

Combination therapies and formulation of antimalarial drug policy

Tutor's Guide



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HIV/AIDS, Tuberculosis and Malaria
Roll Back Malaria

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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

This Tutor's Guide is designed primarily to help those responsible for the training of those health personnel responsible for the planning, execution and evaluation of malaria control activities. Some parts of it should be useful even to the most experienced teacher. In case of individual studies it should be provided to learners together with the Learner's Guide so that the trainee can use it as an "answer book": This module uses a problem-solving approach when the tutor and facilitator do not in general perform supportive functions. If you are not familiar with this training system, read the introduction carefully.

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.

Educational level of learners

As indicated in the Foreword this guide is designed for health personnel responsible for malaria control at different levels of the health care system from district level to national level. These include medical officers, medical assistants, public health inspectors, parasitologists, entomologists and biologists. Most of these people have already basic knowledge about the epidemiology of communicable diseases.

The complete module is designed to be accomplished in 24 hours (3 days). You will find the suggested timetable in one of the following paragraphs.

How is the training designed and what is its content?

The training module is intended to facilitate the teaching of combination antimalarial drugs and drug policies for better management of malaria cases, planning, execution and evaluation of antimalarial activities to health professionals involved in malaria control. The principal objectives of the training are listed in the introduction of the Learner's Guide. Please stop and read these now. This module is conceived to stimulate active learning by going through the series of exercises. These exercises will be performed on the basis of the Learner's Guide preferably in small groups. These exercises emphasis on problem based learning approaches under different eco-epidemiological and the solution to these particular problems are indicated in this tutor's guide. Answers indicated in this guide are only indicative and should not be taken as the sole solutions to the problem.

Learning objectives summarize the knowledge, skills and attitudes that each learner should have acquired by the end of that unit. You and your colleagues must satisfy yourself that each learner has achieved the stated objectives before proceeding to the next learning unit (methods of evaluating progress are described later).

Who runs the course?

It is you who is responsible for organizing and running the course. The Learner's Guide and Tutor's Guide will do much to help you, but the final results will depend upon your efforts. This may be the first time that you have organized and run such a course, or you may be an experienced teacher: in either case, the importance of using the Learner's Guide and the Tutor's Guide together as you proceed through the Learning Units is stressed.

Who helps you in the course?

Your job will be easier, and your teaching more effective, if you have colleagues who will help you. These assistants, who should have knowledge and experience in the subject, are called facilitators. You can then divide learners into small groups of four to eight persons, and allocate one facilitator to each group. The greater interaction this allows between the learners and the facilitators results in better learning and understanding.

As the overall manager of the training on this module, you will be responsible for designing the timetable, explaining the learning tasks to the learners and facilitators whatever help their task is to explain or demonstrate a particular activity and to watch learners perform it. They (facilitators) must also be able to admit to learners when there is something that they do not know and be prepared to refer the question or problem to you. Impress on your facilitators that no one person can be expected to know everything about a particular subject.

There is no shame in saying "I do not know, but I will find out for you". Many problems can be avoided by giving your facilitators plenty of time to read the Learner's and Tutor's Guides, other relevant resources or handouts and discuss with you any part of it that may need clarification. It would be a good idea for you and the facilitators to go through the module together, you could then test their knowledge by asking them appropriate questions.

Why provide a learner's guide?

Providing learners with a full set of notes ensures that:

- All learners have exactly the same basic materials and guidelines on how to proceed with exercises;
- You and the facilitators can refer to any part of the Learner's Guide knowing that all learners can find the right page quickly;
- Learners can spend more time reading the notes, and therefore have a greater chance for thinking, discussion and formulation of ideas;
- There is no chance of learners making errors in note-taking;
- After the course, each learner can take home a copy of this Learner's Guide and the Tutor's Guide as a helpful reference in his or her daily work and perhaps also to use to teach others.

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.

The group compositions can be changed occasionally if you wish or left the same throughout the course. However, the group activities can all take place in the same room and time is saved by not having to change places.

Use of the Tutor's and Learner's Guides

The Tutor's and Learner's Guides may be used together for small group training when qualified facilitators are not available. In this case the tutor must, to some extent, play the role of the facilitator. The Tutor's and Learner's Guides may also be used in combination by individuals for references. Otherwise learners will follow the group training activities using the Learner's Guide plus whatever other materials you provide them with. The Tutor's Guide will be handed to them at the end of the training (upon completion of this particular module or at the end of each learning unit). The way in which you and your facilitators should make the best use of the Guides and the audiovisuals aids will become apparent as you work through the training module.

Training facilities

A number of basic facilities and equipment must be organized before training can begin. In some countries these are readily available but in others you may need to improve or to modify existing resources but do not delay training unnecessarily because you do not have the best equipment.

Ideally, one large room should be available for presentation and group discussions, pictures projected by the overhead and slide projectors will be seen more easily if the level of lighting can be controlled. Whatever the conditions, do your best to ensure that the learners are as comfortable as possible in the circumstances: you may be surprised how much you can achieve even with relatively few facilities.

Teaching equipment

For teaching sessions and group discussions, the following items should ideally be available:

- Overhead projector
- Slide projector
- Screen for slide projection (a white sheet is an adequate substitute but the white-board is unsuitable because it will reflect projected light)
- Flipcharts - one for each small group of learners. Supplies of "butcher's paper" or "newsprint" are usually cheap and readily available.
- Chalk board or white board
- Chalks for blackboard or marker pens for white-board, in a selection of colours.
- Acetate sheets for overhead projector.
- Coloured marker pens for acetate sheets (including some permanent markers for diagrams you may wish to keep).

Learner's equipment

The equipment listed below should be provided for each learner. Where supplies have to be ordered, this should be done well in advance of the course; many items are difficult to obtain at short notice.

- Copy of the Learner's Guide
- Notebook. This should be used only for occasional notes or instructions; as explained earlier, there should normally be no need for notes to be taken during training sessions.
- Sheets of paper for the exercises during the working groups.
- Ballpoint pen.
- Set of pencils (medium-hard graphite, plus red, blue, brown and black) for during charts and graphs during practical sessions.
- Pencil sharpener.
- Eraser.
- Ruler.
- A simple hand held calculator.

Syllabus and timetable

The contents list of the Learner's Guide represents the syllabus - the list of subjects to be covered - for the training course. Go through each learning units in turn and calculate how much time you will need to devote to it and decide what kind of training activity would be most suitable for the topic. Planning the course is made easier by the division of this module into a number of learning units or main topics. Go through each of the Learning Units in turn; for each unit calculate how much time you will need to devote to it and decide what kind of training activity would be most suitable for the topic.

The following is a list of the various learning activities that you might consider using:

- *Group discussion*
Once participants get used to group discussions, the two-way exchange of information between them and the facilitators makes this a very effective learning activity. People share their knowledge and experiences with the rest of the group and stimulate each other's thoughts on the subject in hand.
- *Practical exercises*
Practical exercises may be done individually or in groups in the classroom. Their purpose is to give learners the opportunity to practise the procedures involved. The more practice they have, the more competence they will acquire.
- *Demonstrations, examples*
These are designed to reinforce the learning process. Clear examples help to clarify concepts and establish principles. The tutor and facilitators should have many examples ready to use, but in addition trainees should also be invited to give examples. This is a much stronger reinforcement.

