

Combination therapies and formulation of antimalarial drug policy

Learner's Guide



World Health Organization
HIV/AIDS, Tuberculosis and Malaria
Roll Back Malaria

July 2003

Trial Edition

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Table of contents

Foreword	3
Acknowledgements	5
Introduction	7
Learning Units	
1. Combination therapy with antimalarial drugs	11
Drug resistance and other causes of treatment failures	12
Definition and concepts of combination therapy	12
Antimalarial therapy combination drugs	13
Implementation issues	15
2. Antimalarial treatment policy	17
Definition and purpose of antimalarial treatment policy	17
Development of antimalarial treatment policy	18

Foreword

This module uses a training method based on learning by problem-solving to facilitate the understanding of the antimalarial combination therapies and formulation of treatment policies in different epidemiological situations. The underlying principle is that learners who are actively involved through a series of group exercises and discussions learn more and better than those who simply sit and listen to a single person talking for long periods of time. The reasoning and deduction required in the module makes this subject extremely suitable for this training method, but the success of the module will depend on your active participation in the training activities proposed. The module is addressed to health personnel responsible for malaria control at national and sub-national levels of the health care system who often face the challenges of increasing resistance to antimalarial drugs and policy changes. It requires some basic knowledge of malaria case management (uncomplicated and severe malaria), parasitology, and general epidemiology. However, the contents of the module are flexible enough to allow the emphasis to be placed according to the specific training needs. The main objective of this module is to inform professionals of new elements in combination therapies and methods of drug policy formulations. Combination therapies for malaria are increasingly being taken as best alternatives in countries where there is extensive resistance to antimalarial drugs to a level where the drugs have no more effect in reducing mortality and morbidity. It should therefore facilitate a better understanding of the current antimalarial treatments, their selection in different epidemiological and socio-economic circumstances; and accordingly of changing or revising drug policies.

The module is divided into two parts - Part I the Learner's Guide and Part II the Tutor's Guide. The Learner's Guide covers basic concepts and information together with a series of problems and hints or partial solutions to them. The Tutor's Guide outlines the main points to be learnt, but does not provide definitive and inflexible responses. In this way it is designed to stimulate active learning.

The basic factors influencing the mono-therapies, combination therapies and parasite dynamics are first reviewed and then the module introduces the learner to the principles of antimalarial treatments, selection of drugs, decision making, implementation of antimalarial treatment policies based on relevant epidemiological information and health system and socio-economic situations.

The module has been conceived for group work. The exercises in the Learner's Guide should be carried out in small groups to stimulate discussions and exchange of experience between the participants (who would come from different countries/areas with different experiences), the facilitators and the tutor. The guide can be used for workshops of varying duration depending upon the time available and the rate at which the exercises proceed. The module can be independently given in a separate course or be customized into a course with other subjects depending on the need of audiences. Certain exercises may be completed at a later date by the participants individually provided they have both the Learner's and Tutor's Guides. The complete module is optimally designed to be accomplished in 24 hours (3 days).

Acknowledgements

The contents of this module have been developed by Dr Maru Aregawi with invaluable contributions from the Working Group namely; Dr A. Bosman, Dr P. Olumese, Dr C. Delacollette, and Dr P. Ringwald, Malaria Control Department, WHO Headquarters, Geneva and Dr T. Sukwa from WHO/AFRO, Harare. In addition, WHO staff have made contributions and all of their valuable assistance is greatly appreciated and acknowledged. The module will be field tested in various international training courses over a period of time. Inputs and useful suggestions from tutors, facilitators and participants will be incorporated into the module following the field tests. This module will be used as a trial edition and we would greatly appreciate feedback from all readers.

Introduction

The planning and implementation of a malaria control programme must be based upon epidemiological analysis and application of interventions suitable to specific localities or countries. A sound and updated knowledge on antimalarial therapies, formulation and implementation of treatment policies is fundamental to malaria control programme and policy makers at national level. The aim of this training is to improve your capacity of critical analysis of antimalarial treatment options upon which decisions for policy changes and revisions are made depending on epidemiological circumstances which should be an integral part of planning, management and evaluation of malaria control activities. This module can be used for in-service training or as part of a basic course on malaria control. The operational relevance of the understanding of how this knowledge should be utilized in the latter case, it is recommended that it be taught after parasitology, entomology and basic epidemiology and simple statistics have been covered.

For whom is this training module intended?

The module is designed for health professionals involved in malaria control at national and sub-national levels who have responsibility for policy-making, planning and executing malaria control activities. These include medical officers, medical assistants, public health officers, pharmacists, parasitologists, and biologists. Most of these people will already have a working knowledge of the basic principles of malaria epidemiology and communicable diseases control.

