign in Tumaco, Nariño, conducted under the framework of the RAVREDA AMI project	Development of terms of reference for contracting of consultant Call for bids and contracting of consultant	Scientific article(s) ready and management of publication completed 8/20/09 to 10/19/09	Consultant, resources for publication	Julio Padilla, MPS, José Pablo Escobar PAHO/WHO, Edgar Barillas MSH and Lesly Bustamante COHAN
Inventory of P, D, and A practices in 9 priority departments (Antioquia, Córdoba, Choco, Cauca, Valle, Nariño, Putumayo, Guaviare, and Vichada)	Set up work team at central level. Develop checklist of P, D, A actions Develop plan for collection and analysis of information. Prepare technical report and disseminate to the work group	Checklist applied and analyzed by department and consolidated. Demonstrative evidence by department Technical report baseline inventory of practices 8/10/09 to 10/9/09	Work team personnel Tickets and travel allowances for collecting information in the 9 departments (including MPS – COHAN agreement)	Julio Padilla MPS, Lesly Bustamante COHAN, Jose Pablo Escobar PAHO/WHO Pharmacists MPS – COHAN contract
Adjust the manual of procedures for the antimalarial management subsystem in prescribing, dispensing and adherence and prepare official publication	Work team meeting for technical review and adjustment	Manual adjusted 8/13/09 Medellín, COHAN	Work team personnel	Julio Padilla MPS, Lesly Bustamante COHAN, Jose Pablo Escobar PAHO/WHO
Develop terms of reference for design of printed materials to improve P, D, and A Contract for development of printed material	Define terms of reference, taking subregions' special characteristics into consideration Call for bids and contracting for consultant	Terms of reference Call for bids Contract Designs of printed material 10/10/09 to	MPS work team, PAHO/WHO, MSH and COHAN	Julio Padilla and José Pablo Escobar

Work Plans Presented by the Participating Countries

Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones)	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
		12/9/09		
Inclusion in national and departmental POA first half of 2010, printing of material and plan for training and distribution	Disseminate designs of material at national meeting of ETV [Vector-transmitted disease] coordinators and promote inclusion of printing, training, and distribution in POA 2010	Departmental ETV POA that includes printing, training and distribution Dec. 2 - 4, 2009	National ETV team and departmental teams, PAHO/WHO, MSH and COHAN	Julio Padilla and ETV Departmental Coordinators
Support for priority departmental programs for printing, training, and distribution	Advise each of the 9 departments on printing, training, and distribution	2 technical assistance visits to the 9 departments Printed material available locally and personnel trained May and June 2010	MPS, PAHO/WHO, MSH, departmental programs	National and departmental ETV coordinators

Annex 6.4 Ecuador

Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones) and ending date	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
Updating of guides and standards (use of coblister treatment – cases of <i>P. falciparum</i> , <i>P. vivax</i>)	<ul style="list-style-type: none"> • MSP-SNEM technical meeting for review of current regulations and updating of guide • Technical definition which adopts use of coblister (SP+AS) (CQ+PR) • Printing of guides and other tools (treatment tables, illustrated prescription) • National distribution in National Health System- • Training of public and private prescribers and dispensers 	Updated guide September 15-09 November 30-2009 December 30-2009 April 30-2010.	Institutional MSP-RAVREDA project	MSP-SNEM with support of RAVREDA-PAMAFRO-“FONDO GLOBAL”
Acquisition and distribution of new therapeutic makeup	Request to respective MSP authorities Acquisition in accordance with current regulations National distribution	Request issued (Sept-20-09) Drugs acquired (Jul-2010) Drugs distributed (Aug-2010)	MSP	MSP (PAHO)