This training module

Use of the Learner's Guide

The 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. 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

Judging whether or not the course was a good one is difficult and involves answering the following questions:

- *How well did the group learn?*
This may be determined by evaluating the learner's performance as they work through the Learning Units and again at the end of the training. A further evaluation of how well they have retained their knowledge, skills and competence may be necessary 10-12 months later.
- *How did the learners view training?*
Learners' answers to this question will yield valuable information on how useful they find this type of training, especially if they provide a short evaluation during the course and a longer one at the end of the module.

Feedback provide during the course allows you to assess how well your training is being received and to make any improvements that seem necessary. Feedback received at the end of the course will help you to improve future programmes. If you have prepared the course carefully, feedback is likely to be favourable, which is rewarding both for you and for the facilitators.

Whether this module is used for group training or individual learning, assessment of progress made by the learner in gaining skills and competence in the subject matter is essential to the learner and for the tutor.

This can be accomplished by means of a pre-test in the form of a multiple-choice questionnaire (MCQ), given before the learner reads the Learner's Guide. To be valid it must be clear that the learner must work on it alone. The post-test should be administered only after all the learning units have been completed. Since the answers to the questions, and to the exercises are included in this Tutor's Guide, it is essential that learners do not have access to it until after the training activity has been completed. The pre-and post-test evaluations, participants must be seated apart from one another under examination conditions.

The results of the pre-test can be used in two ways. The Tutor may use it to ascertain the general level of knowledge on the subject amongst the group, and have an indication of general weak areas that need emphasis and areas of general knowledge that can be re-emphasized. It could also be used to identify individuals who might be used as facilitators for certain subject areas. The other major use for the pre-test is as an individual base-line comparator for measuring the gain in knowledge, skills and competence at the end of the training as revealed by the post-test.

To be valid the question in the post-tests should be of the same difficulty as the questions in the pre-test and both tests should be given under the same conditions and the same length of time. The only sure way of knowing that the questions in the post-test are of equal difficulty to those in the pre-test is to give the same questions but in a different order and in the case of multiple choice-questions with the answers also in a different order. It is thus essential that the pre-test papers be collected and retrained (not handed back to the participant): In any event, it

is not necessary for the participant to know the results of the pre-test until the end of the training when it is used to determine progress.

The tutor is encouraged to develop a bank of questions that can be used to pre-and post-testing for subsequent training sessions. The answers are scored equally because each question is considered, in this instance, to be of equal value. The preferred answers have been provided but in some instance, alternative responses are acceptable, and these have been noted.

PROPOSED TIMETABLE

	PERIOD	
	AM (4 hrs)	PM (4hrs)
DAY 1	Introduction to the module (30 min) Pre-test (30mins) Learning Unit 1. Combination therapy with antimalarials -Drug resistance and other causes of treatment failures including 8 exercises (1:30 hrs) -Discussion (0:30)	Learning Unit 1. Combination therapy with antimalarials -Concepts of combination therapies including 9 exercises (1:30) -Antimalarial therapy combination Drugs (2:30).
DAY2	Learning Unit 1. Combination therapy with antimalarials -Antimalarial therapy combination drugs including 6 long exercises (2:30) -implementation of combination therapies including 2 exercises (0:30) -Discussion (0:30)	Learning Unit 2. Antimalarial treatment policy -Definition and purpose of antimalarial treatment policy including 3 exercises 1:30) -Development of antimalarial treatment policy including 3 exercises (1:30) -Decision-making for changing policy including 1 exercises (1:00)
DAY 3	Learning Unit 2. Antimalarial treatment policy -Implementation of antimalarial treatment policy including 2 exercises(1:30) -Monitoring antimalarial treatment policy (0:30) -Additional exercises (group work) (2:00)	Learning Unit 2. Antimalarial treatment policy Group presentation on additional exercises (1:30) General discussion (0:30)

Introduction to the course

Your very first session with the learners in the meeting room should be preferable with the seating in a semicircular arrangement as indicated in the diagram. If the chairs do not have fixed supports for notebooks, it would be helpful to have small desks or tables available.

Introduce yourself first. Write your name on the board or flipchart and tell the learners a little about your background and your job. Then ask each of the facilitators to do the same thing.

The learners should introduce themselves next. It might be helpful to divide the learners into pairs and ask them to exchange names, information about jobs, home towns, etc. Each learner can then introduce his or her partner to the whole group. This method often has the effect of reducing tension, and a relaxed atmosphere is a good learning atmosphere.

The learners will have been given their copies of the Learner's Guide. Allow 10 minutes or so to read through its introduction and then briefly, but carefully, deal with the various topics covered. Explain, for instance, that working in small groups with facilitators should make learning easier. Stress that the course will involve a great deal of exercises, as this is the best way to acquire the necessary skills.

Go through the objectives of the various Learning Units so that the learners understand exactly what they should have achieved by the end of the course. Explain that the learners should keep these objectives in mind throughout the course and always ask for help if they feel uncertain of having achieved them. Each learner is likely to be more aware than the facilitators of how well he or she has understood a particular topic or has mastered a particular skill; it is the job of the facilitators to make the learning process as effective as possible.

There may be other subjects you want to raise at this time, but try also to encourage the learners to discuss the training programme -what they expect of it, what aspects of it are worrying them, and so forth. Explain that you and the facilitators will welcome feedback throughout the course - constructive criticism from the learners may well help you to improve the training programme.

Finally, talk to the learners about evaluation. Explain that evaluation will be continuous process throughout the training course. Stress that the pre- and post-tests should be enjoyed rather than feared; they are part of the learning experience. Their purpose is to allow you and the facilitators to assist the learners starting level and to correct mistakes and clarify misunderstandings. Emphasize the importance of the learners reading all the questions (and any supplementary instructions) very carefully. Explain that everyone will learn at different speeds and that you and the facilitators will make as much allowance for this as possible.

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 combinations therapy options best suited for different epidemiological situations
- determine timing of introduction of combination therapy

Ask learners to divide into small working groups and discuss the tasks outlined in the learning guide. Learners or participants are expected to have some background/reading on antimalarial drug resistance.¹

Give them some guidance in approaching this exercise in a biological reasoning. Allow about 40 minutes for this exercise to be completed by all groups. Assign groups to present different questions and discuss their results and compare their results with the tutors guide.

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 is critical element in the speed at which resistance develops. Drugs with a long terminal elimination half-life enhance the development of resistance particularly in areas of high transmission. In addition increased drug pressure contributes to development of drug resistance. Advise learners to do further reading on drug resistance.

1. Rational use of an effective antimalarial drug has the following advantages:
 - rapid and long lasting clinical cure for malaria patients
 - reduces the risk of uncomplicated malaria to severe disease and death
 - shortens duration of illness
 - reduce consequences of placental malaria infection anaemia of newborn
 - slows down the development of parasite's resistance to antimalarials.
2. In this context 'First-line treatment' is the treatment routinely recommended for a case of uncomplicated malaria. It the first treatment a person suffering from malaria is likely to get, from whatever source.

The 2nd and third-line treatment is the treatment recommended for treating either a case of uncomplicated malaria which has not been cured by the first-line treatment (given to treat failures) or one for which the first-line drug is contraindicated. Second and third-line treatments are therapeutically superior to first-line drug.

The classification or definition imply that 2nd-line treatment can only be available at higher levels of health care. Rather this is more dependent on the severity of the cases.