Objectives

At the end of the training programme based on this Learner's Guide you should have acquired the skills that will enable you to:

- understand the rationale for combination therapy
- select appropriate antimalarial drugs combination options best suited for different epidemiological situations
- determine timing of introduction of combination therapy
- Understand the concepts and purposes of antimalarial treatment policy
- Determine the rationale for drug policy in different epidemiological situations and understand the criteria for changing treatment policy
- Illustrate the steps for formulation and development of drug policy
- Understand the implementation processes of antimalarial drug policy
- Understand monitoring of the implementation of antimalarial drug policies

How is the course run?

Tutor

The tutor has overall responsibility for the planning and management of the course and will also introduce each of the learning units, but the tutor will not give formal presentations of this module.

Facilitators

The tutor is assisted by a number of facilitators who will work with you continuously through small group sessions and provide additional information whenever required. They will also assist the moderators in guiding group discussion. Together with the tutor, they are your constant source of information and experience. If you study in small groups but without a facilitator, the tutors must to some extent play the role of the facilitator.

Presentations

Lectures are kept to a minimum and will be replaced by limited introductory remarks by the tutor at the beginning of each subject and short examples to overcome points of common difficulty.

Small group work

The module is designed for 3 *days* of training, working mainly in *small groups*, say 2 or 3 groups of 6 to 9 learners each. It is desirable for each group to have its own room, with at least one of the following: overhead projector, whiteboard, blackboard, flipcharts. For each unit the group selects, among its members, a *moderator* and a *rapporteur* by rotation, so that, as far as possible, each learner performs each of those two functions at least once.

The sessions provide good opportunities for you and the other learners to give your opinions, develop your ideas and learn from one another. The learners will usually have different backgrounds, in terms of training and experience, so that they should have much to *learn from each other*. The exchange of experiences among participants contributes to most of the training material, the Learner's Guide providing a lead for discussions and work. A moderator chosen by the members of each group will lead discussions on the particular subjects proposed in the learning units. At the end of the group work devoted either by the moderator responsible and discussed by all participants and commented on by the tutor. These presentations and discussions are important but are not meant to be formal as working notes. The overall success of this training module will depend on the active participation of all learners in the group exercises and discussions.

This training module

Use of the Learner's Guide

This Learner's Guide consists of instructional materials and problems designed to enable you and your colleagues to achieve the objectives stated earlier. The Guide is divided into Learning Units. Before each session you should read each Unit carefully and make sure you understand

it, as the tutor will not be giving a detailed presentation of the material to be learnt. If you are unclear about any part of the Learning Unit you should discuss it with your colleagues in the discussion group, your facilitator and with the tutor, if necessary. Each Learning Unit consists of a series of questions (and hints and partial solutions to some of them) to be worked through as a group. The discussions during small group work and during plenary sessions with the participation of facilitators and tutors will facilitate this process.

You must acquire the skills and knowledge contained in one unit before progressing to the next, otherwise you may have difficulty in achieving the objectives of subsequent learning units.

Individually, make maximum effort to read some of the important references and guidelines sited in the document as details are left for further reading. Annexes are given as additional sources for in-depth knowledge.

Use of the Tutor's Guide

During the course, the tutor's guide would be available only to the tutor and facilitators and upon completion of the course/module, all learners would get a copy of the tutor's guide so that they can use the materials for further training and reference.

The module consists, in its present state, of two major learning units addressing. Each unit consists of a Learner's Guide and a Tutor's Guide. The Learner's Guide proposes a series of exercises and offers hints for some of the problems. The Tutor's Guide gives guidance to the tutor for answers to the exercises.

The module aims at developing an *approach*, namely the *critical analysis of antimalarial therapies related to epidemiological situations*, rather than to convey a body of facts (even though many facts may be conveyed in the process). Most facts and details are referred to relevant guidelines and other resource materials.

No document can, and this module does not, exhaust such a wide and dynamic subject. Drug resistance and policy are dynamic issues and so this module is. The module will be successful if it helps the learners understand the mechanics of previous and recent antimalarial therapies, decide, formulate and implement drug policies; and to *continue to update their knowledge as an integral part of their professional activities*.

The Learner's Guide can also be used in conjunction with the Tutor's Guide, for individual active self-learning.

Evaluation

Evaluation of the learner: The evaluation of individual progress and achievement will be carried out by the tutor, the facilitators and yourself. It will include :

- *Spot tests*

At regular intervals, a series of "spot tests" will be set out for you to comment on. They are designed to help you and the tutor assess how well you have mastered the skills and developed the competence to carry out your work.