Annex 6.5 Peru

Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones) and ending date	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
Strengthening of the human resource's competencies	<ol style="list-style-type: none"> 1. Distribution of NT [<i>Translator</i>: possibly "technical standards"] 2. Monitoring of stock and use 3. Updating of Pocket Manual 4. Training workshops by occupational group 5. Updating of self-instructional module - personnel. 6. Continuous training by occupational group (Prescribers and Treatment administrators) 7. Indirect evaluation – monthly – of self-instruction. 8. In-Service Training Centers 	August – September ...Permanent	Freight, travel expenses for monitoring, Financial support for training workshops Consulting services	MINSA – Health regions
Training and monitoring of Health outreach workers	<ol style="list-style-type: none"> 9. Updating of "padrón de ACS" [<i>Translator</i>: possibly "community health agents register"] 10. Reproduction of Outreach Worker's Guide 11. Adaptation of illustrated prescription - simplified 12. Follow-up – analysis meetings 13. of evaluation and dissemination of experiences 14. Provision of Basic Kits for ACS 	August September Ongoing October	Expenses for reproduction of the guide. Financial support for workshops Financial resources for acquisition of Kits	
Implementation of illustrated prescription	<ol style="list-style-type: none"> 15. Design – validation, reproduction, distribution, and training – differences by species 16. Inclusion in national guideline 17. Evaluation 	October	Logistical-financial support	
Directly observed treatment in accordance with scenarios (health establishments, community agents)	<ol style="list-style-type: none"> 18. Training 19. Monitoring and follow-up 20. Consultative Committee Meeting – ESN. 21. Analysis of cost-effectiveness (area of high and low endemicity) 	Permanent October November 2009 (start)	Consulting services	
Inclusion of the malaria issue in Coordination with institutions of higher education – include malaria in the curriculum.	<ol style="list-style-type: none"> 22. Coordinate with Ministry of Education - Framework of the Education - Health agreement 23. Extend the experience of curricular diversification 24. Manage incorporation into the health professions' curriculum 	August November Manage bi-ministerial RM.	Operating expenses workshops- Consulting services	
Incorporate the coblister into treatment of P.	<ol style="list-style-type: none"> 25. Implementation in pilot area with intensive surveillance of the RAM [<i>Translator</i>: possibly "adverse reaction to medication"] 	October – December	Operating expenses for follow-up	

Name of the practice / intervention	Description of steps / sequences for the introduction / extension of the intervention	Products (milestones) and ending date	Necessary resource[s] (technical assistance materials / resources)	Party responsible for implementation
falciparum malaria	(mefloquine on the first day) – safety.		Logistics (Co-blister)	
Supervision and Technical assistance in accordance with scenarios	26. Strengthening of the “GAL” 27. Meeting with ESN [<i>Translator</i> : possibly “national health strategy”] Consultative Committee.- determination of interventions by scenarios. 28. Updating and dissemination of the supervision [<i>Translator</i> : or “oversight”] guide by levels 29. Development of monitoring software 30. Evaluation meetings - progress	August – October October Nov. – December....	Operating expenses Consulting services for one month Operating expenses – workshop	

Annex 6.6 Suriname

Name of the practice/intervention	Description of steps required for the introduction/extension of the intervention	Products (goals) and conclusion date.	Required resources (materials/technical assistance)	Responsible of the implementation
Increasing the accessibility and availability of malaria diagnosis & treatment: Training of volunteers in diagnosis of malaria & treatment of uncomplicated malaria (increase the MSD network from 26 to at least 100 in 5 years)	To multiply training format To multiply simplified protocol To select trainees & Localities Training of MSD	Training format multiplied Simplified protocol multiplied 10 volunteers trained in gold mining areas by December 2009 At least 75 MSD's trained by July 2014	MoH Malaria prog. staff (Diagnosis & Treatment Unit) GF funds	H. Cairo
Name of the practice/intervention	Description of steps required for the introduction/extension of the intervention	Products (goals) and conclusion date.	Required resources (materials/technical assistance)	Responsible of the implementation
To develop additional graphical patient instruction (multiple language)	To design the graphical instruction To test the graphical instructions in selected clinics/dispensers To multiply the instructions To train the personnel in using the instructions To distribute the instructions	Graphical instruction (leaflet) Graphical instructions distributed to all dispensers by July 2010 Accessibility and availability to free malaria diagnosis and treatment increased	GF funds	H. Cairo
To strengthen supply management system	To develop management tool To train the stake holders in the use of the tool	Management tool developed Malaria supply management improved	Technical assistance and funds from MSH	H. Cairo
To develop informational folders, posters and flyers (promoting MSD's, discouraging self-medication and encouraging adherence message)	To design the messages To multiply the materials To distribute informational materials	Informational material developed and distributed in all gold miner 's communities	GF funds	MoH malaria program social scientist
To perform adherence study in gold miner 's	To develop study protocol To develop questionnaire	Study report by July 2010 Actions identified to improve	PAHO/RAVREDA/MSH	H. Cairo

Name of the practice/intervention	Description of steps required for the introduction/extension of the intervention	Products (goals) and conclusion date.	Required resources (materials/technical assistance)	Responsible of the implementation
population	To assign and train study team To implement study	adherence based on results of the study		
Name of the practice/intervention	Description of steps required for the introduction/extension of the intervention	Products (goals) and conclusion date.	Required resources (materials/technical assistance)	Responsible of the implementation
To perform KAP study in gold miner 's population	To develop study protocol To develop questionnaire To implement study	Study report by September 2009 Actions identified to improve adherence based on results of the study	GF funds	H. Cairo