3. An effective first-line antimalarial treatment would have more impact on mortality than merely improved second-line antimalarial treatment. Because uncomplicated cases would be properly cured before turning to severe cases that leads to death.
4. Resistance to antimalarial drugs
 - a) The definition could be either:
 - the ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended, but within the limits of tolerance of the subject. Others may give a brief definition as:
 - an inadequate effect of a given drug concentration on the parasites or
 - an inadequate response of parasitaemia to a standard treatment regime, or

Please indicate to learners that there are degrees of variation in resistance and geographical differences in the level of resistance

- b) Resistance to anti-malarial drugs arises as a result of spontaneous mutations that affect the structure and activity at the molecular level of the drug target in the malaria parasite or affect the access of the drug to that target.

Mutant parasites are selected if anti-malarial drug concentrations are sufficient to inhibit multiplication of susceptible parasites but are inadequate to inhibit the mutants, a phenomenon known as "drug selection"

- c) The parasite factors associated with drug resistance are the Plasmodium species involved and the host factors are widespread of incorrect use or irrational use of antimalarial drugs and possibly the level of host immunity. Intensity of transmission is another factor that relates to development of resistance.
- d) Apart from drug resistance parasites, other causes of treatment failures could be:
- diagnostic errors (misdiagnosis)
 - defective drug preparation (formulation) or counterfeit drugs
 - inadequate dosage
 - poor compliance
 - re-infection
 - poor absorption,
 - rapid elimination
 - different physiological metabolism
5. Drug resistance is suspected in the field when there is either a significant rise in malaria mortality and increased incidence of severe malaria despite provision of antimalarial treatment.

Therefore, consequences of drug resistance are:

- increased morbidity (prolonged clinical episodes),
- increased severe cases, increases malaria mortality (in the risk groups). Examples include: East Africa, Senegal in West Africa.
- increased frequency and severity of malaria epidemics is also documented.

Definition and concepts of combination therapy

6. Combination therapy with antimalarial drugs is the simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biological targets in the parasite.
- a) The aim of combination therapies is to improve efficacy and to retard the development of resistance to the individual components of the combination.
- b) Combination therapies can be either fixed-combination medical products in which the components are co-formulated in the same tablet or capsule, or multiple drug therapy, in which the components are co-administered in separate tablets or capsules.
7. Multi-drug therapies including non-antimalarial drugs can not be considered as combination therapy as they do not act on the blood schizonts and only enhance the antimalarial effect.

- Example:
- i) Chloroquine plus chlorpheniramine
In this case chlorpheniramine is non-antimalarial drug that enhances the action of chloroquine.
- ii) Chloroquine plus primaquine (tissue schizonticidal or gametocidal drug)
- iii) Sulfadoxine-pyrimethamine can not be considered as combination therapy as neither of the individual components would be given alone for antimalarial therapy. Operationally, they fit the criteria of a synergistic fixed-dose combination as a single product.

Other examples of such type of drugs include:

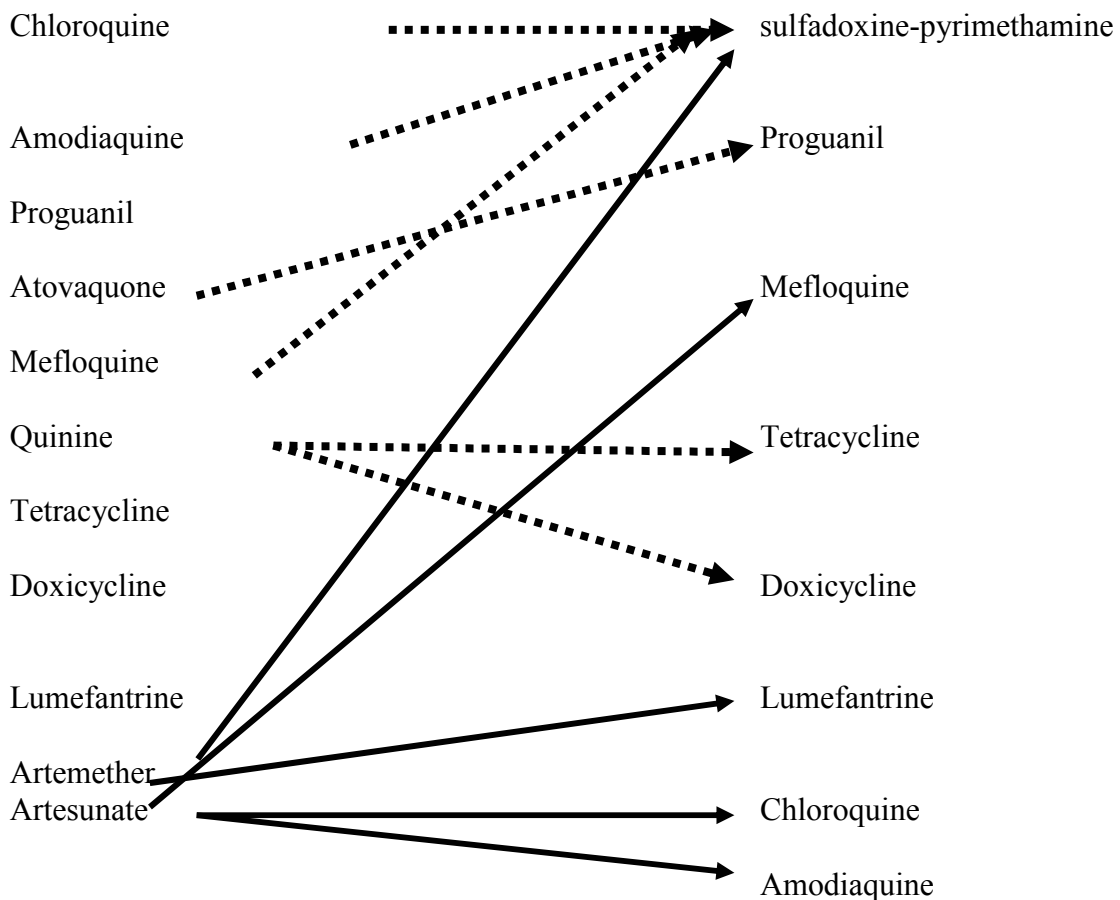
- proguanilchlorproguanil-dapsone,
- atovaquoneproguanil-proguanil

8. The concept of combination therapy has been realized in the multi-drug therapy for other diseases such as leprosy, tuberculosis, cancer, and recently in antiretroviral treatments.
9. Lead learners to understand the answer to the two questions relating to mutation resistant and explain the comparative advantages of the combination therapy using this mathematical exercise:
 - a) **The probability** of a mutation resistant to both drugs is the product of the respective mutation rates, multiplied by the number of parasite cells exposed to the drugs (usually the number of asexual parasites (parasite biomass) during an acute malaria infection is almost 10^{10} . Therefore $10^{-10} \times 10^{-10} = 10^{-20}$ (or one in 10^{20} nuclear divisions).
 - b) **Interpretation:** the probability that a mutant will arise that is simultaneously resistant to both drugs is by far less likely hence, slows down the development of resistant as compared to the probability when a drug is used alone (one in 10^{10} is more frequent than one in 10^{20}).

Antimalarial therapy combination drugs

10. Ask individuals from the small working groups to indicate possible non-artemisinin and artemisinin combinations listed in the two columns below. Advice learners to show combinations using dotted (---- ->) arrows for Non-ACT and smooth (→) arrows for ACT as indicated below.