Correct answers will be supplied after the spot tests and a discussion will take place. This is intended to improve the process of learning and help you to identify those activities in which you need further practice.

- *Multiple-choice quizzes*

In multiple-choice quizzes, each question is provided with a list of possible answers from which you must select the one you think is correct. At the end of these sessions you will not necessarily be given the correct answer to each question, but the tutor will analyse the results to identify topics that were not clearly understood. The tutor may also tell you where you made mistakes and point out areas where mistakes were made and point out areas where you need to improve.

This part of the evaluation is designed to help you and the tutor to assess how well you understand the course. Multiple-choice tests will take place at the end of the module to assess the achievement of technical competencies by the participants.

Evaluation of the training by the learner

At the end of the course you will be asked to complete a questionnaire to tell the tutor how you think the training has helped you and how it might be improved. This evaluation will take place at the end of the training period in order to provide as much feedback from the learners as possible. During the course you should also feel completely free to make suggestions for improvements on the part of the tutor and facilitators as well as in the content of the course and the training facilities. This will help your colleagues in a future training course!

Learning Unit 1**Combination therapy with antimalarial drugs****Learning objectives**

By the end of this Unit you should be able to:

- understand the rationale for combination therapy
- select appropriate combination therapy options best suited for different epidemiological situations
- determine timing of introduction of combination therapy

The emergence and rapid spread of *P. falciparum* resistance to commonly used antimalarial drugs poses a serious challenge to the effectiveness of early diagnosis and prompt treatment as a priority strategy within the current malaria control. Effective treatment, as an intervention, depends highly on antimalarial drugs which should be safe, effective, available, affordable and acceptable to populations at risk.

Learners or participants are expected to have some background/reading on antimalarial drug resistance.¹

Working in small groups with your colleagues discuss all the exercises below and present your results for the questions you are assigned to.

¹ The use of antimalaria drugs. Report of WHO informal consultation. WHO/CDS/RBM/2001.33.

Drug resistance and other causes of treatment failures

Various factors relating to drug, parasite and human host interactions contribute to the development and spread of drug resistance. The molecular mechanisms of drug action are critical element in the speed at which resistance develops. Drugs with a long terminal elimination half-life enhance the selection of resistance parasites particularly in areas of high transmission. In addition increased drug pressure contributes to development of drug resistance.

- 1) Mention at least three advantages of rational use of an effective antimalarial drug based on biological and operational reasoning.
- 2) Discuss with your colleagues how you understand the terms 'first-line, second and third-line treatment'. Does this classification strictly indicate the levels of health care at which these drugs should be available?
- 3) Which of the “two lines of treatments” would have greater impact on reducing mortality.
 - an effective first-line antimalarial treatment or
 - improved second-line treatment or case management of severe malaria?

Discuss Why?

- 4) Discuss with your colleagues about antimalarial drug resistance. Answer to the following questions.
 - a) How do you define drug resistance?
 - b) How does drug resistance emerge?
 - c) What parasite and host factors are associated with development of drug resistance?
 - d) What other factors, apart from drug resistance, do you know as possible cause of treatment failures?
- 5) How does one suspect the occurrence of drug resistance and what are the associated epidemiological consequences of drug resistance?

Definition and concepts of combination therapy

The concept of combination therapy is based on the synergistic or additive potential of two or more drugs, to improve therapeutic efficacy and also delay the development of resistance to the individual components of the combination.

- 6) What is combination therapy with antimalarial drugs?
 - a) And what is the aim of applying combination therapy?
 - b) In what form could products of combination drugs be presented?
- 7) In accordance with your definition, can multi-drug therapies including non-antimalarial drugs be considered as combination therapy?

Give examples of such drugs.

- a) Is sulfadoxine-pyrimethamine a combination therapy? Give biological and operational reasons.

- 8) Is the concept of multi-drug therapy applied in diseases other than malaria? If yes mention some examples.
- 9) Suppose country A is using two antimalarial drugs and a single event causes a complete drug resistance and the probability of such frequencies for each drug is in 10^{-10} nuclear divisions. The assumption is that both drugs have independent modes of action on the parasite.
- What is the probability of a mutation resistant to both drugs when used together?
 - Interpret your results

Antimalarial therapy combination drugs

Categorically, there are two types of combinations of antimalarial treatments:

- i) Non-Artemisinin-based combinations and ii) Artemisinin-based combinations (ACT)

Working in small groups, discuss the following and try to provide examples.

- 10) Based on your former and recent knowledge, connect possible Non-artemisinin-based combinations and artemisinin-based combination drugs (ACT) listed in the two columns in **table 1** below. Show combinations using (---->) arrows for Non-ACT and smooth (→) arrows for ACT.

Table 1. Possible combinations of antimalarial drugs

Chloroquine	sulfadoxine-pyrimethamine
Amodiaquine	Proguanil
Proguanil	
Atovaquone	Mefloquine
Mefloquine	
Quinine	Tetracycline
Tetracycline	
Doxycycline	Doxycycline
Lumefantrine	Lumefantrine
Artemether	
Artesunate	Chloroquine
	Amodiaquine

Non-Artemisinin-based combinations

These are combinations in which an artemisinin derivative is not part of the combination. They are blood schizontocidal drugs acting on different biochemical targets in the parasites. They may come as loose individual drugs for co-administration or as fixed combination drugs. Combinations have been shown to have higher cure rates than mono-therapy

- 11) Suppose in country A, *P. falciparum* is predominant and resistance to Chloroquine is high. The drugs of choice you can possibly use for operational and affordability reasons are SP and CQ only. Would you recommend combination therapy using SP and CQ as a first-line treatment for this country? If your answer is Yes, explain the added value of combining both drugs over using SP alone. If you say No, give a reason.
- 12) Maintaining the situation mentioned above in (11), would the high resistance of *P. falciparum* to CQ hinder the use of SP alone? Explain your answer.
- 13) If in country B, unlike to country A, both *P. falciparum* and *P. vivax* equally prevail, and resistance of *P. falciparum* to CQ is moderate but sensitivity of *P. vivax* to CQ is high, would you recommend combination therapy with SP and CQ?
- 14) When combination therapy of two drugs is applied, what is your understanding on the dosage of the combination if not formulated in one tablet or capsule? Do you give the full dose of the individual drugs as would have been used in monotherapy or do you reduce the dose of each component of the combination?

Artemisinin-based combinations (ACT)

Various artemisinin compounds have been used in different formulations as treatment for malaria since the early 1980s, initially in China where they were first developed, and subsequently in many other countries. ACTs are relatively new with lots of comparative advantages. Artemisinin (qunghaosu), artesunate, artermether and dihydroartemisinin have all been used in combination with other antimalarial drugs for the treatment of malaria. Most of all clinical information of artesunate seems to have been well documented.

- 15) List some properties, advantages and potential challenges of ACT.
- 16) Briefly summarise in a tabular form, the pros and cons of the possible non-artemisinin-based and artemisinin-based combinations and suggest for which type of epidemiological situations they could be applied.

Hint: You may use the following chart and headings and you may refer to recent reports.²

² Report of technical consultation, WHO, Geneva. WHO/CDS/RBM/2001.35.

Table 2. Pros and cons of possible combination therapies and suggested epidemiological situations

Combination	Pros/advantages	Cons/limitations	Suggested epidemiological setting (transmission and type of plasmodium parasite and resistance)
Non-Artemisinin based combinations			
Artemisinin-based combinations			

Compare your results with the answers given by the tutor.

Implementation issues

We have seen in the above exercises that not all combination therapies are viable for different epidemiological settings either for biological or operational reasons and critical analysis is required by taking some defined criteria for selection of candidates of combinations upon which final decisions are made based on the relative merits. Implications of shifts from certain drugs to others is enormous unless careful synthesis of the factors are done prior to implementations.

Working in small groups, discuss the following exercises and relate them to the situations in your country or working place.

- 17) Identify at least 6 selection criteria that would assist in consensus for decision making of combination therapy.
 - a) Group the selection criteria identified above as biological and operational matters.

Table 3. Favouring and prohibiting factors for the introduction of Artemisinin-based combination therapy in the African region

In favour	Potential prohibitive factors
<ul style="list-style-type: none"> • Current inadequacy of first-line treatments in many countries, including possible hidden burden from malaria and chronic anaemia • High efficacy of artemisinin derivatives in rapid clearance of symptoms and parasites • No documented resistance to artemisinin and its derivatives at present • Possible delay or slowing of spread of resistance to available effective and affordable antimalarial drugs, if included in combination therapy • Potential for transmission reduction due to the effect of artemisinin derivatives on gametocyte carriage rate (applicable to areas with low or moderate malaria transmission) 	<ul style="list-style-type: none"> • Potential misuse of artemisinin derivatives, risking their value in treatment of severe malaria • Limited knowledge and use of combination therapies with or without artemisinin derivatives • Problems of adherence to co-administered (non-fixed) combinations, particularly at the household level • Lack of evidence of its effectiveness in delaying development of resistance in areas of high transmission • Higher cost of artemisinin derivatives • Effort and cost of changing treatment policy

Please read carefully the next Unit of this module before commencing the session to which it relates.