Table 1. Possible combinations of antimalarials



Non-Artemisinin-based combinations

These are anti-malarial drug combinations not involving Artemisinin derivatives acting at different sites as blood schizontocidal drugs used as free individual drugs or as fixed combination drugs. These drugs have been in use for a longer period in which the use of some of these drugs as a mono-therapy has been exhausted as a result of drug resistance. Combinations have been shown to have higher cure rates than mono-therapy

11. The answer is No. combination of SP and CQ may not have comparative advantage over the use of SP alone in areas where *P. falciparum* is predominant and resistance to Chloroquine is high. This is the case in most African countries. Hence, other combination possibilities would be better for such situations.
12. The answer is No. Because SP and CQ do not have cross resistance.
13. In the case of country B, a combination of SP and CQ may be used as a first-line treatment. But the efficacy of the combination would be dependent on levels of resistance to the individual components.
Allow learners to mention examples of countries that implement such combination and relate the use of such drugs to these particular situations. Examples could be Peninsular Malaysia, Papua New Guinea and Ethiopia all of which are areas with *P. falciparum* and *P. vivax*.
14. In principle, combination therapies when co-administered, would be given the same dose regimen as mono-therapy. Co-formulation is more feasible and preferable as it enhances adherence and compliance in addition to its easiness for operational implementation.

Artemisinin-based combinations (ACT)

Various artemisinin compounds have been used as treatment for different forms of malaria since the early 1980s, initially in China where they were first developed, and subsequently in many other countries. 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. Properties, advantages and disadvantages of ACT

Properties

- artemisinin compounds are derived from plant extracts
- short half-time and hence their use as monotherapy requires a multiple dose regimen (7 days)

Advantages

- combining with drugs that have longer half-time reduces the duration of artemisinin treatment, enhances the efficacy and reduces the likelihood of resistance development of the partner.
- therapeutic efficacy of ACT is dependent on the level of pre-existing resistance of the partner drug
- rapid substantial reduction of the parasite biomass
- rapid resolution of clinical symptoms
- effective action against multi-drug resistant *P. falciparum*

- reduction of gametocyte carriage, which may reduce transmission of resistant alleles (in areas with low or moderate malaria transmission).
- no parasite resistance documents
- few reported adverse clinical effects

Potential challenges

- operationally, as the artemisinin derivatives are extracted from plants that need at least 2 year lead-time to cultivate, supply of raw materials could become a problem and slow down deployment of ACT.
- high cost
- As most ACT require multiple dose, they may be less useful in acute phase of complex emergencies or during malaria epidemics
- non-fixed dose combinations may affect compliance particularly at household level
- effort, time and cost of changing treatment policy
- lack of evidence on effectiveness of ACT in delaying resistance in high transmission areas is not yet documented

16. Combination therapy is an evolving situation and based on recent studies and developments, a summary is shown below. This situation may change over time. You may refer learners to recent reports on antimalarial drugs.²

Combination	Pros/advantages	Cons/limitations	Suggested to be used in epidemiological setting (transmission and type of plasmodium parasite and resistance, target group)
Non-Artemisinin-based combinations			
Cloroquine (CQ) Plus Sulfadoxine-pyrimethamine (SP)	<ul style="list-style-type: none"> • Suitable for combination as both have different biochemical targets in the parasite • No cross resistance documented • The antiinflammatory effect of CQ enhances the effect of CQ+SP with a more rapid resolution of symptoms • Cost effective 	May not be used In areas where <i>P falciparum</i> resistance to CQ is high	In areas where: <ul style="list-style-type: none"> • there is moderate resistance of <i>P falciparum</i> to CQ • in areas where <i>P falciparum</i> and <i>P vivax</i> are common
Amodiaquine (AQ) Plus Sulfadoxine-pyrimethamine (SP)	<ul style="list-style-type: none"> • Technically suitable for combination as both have different biochemical targets in the parasite • AQ has antipyretic and anti-inflammatory with faster recovery 	<ul style="list-style-type: none"> • Severe adverse reactions when used as prophylactic 	In areas where: <ul style="list-style-type: none"> • There is less resistance to AQ than those to CQ
Atovaquone-Proguanil	<ul style="list-style-type: none"> • Good synergistic effect and more efficacious against <i>P falciparum</i> including strains resistant to CQ and MQ • the recrudescence of parasitaemia (when Atovaquone is used alone) is minimized 	<ul style="list-style-type: none"> • Hypersensitivity • Presence of renal insufficiency • High cost and less available 	<ul style="list-style-type: none"> • Currently not recommended in young children (<11 kg), pregnant and breast feeding women

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

Combination	Pros/advantages	Cons/limitations	Suggested to be used in epidemiological setting (transmission and type of plasmodium parasite and resistance, target group)
Mefloquine Plus Sulfadoxine-pyrimethamine (SP)	<ul style="list-style-type: none"> No pharmacokinetic interaction between components Long elimination half-life of Mefloquine (20 days in adult) for single treatment (so used as chemoprophylactic) 	<ul style="list-style-type: none"> Poor match of half-life of Mefloquine (long) and SP (short) Residual drug level for long duration causes rapid development of resistance to Mefloquine adverse reactions 	Not recommended for areas with intense malaria transmission
Quinine Plus Tetracycline or Doxacycline	<ul style="list-style-type: none"> high cure rate in areas with decreasing susceptibility of <i>P falciparum</i> to Quinine Doxicycline has long half-life and has operational advantage as one day regimen is enough compared to tetracycline (given 4x a day) -better adherence and safety for second-line treatment 	<ul style="list-style-type: none"> Difficult to recommend as first-line treatment 	<ul style="list-style-type: none"> Not recommended for pregnant & breast feeding women, children <8 yrs of age. Recommended for 2nd -line treatment

Combination	Pros/advantages	Cons/limitations	Suggested to be used in epidemiological setting (transmission and type of plasmodium parasite and resistance, target group)
Artemisinin-based combinations			
Artesunate plus Chloroquine	<ul style="list-style-type: none"> • Well tolerated efficacy • No adverse reaction 	<ul style="list-style-type: none"> • Less parasitological cure rate (sub-optimal efficacy of combination) 	<ul style="list-style-type: none"> • Not viable combination in areas with pre-existing moderate to high <i>P. falciparum</i> resistance to CQ
Artesunate plus Amodiaquine	<ul style="list-style-type: none"> • Well tolerated efficacy 	<ul style="list-style-type: none"> • 	<ul style="list-style-type: none"> • appears to be a viable option in areas where CQ efficacy is already compromised
Artesunate plus Sulfadoxine-pyrimethamine	<ul style="list-style-type: none"> • Well tolerated efficacy • Good results with 3 day regimen of artesunate 	<ul style="list-style-type: none"> • Increasing level of resistance to SP may limit the use of this combination 	<ul style="list-style-type: none"> • A viable option where resistance to SP is lower. e.g some countries in West Africa
Artesunate plus Mefloquine	<ul style="list-style-type: none"> • Combination results in reduced adverse reactions of high Mefloquine dose than when used alone 	<ul style="list-style-type: none"> • multiple dose • severe adverse reaction (e.g neural and cardiac effects) • difficult to monitor adverse reactions in unsupervised large-scale use 	<ul style="list-style-type: none"> • not viable option as a first-line treatment in intense transmission areas because of the long half-life of Mefloquine
Artemether-lumefantrine	<ul style="list-style-type: none"> • combination effective and well tolerated • no adverse reaction • increased compliance as it exists in a fixed-dose formulation 	<ul style="list-style-type: none"> • multiple dose • not recommended for pregnant and breast feeding women 	<ul style="list-style-type: none"> • This is the most viable combination option for areas with intense malaria transmission with high immunity (4 dose) and 6 dose regimen in 3 days for non-immune population

It is worth mentioning that there are a number of combination therapies that are on pipeline and some of these in development are with new chemicals which may prove to be efficacious and development of resistance to these new combinations may be slower.

Examples of combinations on pipeline include:

- Piperaquine-dihydroartemisinin
- Pyronaridine plus artesunate
- Naphthaquine plus dihydroartemisinin
- Chlorproguanil-dapsone plus artesunate (CDATM or Lapdap plusTM)

Implementation issues

Remind learners as has been shown in the above exercises, not all combination therapies are viable for different epidemiological settings either for biological or operational reasons. 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 to them to the situations in your country or working place.

17. Selection criteria for combination therapy (in descending order of their significance).

- Therapeutic efficacy of the combination irrespective of individual efficacy
 - Clinical safety in different target groups (age, sex, physiological status, patients with other diseases)
 - Potential for wider use in different health care settings (community or home management, clinics/health centres, hospitals)
 - Potential for compliance (product formulation, dosage schedule, acceptability, dosage formulation for adult and children)
 - Cost and cost-effectiveness (affordability, sustainability, etc)
 - Potential to delay or prevent resistance (compatible half-life, mode of action, gametocidal activities)
 - Availability (production capacity, reliable source, local vs imported, reach to region in need, etc)
- a) Group the selection criteria identified above as biological and operational matters.
- Biological*
- Therapeutic efficacy of the combination irrespective of individual efficacy
 - Clinical safety in different target groups (age, sex, physiological status such as pregnancy, lactating, patients with other diseases, etc)
 - Potential to delay or prevent resistance
- Operational*
- Potential for wider use in different health care settings
 - Potential for compliance
 - Cost and cost-effectiveness
 - Availability (production capacity, reach to region in need, etc)

Please provide learners with a copy of Annex 1 (dosage for the different drugs) and Annex 2 (matrix on selection criteria for combination therapies) at the end of this session.

Learning Unit 2**Antimalarial treatment policy****Learning objectives**

At 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

The worsening problems of drug resistance in many endemic countries has led to increasing difficulties in the use of antimalarial treatments. This has compromised the impact of drugs that had been in the past effective on reducing mortality and morbidity. Resistance to the first-line treatment mainly Chloroquine, which has been effective and affordable, has been widely reported in Eastern, Central and Southern Africa. This has prompted these countries 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 not changes have been made in the first-line treatment policies.³

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

Definition and purpose of antimalarial treatment policy

Group participants into small working groups, mix them according to countries that have different drug policies in order to do the following exercises. Let groups with different policies present their results to the class for general discussion.

- 1) Antimalarial treatment policy could be defined as a set of recommendations and regulations concerning the availability and rational use of antimalarial drugs in a country. Also remind learners that such policies should :
 - reconcile with the national essential drug policy and overall national health policy. Essential drugs are those drugs that satisfy the health care needs of a majority of the population; and should be available all times at prices the community can afford in adequate amounts and in appropriate dosage.
 - be able to provide decision-makers with evidence-based recommendations
 - give health workers clear guidelines for providing early diagnosis and prompt treatment appropriate to the local context.
- 2) Purpose of antimalarial treatment policy is to enable the population at risk of malaria infection to have access to safe, good quality, effective, affordable and acceptable anti-malarial drugs.
- 3) Effective treatment could have different meaning and objectives of malaria control programmes would vary depending on the epidemiological situations among countries or within a country:

In areas of intense transmission where population immunity is high, infected adults often remain asymptomatic and when symptomatic, can often achieve clinical cure (no reappearance of signs in 14 days following treatment) without necessarily parasitological cure (elimination of all parasites from the body).

In areas of low transmission and low population immunity, where asymptomatic infections are rare, effective treatment would achieve clinical cure with parasitological cure.

- 4) Consequences of not changing a treatment policy in time could include:
 - further costs resulting from treatment failures and re-treatment
 - treating infection that progress to severe diseases
 - loss of productivity
 - increased mortality
 - increased mortality

Development of antimalarial treatment policy

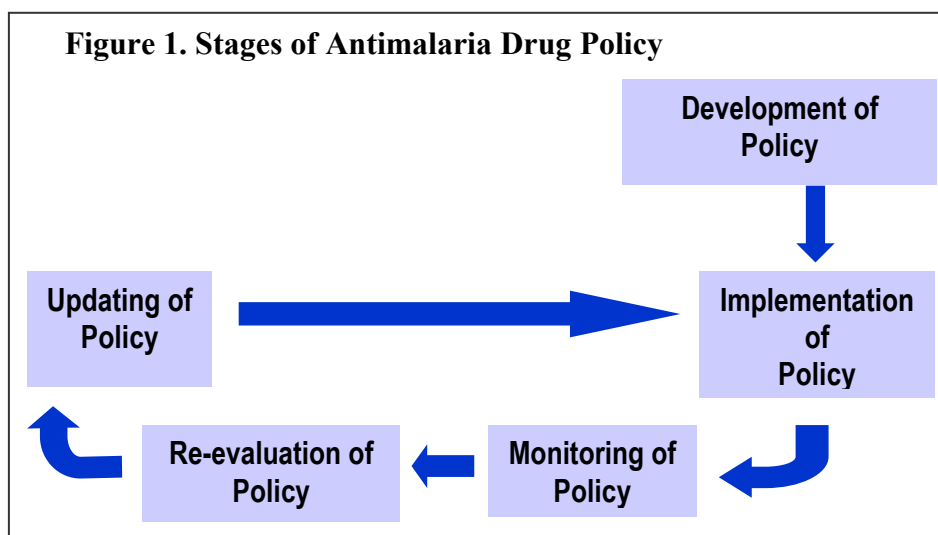
Learners should be able to understand that development or revision of antimalarial treatment policy is a dynamic process and policies in countries differ depending on diseases epidemiology, transmission, drug resistance patterns and political and economic contexts. Development of policies should be based on evidences that are obtained from studies, standardised assessments or other reliable sources.

This section would also need working in small groups, so that participants exchange experiences and challenges that countries **face in** the development of policies for antimalarial treatments.

Gathering information and establishing evidence for change of policy

Emphasise to learners the need to have standardised methods and process of data collection within a country to ensure consistency, interpretation of data and allow countries to assess the evolution of drug resistance over time. Equally, internal and external validation of collected data is important in evaluation of an antimalarial drug policy.

- 5) Ask groups to produce their logical stages of antimalarial treatment policy first by themselves and compare their result with **figure 1**.



- 6) Primary indicators to consider as evidence for changing treatment policies are:
- Evidence on therapeutic efficacy of drug in use.
(Data from tests conducted using the standardised WHO protocol⁴)
 - increased malaria-associated mortality and morbidity
(data from health facilities and health management information system (HMIS), Integrated Disease Surveillance (IDS))
 - consumer and service provider dissatisfaction with the policy/drugs in use
(data from KAP)
 - evidence of availability of new drugs and strategies
(new knowledge from biological and social science research, drug industries)
- 7) Kind of information required for the synthesis of policy development include the following epidemiological and operational situations:

Efficacy: drug sensitivity of plasmodium species, pharmacokinetics and half-time Vs resistance.

Acceptability: this would assess behavioural and economic factors such as duration of treatment, number of daily doses, clinical response (particularly the antipyretic effect), adverse effects, affordability, presentation (packaging); taste, colour and size of tablet or volume of suspensions.

Effectiveness: the better the efficacy and acceptability of drugs the better the effectiveness.