Learning Unit 2

Antimalarial treatment policy

Learning objectives

By the end of this session, you will be able to:

- Understand the concepts and purposes of antimalarial drug policy
- Determine the rationale for drug policy in different epidemiological situations and describe the criteria for changing treatment policy
- Illustrate the steps for formulation and development of drug policy
- Describe factors influencing antimalarial treatment policies
- Describe implementation of antimalarial drug policy and access to antimalarial drugs
- Understand monitoring of the implementation of antimalarial drug policies over time

The worsening problem of drug resistance in many endemic countries has led to increasing difficulties in finding suitable antimalarial treatments. This has compromised the impact of drugs that had been in the past effective on reducing mortality and morbidity. Resistance to chloroquine, which has been effective and affordable first line treatment, has been widely reported. Although Sulfadoxine-pyrimethamine was, until recently, seen as a successor to chloroquine, resistance to this drug is developing quickly and hence the need for other policies that prolong the therapeutic lives of the few available and affordable drugs and at the same time reducing the effects of treatment failures. This has prompted many countries in Eastern and Southern Africa to change their drug policies. In West Africa, rates of resistance vary, but tend to be lower than those in Eastern and Southern Africa and as yet no changes have been made in the first-line treatment policies.³

A change of antimalarial drugs policy to either mono-therapy or combination therapy has to balance between the implications of new policy and the consequences of not changing treatment policy.

Definition and purpose of antimalarial treatment policy

Working in small groups, discuss the following and come up with brief answers.

- 1) Define antimalarial treatment policy. Let colleagues in the small working group discuss the current antimalarial treatment policies in their respective country or working place. Discuss the rationale (epidemiological setting) and relate them to those policies. Indicate if change to new antimalarial treatment is needed. Discuss how you would relate your definition with national drug policy and essential drug list.
- 2) What are the purposes of antimalarial treatment policy?

³ Guideline on the use of combination therapy in malaria in the African region (in progress for publication).

- 3) Do malaria control programmes of different countries have similar objectives in terms of achieving 'effective treatment'? Explain your answer.

Hint: think of different epidemiological situations (transmission, population immunity)

- 4) Discuss with your colleagues on the consequences of not changing a treatment policy when it should.

Development of antimalarial treatment policy

The development or revision of antimalarial treatment policy should be based on evidence obtained from studies, standardised assessments or other reliable sources.

While developing or updating antimalarial drug policies the following essential components should be considered.⁴

- Technical, social and economic issues related to malaria control, drug resistance, potential interventions and consequences of action or inaction
- Decision-making environment
- Consensus-building among relevant stake holders supervision
- Regulatory mechanisms

Gathering information and establishing evidence for change of policy

Information is required from multiple sources, some of which is country specific and some from global sources. In order to define which effective, affordable drug can be provided safely to satisfy the health care needs of the majority of the population, information is required on the following:

- epidemiological situation
- profile of available or alternative drugs, including efficacy
- human behaviour
- cost and cost effectiveness of alternative therapies (private and public sectors)
- health systems capacity to implement the policy (this should include analysis of the existing supportive regulations and legislation).

The following questions would need working in small groups so that participants exchange experiences and challenges that countries face in the development of policies for antimalarial treatments.

- 5) Discuss with your colleagues on logical stages of antimalarial treatment policy and show your result in drawing.
- 6) What primary indicators would you consider as evidence for changing or re-evaluation of antimalarial treatment policy? Where would be the source of such data or information?

⁴ Framework for developing, implementation and updating of antimalarial drug policy in Africa. A guide for country malaria control programmes. (Publication in progress).

- 7) Several factors may influence the selection of antimalarial therapies. What kind of information would you need during the process of synthesising antimalarial treatment policies in terms of the following factors: *efficacy and half life, acceptability and adherence to treatment, quality, drug interactions and adverse effects; use in special groups, capacity of health system to implement policy, cost and cost effectiveness, reported resistance, useful therapeutic life and health seeking behaviour?*

Standardization and validation of data

Standardised methods and process of data collection within a country is necessary for consistency and interpretation of data. Utilisation of the same method to assess efficacy of a drug allows a country to have a long-term perspective of the evolution of resistance to the drug and the rate of such resistance over time.

While it is important to use standardised methods for measuring efficacy, it is equally important to internally and externally validate data collected for the purpose of evaluating an antimalarial drug policy.

Decision for changing policy

The decision to change antimalarial treatment policy is based on a range of factors including the prevalence, geographical distribution of documented treatment failures, impact on morbidity and mortality, political-economic situation and availability of alternatives. There are no well defined criteria for determining the level of clinical or parasitological failures with the current antimalarial therapy at which a first-line drug should be replaced. A cut-off level of 25% treatment failures has been widely used in many countries. This figure may not be acceptable to richer endemic countries.