⁴ Antimalarial Drug Therapeutic Efficacy Testing for District Health Workers (in press).

Drug quality: considered at all stages of drug management cycles including pre-registration and post-marketing surveillance. Cross resistance is also a factor to consider. Drug quality for antimalarials share that of the criteria for selection of essential drugs.

- Adequate evidence data on efficacy and safety
- Bio-availability
- Stability under different conditions

Adverse effects: mild (itching and gastrointestinal effects), and severe reactions (neuropsychiatric, cardiac, etc).

Use in special group: many antimalarial drugs are contraindicated in pregnancy; infants, first-line drugs used in non-immune versus immuned populations, HIV patients may have different effects.

Capacity of health system to implement the policy: political support, financial, managerial, technical, and human resource to manage the drug supply through the formal and informal health sector.

Cost-effectiveness: average cost per treatment (costs of first and second-line drugs), costs associated with implementation (policy development, production of guidelines, training health workers, communication, supervision, etc), costs of action and inaction, productivity, benefits as a result of reduced morbidity and mortality. Gathering information on costs of antimalarial drugs is important exercise and can be referred to WHO AFRO document.⁵

It is also important to consider the *health seeking behaviour* to ensuring the development and implementation of a rational drug policy and that the purpose of the treatment policy is attained. Consumers' choice of therapy and compliance are influenced by many factors that are related to the disease and the health system; and the service providers.⁶ Optimising provider and consumer behaviour will increase compliance, promote the likelihood of clinical cure and could help limit the development of drug resistance.

Also remind learners to include in the analysis the selection criteria for combination therapy (discussed above in question 13, learning unit 1 and annex 3).

⁵ WHOAFRO: Essential Drugs Price Indicators.

⁶ Framework for developing, implementation and updating of antimalarial drug policy in Africa. A guide for country malaria control programmes. (Publishing in progress).

Decision-making for changing policy

Decision-making is a complex and dynamic process involving many agendas and interests. There should be a clear recognition of the problem of drug resistance, and definition of the options available, which should be articulated to decision-makers to create the political will for policy-making. If evidences arising from individual researchers or observations are not well articulated and justified to win the support of decision-makers, the status quo may lead to prolongation of the problems (treatment failures) with no action taken.

- 8) The goal and strategies of early diagnosis and prompt treatment and minimizing drug resistance are in general as follows. Any decision would have to look into the balance of these factors.

	Early diagnosis and prompt treatment	Minimise drug resistance
Goal	Reduce mortality and morbidity	Delay or reduce drug resistance
Strategies	<ul style="list-style-type: none"> • Broad access to antimalarials • Through community and household management • Requires high sensitivity 	<ul style="list-style-type: none"> • Restrictive access • Through regulation and control of drug use • Requires high specificity

Implementation of antimalarial treatment policy

- 9) Implementation process in general involves the following:
- Develop implementation plans and make early preparation for change (including preparatory, transitional and maintenance phases) with clear time-line, strategies, implementers and collaboration, estimated costing and resources, supervision, monitoring and evaluation.
 - Develop policies to enable public and private health sector implement the treatment policy
 - Registration of the selected drugs in line with the national drug regulations (pre-registration and post-marketing quality assurance)
 - Incorporate the new changes into national treatment guidelines and essential drugs list.
 - Develop protocols for monitoring therapeutic efficacy and safety on the newly introduced drugs or combinations
 - Training of health workers including drug vendors to disseminate new recommendations and create acceptance of the new policy within the given human resource and financial constraints
 - Ensure adequate supplies of all necessary drugs to all levels (drug procurement -sourcing, purchasing, storage and distribution)
 - Define responsibilities of health care at each level
 - Create public awareness and acceptance of the policy through development and production of communication materials
 - Monitoring and evaluation of the policy
 - Quality control and continuous quality improvement
 - Post implementation surveillance
- 10) The outcome of implementation of good antimalarial treatment policy would be:
- rapid and long lasting clinical cure for individual malaria patients
 - prevent progression of uncomplicated malaria to severe disease
 - reduce malaria-associated anaemia in areas of high malaria transmission
 - reduce consequences of malaria infection and anaemia during pregnancy
 - delay development and spread of resistance to antimalarial drugs
 - reduced morbidity and mortality

Monitoring antimalarial treatment policy

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

Remind learners to consider the indicators for signalling antimalarial treatment policy changes mentioned above.

Provide learners with a copy of Annex 1 at the end of this session to show them the decisions made on antimalarial treatment policies by different endemic countries in different regions.

Case scenario for process of changing treatment policy

Remind learners that 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.

Divide learners into small groups and let them discuss with their colleagues on the following scenarios and suggest solutions and advice them to emphasis all the given operational conditions into account while proposing alternatives.

11) Scenario 1 of antimalarial treatment policy in Country A

Plasmodium species:	85% <i>P. falciparum</i> , 15% <i>P. ovale</i> and <i>P. malariae</i>
Population immunity:	high
Currently used first-line drug:	Choloroquine
Second-line treatment:	sulfadoxine-pyrimethamine
Drug resistance:	<p>In 1978 and 1980, WHO missions found no evidence of chloroquine resistance.</p> <p>In 1983 clinicians noted increasing slide-confirmed chloroquine-resistant malaria with a rise in admissions for the disease.</p> <p>In 1984 six sentinel sites were established across the country, and the 7-day WHO <i>in vivo</i> efficacy test was used to evaluate chloroquine efficacy.</p> <p>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.</p> <p>From 1985 to 1991, the proportion of overall hospital deaths in children under 5 years increased from 10% to 20%.</p>

Decisions:	<p>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</p> <p>In 1993, new policy was officially launched.</p> <p>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%).</p>
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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. The major reasons for delay in implementation could be attributed to time taken for consensus-building and information dissemination among key groups, production of treatment guidelines, education and communication materials, and procurement of adequate stocks of the new drug i.e. SP.
- With the increased treatment failure to 13% and parasitological failure of 25%, as the area is high malaria transmission, treatment failures should be considered for decision making process. In this case it is at the stage of **Alert period** in which analysing the drug resistance of SP and selecting alternative drugs is required.
- Yes! the shift from CQ to SP monotherapy could affect as the resistance level to SP would rapidly increase thereby reducing the future possibility of using ACT mainly, Artemisinin with SP.
- Assuming the country would afford combination therapies and this could be sustained, **Artemether-lumefantrine** or **Artemether-Amodiaquine** as the area is high malaria transmission and with already high resistance to CQ and the moderate resistance to SP is likely to increase soon.
- HIV prevalence in country A is high, so treatment of concomitant malaria infection with SP could result in high increased frequency of sulfa-drug associated toxicity in HIV patients. Close observation of clinical outcomes and care for such patients would be necessary.

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%. <i>P. vivax</i> dominates during the dry season, while <i>P. falciparum</i> occurs after the rains.
Population immunity:	0 with more of seasonal malaria transmission
Currently used first-line drug:	Chloroquine
Second-line treatment:	Sulfadoxine-pyrimethamine
Severe cases:	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 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. Why? This could be because the first report was not articulated enough and the later studies which followed WHO protocols got more attention because they were perhaps done in a standardised manner and articulated to convince policy makers. In addition, consensus-building exercise takes long time until more evidences are collected from e.g. consumer and service provider satisfaction level, drug efficacy tests, observations on clinical cure, mortality and morbidity.
- b) Given the profile and economic situations of **country B**, the most viable solution of the three antimalarials drugs would be **alternative (iv)** as this would yield to relatively better cure (rapid resolution of symptoms) and retarded development of resistance to SP. The use of SP for laboratory-confirmed cases of *P. falciparum* and CQ to laboratory confirmed *P. vivax* would enable more rational use of the drugs.
- Alternative (i) i.e continuing with CQ is not acceptable given the resistance level (65%)
 - Alternative (ii) i.e replacing SP with CQ is also not acceptable as SP has low efficacy on *P. vivax*
 - Alternative (iii) i.e. alternate use of sulfadoxine-pyrimethamine and chloroquine in different seasons is also not operational possible to implement and although seasonal variations in the prevalence of the diseases, there are still substantial percentage of cases mixing from wither of the parasites.
 - Alternative (v) i.e. to change the first-line from chloroquine to amodiaquine is also not deemed plausible because of the high resistance to Amodiaque (35%).
 - The country should however be advised on the advantages of ACTs - Alternative (vi), as the useful therapeutic life of monotherapy is limited and this change can only be an interim approach. The need to source external resources to allow for effective antimalarial policies should be explored. Sources of fund includes GFATM, other developmental banks and bilateral agencies among others.
- c) The option selected (use of combination of SP plus CQ) would not be used for long time. Because the trend is that SP resistance increases rapidly in areas where resistance to CQ had already been well established. But this could be used as an inter-rim solution until other more viable combinations are made available. The measures after starting implementation could be:
- to monitor the therapeutic efficacy and safety of chloroquine + sulfadoxine-pyrimethamine
 - to gather more information of other candidate drugs, costs, health seeking behaviour, etc to prepare for the next moves.

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 196th
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%

Health system: Decentralised

a) The new antimalarial treatment policy for the coastal and northern regions based on the facts of drug resistance in these respective places and the drug of choices given could be:

For the Coastal region: Combination therapies with sulfadoxine-pyrimethamine plus artesunate for uncomplicated *P. falciparum* because resistance of *P. falciparum* to SP in the coastal region is below 5% and the therapeutic life of SP which is cheaper than Amodiaquine can be prolonged by combining it with artesunate.

For the Northern region: Combination therapies with artesunate plus mefloquine as new first-line treatment for uncomplicated *P. falciparum* malaria. In this case, the resistance of the *P. falciparum* to SP is high (>50%) so better to shift to Mefloquine.

Note that resistance to CQ in both regions is high and would not be proposed for combination in any of the regions.

b) It should be possible to have more than one drug policy in one country for a first-line drug to address different epidemiological situations of the different regions as long as the country puts efficient drug management system in place with relevant treatment guidelines and efficient monitoring of the drugs in use.

The system has to also ensure that the movement of people from one to another region (two epidemiologically different places with different drug policies) does not increase the risks of treatment failures. Particular emphasis should be given, in the case of the above example (b), to those travelling from Northern region (where *P. falciparum* is highly resistant to SP) to the Coastal region where Artemisinin-SP is given as first-line treatment. Taking history e.g origin of place could be important in treatments of such patients (traveller).

- c) Although the use of ACTs is increasingly implemented in other groups, they should not be used for pregnancy as there is not yet enough evidence on safety and efficacy in this group. The use of Intermittent Pregnancy Treatment (IPT) with SP could be a solution as its safety has been rather well established. However, artesimining-based combinations (ACTs) should not be withheld if treatment is considered to be lifesaving for the mother and other antimalarials are considered to be unsuitable.

Distribute copies of Annex 3 that show examples of antimalarial treatment policy changes in some countries from different regions.

Annex 1

Drug dosage tables

Sulfadoxine-Pyrimethamine:

The following table was drawn up as the result of a joint effort between field experts and WHO using weight-for-age data set from WHO containing weight relative to age from children and adults in developing countries. The weight-for-age data set was standardized by age and sex to represent the age distribution of a typical population of a developing country.

		Sulfadoxine 500mg –Pyrimethamine 25 mg single Dose treatment	
Weight (Kg)	Age (years)	Number of tablets	Intramuscular injection (ml)
5-10	2-11 months	0.5	1.25
10-14	1-2	0.75	1.90
14-20	3-5	1	2.50
20-30	6-10	1.5	3.75
30-40	9-11	2	5.00
40-50	12-13	2.5	6.25
> 50	14+	3	7.50

Note: Sulfadoxine-Pyrimethamine should be given as single dose on day 1 with Amodiaquine first dose, then continue with Amodiaquine on day two and three as in the table 7 below.

Amodiaquine:

Table 7: Amodiaquine Dosage table for the two formulations

Weight (Kg)	Age (years)	Number of tablets					
		153 mg base tablets			200 mg base tablets		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5-6	<4 months	0.5	0.5	0.25	0.5	0.25	0.25
7-10	4-11 months	1	0.5	0.5	0.5	0.5	0.5
11-14	1-2	1	1	1	1	0.5	0.5
15-18	3-4	1.5	1	1	1	1	1
19-24	5-7	1.5	1.5	1.5	1.5	1	1
25-35	8-10	2.5	2.5	2	2	2	1.5
36-50	11-13	3	3	3	3	2	2
50+	14+	4	4	3	3	3	3

Artesunate plus Sulfadoxine-Pyrimethamine:

Artesunate plus Sulfadoxine-Pyrimethamine free individual drugs combination blister packs available through WHO and IDA by providing a new GMP 2-strength formulation of artesunate with SP. The following table will be used for dosing

Table 8: Dosage schedule for Artesunate plus Sulfadoxine-Pyrimethamine free combination

		Number of tablets			
Weight (Kg)	Age (years)	Artesunate 25 mg tablets			Sulfadoxine-Pyrimethamine
		Day 1	Day 2	Day 3	Day 1
5-10	Infants	1	1	1	1
11-24	1-6	2	2	2	1
		Artesunate 100 mg tablets			Sulfadoxine-Pyrimethamine
24-50	7-13	1	1	1	2
50+	14+	2	2	2	4

Artesunate plus Amodiaquine:

Artesunate plus Amodiaquine free combination blister packs available through WHO and IDA by providing a new GMP 2-strength formulation of artesunate with Amodiaquine, which will be co-packaged. The blister packs will allow for equal daily divided doses for three days as in the following table 9.

Table 9: Dosage schedule for Artesunate plus Amodiaquine free combination

		Number of tablets					
Weight (Kg)	Age (years)	Artesunate 25 mg tablets			Amodiaquine 75 mg base tablets		
		Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
5-10	Infants	1	1	1	1	1	1
		Artesunate 50 mg tablets			Amodiaquine 150 mg base tablets		
11-24	1-6	1	1	1	1	1	1
24-50	7-13	2	2	2	2	2	2
50+	14+	4	4	4	4	4	4

Artemether-Lumefantrine:

WHO treatment guidelines on the use of artemether-Lumefantrine were published in 2001. These state that the 6-dose regimen should be adopted as standard treatment for all age groups and in all situations to avoid confusion and ensure the highest efficacy and reliability with this combination. The following table 10 gives the dosing schedule.