The following classification of clinical failure rates, has been used as guiding process in changing policies:

- **Grace period-** <5% treatment failures: build consensus, conduct studies, analyse trends
- **Alert period-** 6-15% treatment failures: set up mechanisms for the process and timing for change, analyse efficacy and resistance of current first-line drug, select alternative drugs.
- **Action period-** 16-24% treatment failures: initiate change according to agreed strategies, ascertain treatment failures, potential of alternative drugs, channel of distribution
- **Change period-** >25 treatment failures: consensus is reached to change, development of the policy, preparation of guidelines, registration of alternatives drugs.

⁵The cut-off points of these periods are arbitrary and only meant to help countries to identify their positions, establish or reinforce their mechanisms for continuous monitoring of the drug resistance and use the collected information for action.

⁵ A new threshold for changing policy was adopted by WHO/AFRO (August 2003) which specifies that the drug policy should be changed at a maximum of 15% clinical failure and 25% parasitological failure (report in progress).

Factors that impede decision-making:

- Insufficient evidence to define and develop consensus on the local problem and best solution (there is a need for comprehensive scientific research including drug efficacy studies that is representative of the local population, social science and health systems research)
 - A communication gap between researchers (national and international) and the national programs and implementers. The research agenda is driven by researchers and not by practice
 - Limited information gathered by monitoring and evaluation of the existing policy and policies of neighbouring countries
 - Problem and solutions are not articulated clearly to decision makers, focusing on technical issues of drug resistance rather than the more compelling consequential morbidity, mortality and economic implications and available options
 - Lack of analysis of the decision makers and other stakeholders priorities, interests and agendas
- 8) The key challenge facing anti-malarial treatment policy development is how to achieve a balance between competing principles of ensuring ***prompt treatment of malaria*** and ensuring ***that anti-malarial drugs have a maximum useful therapeutic life***. If at all possible, the desired outcome of the two principles is a resultant reduction in mortality while at the same time delaying or reducing drug resistance. Compare the goal and strategies of the two principles.

Policy implementation and access to antimalarial drugs

Once decisions are reached for policy changes or revisions, the challenge will be implementation and maintaining the interventions to attain the required results. The implementation of a revised antimalarial drug policy requires a framework of political commitment, planning, mobilisation of resources, co-ordination, a regular budget and a sustainable programme. There are good lessons learnt from countries that have recently implemented policy changes.

The duration between decision making and implementation of policy change will vary from country to country depending on availability of evidences (information), resources, political commitment, health system and other factors. Critical will be the timeliness of decisions at national and district level to implement change without undue delays which will be costly in terms of preventable deaths that will occur if this does not happen.

Working in small groups, discuss the following questions.

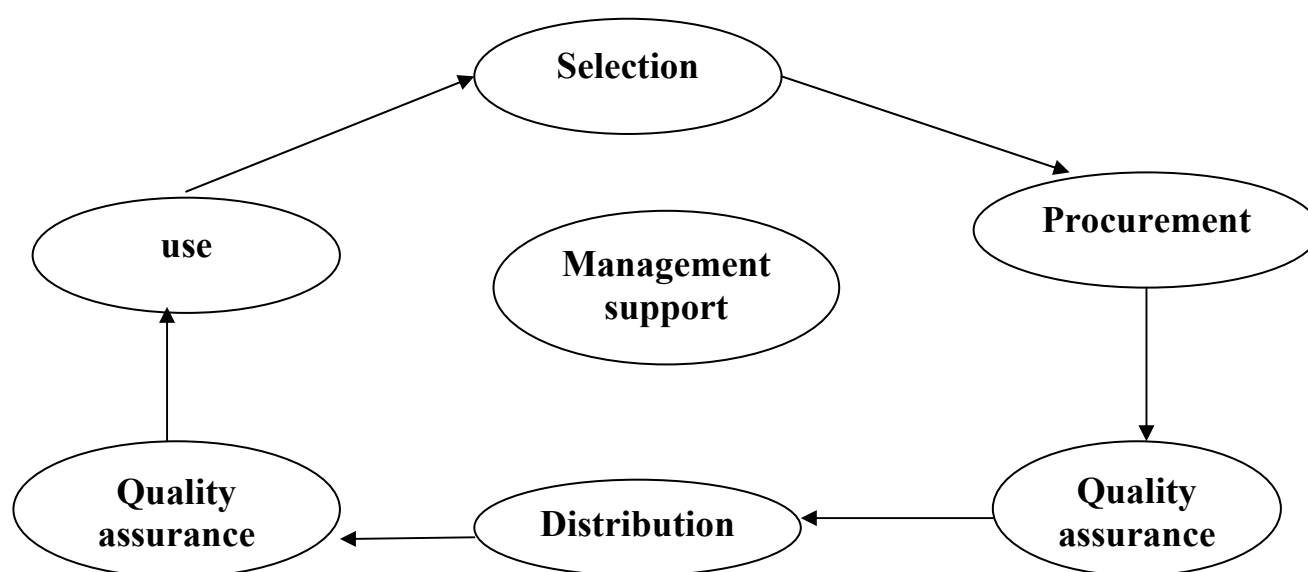
- 9) Outline implementation process in a logical frame. Plans, activities and accomplishments may vary from country to country depending on the socio-economic status, commitment and availability of resources.
- 10) Assuming all elements of implementation have been satisfactorily met, what would be the outcomes of implementation a good antimalarial drug policies?

Expanding access of the selected antimalarial drugs with new policy to populations at risk is a fundamental component of implementation, a challenge that requires the participation and support of a range of stake holders. Access could be physical availability, financial affordability and equity; and

rational use. Availability of infrastructure and human resource are also factors that influence access of appropriate health care and antimalarial treatments to rural communities.

When new antimalarial policies are formulated, it is necessary to plan for their integration into existing health programmes such as IMCI and other relevant areas. There need to be also a mechanism for using the drugs for home management with increased compliance so as to ensure access to the population at risk and reduce morbidity and mortality.

Figure 2. Drug management cycle



Monitoring of antimalarial treatment policy

Continued monitoring of the following variables is necessary to ensure acceptance of the policy and prolonged therapeutic life of the drugs.

- Efficacy of the present therapy and alternatives, preferably at the sites used for initial testing and comparing with baseline data.
- Adverse drug reactions (ADR). Such a system will address the issue that adverse effects and tolerance of the drug may compromise disease management by altering the provider and consumer confidence and compliance. In addition, the proportion of severe and life threatening events may influence whether the drug is appropriate for first line therapy.
- Availability, acceptability, and affordability of effective drugs to the consumer through methods of social research, ranging from focus groups to interviews, health seeking behaviour (including consumer and providers opinion and adherence to the policy and quality of care).
- The impact of the policy changes using appropriate indicators (such as mortality, incidence of severe cases, anaemia etc).
- In addition, indicators for assessing the cost of not changing policy at an appropriate time should be developed in order to influence change.

Case scenario for process of changing treatment policy

Epidemiological situations, health system and affordability are three major factors that influence selection of drugs for policy changes in poor endemic countries. In the absence of adequate resources, the best possible drug could be passed over for cheaper, possibly less effective drugs. This is the situation most African endemic countries are facing.

Working in small groups, discuss with colleagues on the following scenarios and suggest solutions that take all the given operational conditions into account.

11) Scenario 1 of antimalarial treatment policy in Country A

Plasmodium species: 85% *P. falciparum*, 15% *P. ovale* and *P. malariae*

Population immunity: High, with stable malaria transmission

Currently used first-line drug: Chloroquine

Second-line treatment: sulfadoxine-pyrimethamine

Drug resistance:

In 1978 and 1980, WHO missions found no evidence of chloroquine resistance.

In 1983 clinicians noted increasing slide-confirmed chloroquine-resistant malaria with a rise in admissions for the disease.

In 1984 six sentinel sites were established across the country, and the 7-day WHO *in vivo* efficacy test was used to evaluate chloroquine efficacy.

In 1990, parasitological resistance to chloroquine had increased from between 10% and 40% to about 83% in children under 5 years of age. In addition, RIII resistance had increased from 8% in 1984 to 26% in 1990.

From 1985 to 1991, the proportion of overall hospital deaths in children under 5 years increased from 10% to 20%.

Decisions:

In 1991, the following decisions were made:

First-line drug: sulfadoxine-pyrimethamine to replace CQ

Severe malaria: Quinine

Intermittent treatment in pregnant women (IPT): SP

In 1993, new policy was officially launched and the Ministry of Health has reported a reduction in deaths and hospital admissions due to malaria as a result of the drug change. Regular sulfadoxine-pyrimethamine efficacy monitoring is continuing.

Recently, same drug is in use and the SP parasitological failure rate is now about 25% and the treatment failure rate (ETF + LTF) has increased from < 5% in 1991 to a national average of 13% (11-17%).