Weight (Kg)	Number of tablets per dose (at 0h, 8h, 24h, 36h, 48h and 60h)	Content of Artemether (A) + Lumefantrine (L) per dose
<10	Not recommended	
10-14	1	20 mg A + 120 mg L
15-24	2	40 mg A + 240 mg L
25-34	3	60 mg A + 360 mg L
>35	4	80 mg Kg + 480 mg L

Annex 2

Combination therapy comparative matrix

Criteria	Drug A	Drug B	Drug C	Drug D
1. Therapeutic efficacy of the combination (Treatment failure < 5%; 6%-15%; 16%-24% and > 25%) <ol style="list-style-type: none"> Efficacy studies Comparative efficacy studies 				
2. Clinical safety (Recommended for clinical use; Not recommended for clinical use) <ol style="list-style-type: none"> All age group Children under 5 years Infants Pregnant women Breastfeeding mothers People living with HIV/AIDS 				
3. Potential for widespread use in different health care settings (Ability to use at all levels; Other levels except community/home management; Hospitals alone) <ol style="list-style-type: none"> Community/home management Clinics/health centers Hospitals 				
4. Potential for consumer acceptability and compliance <ol style="list-style-type: none"> Product formulation (Co-formulation; Co-administration) Dosage schedule (Number of daily dose multiplied by the duration of treatment dose) Acceptability (Acceptable; score increases to a maximum of 4 with reducing acceptability based on factors such as side effects, taste, color, number of tablets per dose, etc.) Dosage formulation (adult/pediatric) 				
5. Cost and cost effectiveness				
6. Potential to delay drug resistance <ol style="list-style-type: none"> Compatible half-life (compatible half-lives; Non-compatible half-lives) Mode of action (Synergistic; additive action; antagonistic activity) Gametocytocidal activities (Gametocytocidal activity; No gametocytocidal activity) 				
7. Availability <ol style="list-style-type: none"> Reliable production source (GMP standards: yes; no) Adequate production capacity (Reliable product capacity: yes; no) <i>Local availability</i> <ol style="list-style-type: none"> Registered (Registered for use: yes; no) Available at affordable cost (for wide spread use: yes; no) 				
8. Potential for wide geographical application (Potential for wide spread use; limited application) Regional spread of application				

Annex 3

Examples of emergence of drug resistance and antimalarial treatment policies in different endemic countries

Selected African countries^a

Country	Drug for which reduced susceptibility of parasite reported (Year of reporting if known)	Current first-line policy (June 2002)	Current second-line policy
Botswana	CQ (1984)	SP	Quinine
Eritrea	CQ (1998) SP (2001)	CQ + SP (if no microscopy available, otherwise CQ for <i>P. vivax</i> and SP for <i>P. falciparum</i>)	Quinine
Ethiopia	CQ (1987)	CQ + SP (if no microscopy available, otherwise CQ for <i>P. vivax</i> and SP for <i>P. falciparum</i>)	Quinine
Ghana	CQ (1987) SP	CQ	SP
Kenya	CQ (1979) SP (1998)	SP	AQ
Malawi	CQ (1984)	SP	Quinine
Mali	CQ SP	CQ	SP
South Africa			Quinine
Kwazulu Natal	-	Coartem	
Mpumulanga	-	SP	
Uganda	-	CQ + SP	Quinine
United Republic of Tanzania			
Main land	CQ (1978) SP (1982)	SP	AQ
Zanzibar	CQ (1999) SP (2001)	Artesunate + AQ	Coartem
Zambia	CQ (1978) SP (1995)	CQ (new recommendation is SP but not officially adopted)	SP
Zimbabwe	CQ (1987) SP (2000)	CQ + SP	Quinine

AQ, amodiaquine; CQ, chloroquine; Q, quinine, SP, sulfadoxine–pyrimethamine

^aIn countries not listed in the table, chloroquine is used as first-line and sulfadoxine–pyrimethamine as second-line drug treatment.

Selected Asian countries

Country	Drug for which reduced susceptibility of parasite reported (year of reporting if known)	Current first-line policy (November 2000)	Current second-line policy
Afghanistan	CQ	CQ	SP
Bangladesh	CQ (1970) SP (1985)	CQ + PQ (<i>P. vivax</i> : CQ)	Q-3 + SP or Q-7
Bhutan	CQ (1985) SP (1990)	ASU or ATM (laboratory confirmed) (<i>P. vivax</i> : CQ)	ATM + Q
Cambodia	CQ (early 1960s) SP (late 1960s) MQ (1995)	CQ (limited areas); ASU-3 + MQ (20 mg/kg) (following RDT in other areas)	Q-7 + T-7
India	CQ (1973) SP (1979) <i>P. vivax</i> resistance to CQ (1991)	CQ (25 mg/kg) + PQ (<i>P. vivax</i> : CQ)	SP + PQ (45 mg/kg)
Malaysia	CQ (1987) SP (1982) <i>P. vivax</i> resistance to CQ	CQ	SP
Myanmar	CQ (1969) SP (1986) MQ Q <i>P. vivax</i> resistance to CQ (1991)	CQ or SP + PQ (<i>P. vivax</i> : CQ)	MQ (15–20 mg/kg) + PQ (immunes); Q-7 + PQ (non-immunes and children)
Thailand	CQ (1962) SP (1984) MQ (1990) Q + T (1982–1984)	MQ + PQ (in all areas except as below); MQ + ASU + PQ in multidrug-resistant areas (borders) (<i>P. vivax</i> : CQ)	Q-7 + T-7 + PQ (30 mg/kg)
Viet Nam	CQ (1967) SP MQ (southern provinces)	CQ (north); ATM-5 or ASU-5 (other) (<i>P. vivax</i> : PQ-5)	ASU-3 + MQ (25 mg/kg) (north); Q-5 + T-5 (other)
Yemen	CQ	CQ	SP

AQ, Amodiaquine; ASU, Artesunate; ATM, Artemether; CQ, Chloroquine; MQ, Mefloquine; PQ, Primaquine; Q, Quinine;

RDT, Rapid Diagnostic Testing; SP, Sulfadoxine-Pyrimethamine; T, Tetracycline; ASU-3, Artesunate for 3 days

Selected Oceanic countries

Country	Drug for which reduced susceptibility of parasite reported (year of reporting if known)	Current first-line policy (November 2000)	Current second-line policy
Papua New Guinea	CQ (1976) AQ (1987) Q SP <i>P. vivax</i> resistance to CQ (1989-90)	CQ + SP (adults) AQ + SP (children < 5 years)	ASU + SP
Solomon Islands	CQ (1980) SP (1995)	CQ (plan to change to CQ + SP)	CQ + SP (Q)
Vanuatu	CQ (1987) SP (1991)	CQ + SP	Q

AQ, Amodiaquine; ASU, Artesunate; CQ, Chloroquine; Q, Quinine; SP, Sulfadoxine-Pyrimethamine

Selected countries in the Americas

Country	Drug for which reduced susceptibility of parasite reported (year of reporting if known)	Current first-line policy (November 2000)	Current second-line policy
Brazil	CQ (1987) SP (1970s) <i>(P. vivax</i> resistance to CQ) MQ (1996)	Q-7 + T-7	MQ 15 mg/kg
Colombia	CQ (1958) SP (1985)	AQ + PQ + SP	SP
Guyana	CQ (1987) SP (1993) <i>(P. vivax</i> resistance to CQ)	Q-3 + CD	SP
Peru	CQ (1987) SP (1997)	Q-7 + T-7 (will change very soon to SP + ASU on Pacific Coast and to MQ + ASU in Amazon region)	SP
Venezuela	CQ (1987) SP (1978)	CQ + PQ	Q + D

AQ, Amodiaquine; ASU, Artesunate; CD, Clindamycin; CQ, Chloroquine; D, Doxycycline; MQ, Mefloquine; PQ, Primaquine; Q, Quinine; SP, Sulfadoxine-Pyrimethamine; T, Tetracycline