HIV/AIDS prevalence: 16%

Popn. below poverty line: 54%

Health coverage:	60%
Health expenditure (% of GDP):	7.6%
Government's and donor's share to financing health care:	60% and 40%
Health system:	Decentralised

- While decision for change was made in 1991, new policy was officially launched in 1993. What could be the major reasons for such delay in implementation?
- With the increased treatment failure to 13% and parasitological failure of 25%, Do you recommend any change to occur or continue using the first-line drug? If you are in favour of change, what stage are you considering? would do you consider treatment failure or parasitological failure as a basis for your decision to a new drug? Why?
- Does the shift from Chloroquine monotherapy to SP monotherapy pose any concern for future utility of some ACTs, in particular SP plus Artesunate?
- Assuming the country would afford combination therapies what would you suggest as viable alternative drugs taking the epidemiological situations into account?
- What special group would be your major concern with the SP treatment regimen take?

12) Scenario 2 of antimalarial treatment policy in Country B

Plasmodium species:	<i>P. vivax</i> 30-40% and <i>P. falciparum</i> 60-70%.
Population immunity:	Low with more of seasonal malaria transmission
Currently used first-line drug:	Chloroquine
Second-line treatment:	sulfadoxine-pyrimethamine
Severe malaria:	Quinine
Drug resistance:	Chloroquine resistance first detected in 1986. Although <i>in vivo</i> studies conducted between 1991 and 1996 demonstrated increasing resistance to the drug, the methodology used was variable, making comparisons extremely difficult. Following the standardized WHO protocol, a series of <i>in vivo</i> studies were undertaken at representative sites between 1997 and 1998. The total treatment failure rate for chloroquine <i>with p falciparum</i> was 65%. Evaluation of sulfadoxine-pyrimethamine efficacy at four sites demonstrated an adequate clinical response rate of 92.3%. Sulfadoxine-pyrimethamine was considered to be the most appropriate replacement for chloroquine for <i>falciparum</i> malaria; however, it has a low efficacy against <i>P. vivax</i> . Resistance to amodiaquine is 35%.
HIV/AIDS prevalence:	7.3%
Popn. below poverty line:	45%
Health coverage:	50%
Health expenditure (% of GDP):	4.6%
Health expenditure per capita:	\$4
Government's and donor's share to financing health care:	55% and 42.5%
Health system:	Decentralised

- a) While drug resistance was first reported in 1986, policy change was only made after 1998 (i.e. after 12 years). Why?
- b) Given the above basic information and country profile which of the following antimalarial drugs would you propose as viable and feasible first-line drug?. Note that ACTs are not sought as alternatives because of the cost associated and sustainability. Justify your suggestion.
- Continue with chloroquine
 - Replace sulfadoxine-pyrimethamine with Chloroquine as first-line in stead of using SP as a 2nd -line treatment
 - alternate use of sulfadoxine-pyrimethamine and chloroquine in different seasons
 - Use combination of chloroquine + sulfadoxine-pyrimethamine
 - Use Amodiaquine as first-line
 - Would you still recommend an ACT? if yes, give reasons and how would you advice the country to proceed with this option?
- c) Do you think your option will last longer and prolong the therapeutic life of the drugs? What would you monitor after starting implementation of the changes?
- d) Which part of Africa would you think country A and B (Scenario 1 and 2) belong to?

13) Scenario 3 of antimalarial treatment policy in Country C

Plasmodium species:	<i>P. falciparum</i> dominant during the high transmission season
Population immunity:	Limited population immunity with malaria re-emerging after eradication in the 1960 th .
Currently used first-line drug:	Choloroquine
Second-line treatment:	sulfadoxine-pyrimethamine
Drug resistance:	Between 1990 and 1997 , a major resurgence of malaria occurred in two most highly endemic areas of Country C , the Coast and the Northern region. In 1998 , RII/RIII resistance levels was found to be > 50% to both CQ and SP at several sites in the Northern region and > 50% to CQ but < 5% to SP at the coast.
Decision:	In 1999 , it was proposed that the national antimalarial treatment policy should be changed to combination therapy. Drugs of choice were sulfadoxine-pyrimethamine, artesunate, and mefloquine, for which combination tests showed very good efficacy.
HIV/AIDS prevalence:	0.4%
Popn. below poverty line:	51%
Health coverage:	60%
National health expenditure per capita:	\$128
Health expenditure (% of GDP):	5.5%

- a) What new antimalarial treatment policy would you propose for the coastal and northern regions based on the facts of drug resistance in these respective places and the drug of choices given? Explain your suggestion.
- b) Is it possible to have more than one drug policy in one country for a first line drug? Discuss the operational implications of such possibilities.
- c) Pregnant women are the most at risk in such situations. With the new drug policy decisions in (a) what would be your recommendations for pregnant women?