

Strategies for Implementation of the New Antimalarial Drug Policy in Uganda: Workshop Report, Entebbe, October 4–5, 2006

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ACRONYMS AND ABBREVIATIONS

ACT	artemisinin-based combination therapy
ADR	adverse drug reaction
AL	artemether/lumefantrine
AMDP	antimalarial drug policy
AQ	amodiaquine
ARV	antiretroviral medicine
AS	artesunate
CNF	Committee on the National Formulary [NDA]
CQ	chloroquine
DRA	drug regulatory agency
GMPs	Good Manufacturing Practice
HBMF	home-based management of fever
HBMM	home-based management of malaria
HIV/AIDS	human immunodeficiency virus/acquired immunodeficiency syndrome
IPTp	intermittent presumptive treatment in pregnancy
IV	intravenous
MCP	Malaria Control Programme
MIP	malaria in pregnancy
MOH	Ministry of Health
MSH	Management Sciences for Health
NAMTP	New Anti-Malaria Treatment Policy
NDA	National Drug Authority
NDP/A	National Drug Policy and Authority Act
NMS	National Medical Stores
OTC	over-the-counter
PNFP	private, not for profit
POM/PIM	prescription-only medicine/pharmacist-initiated medicine
PSU	Pharmaceutical Society of Uganda
PV	pharmacovigilance
RPM Plus	Rational Pharmaceutical Management Plus Program [MSH]
SP	sulfadoxine/pyrimethamine
TB	tuberculosis
UGX	Uganda shillings
USAID	U.S. Agency for International Development
USP	United States Pharmacopeia
WHO	World Health Organization

INTRODUCTION

The National Drug Authority (NDA) of Uganda, with funding from the U.S. Agency for International Development's Uganda Mission through the Rational Pharmaceutical Management Plus Program of Management Sciences for Health, held a national consultative workshop to discuss NDA's action plan for implementation of the new antimalarial medicine policy, which includes artemisinin-based combination therapy as first-line treatment for uncomplicated malaria.

A team of 28 stakeholders was drawn from national and support agencies in Uganda for a two-day workshop (October 4–5, 2006). The workshop targeted stakeholders providing support for the new antimalarial treatment policy by executing malaria control and pharmaceutical management activities. Participants included researchers, policy makers, clinicians, pharmacists, procurement specialists, and district health workers, as well as members or staff from health professional associations, development partners, and agencies responsible for implementing public health policy.

OBJECTIVES AND EXPECTED OUTCOMES

The workshop was intended to provide a national forum to share and exchange ideas on regulatory considerations and actions required for implementing the new malaria treatment policy in the Uganda public and private sectors. The workshop was also expected to provide guidance on technical and other issues related to implementing agreed-upon interventions.

Specific objectives of the workshop were to—

1. Identify the key mandate of the NDA and agree on its role in supporting implementation of the new malaria treatment policy.
2. Identify the key regulatory actions necessary to support policy implementation.
3. Identify common challenges in the NDA's support to ACT policy implementation, both technical and managerial, and share experiences and lessons learned from previous and current policy changes.
4. Finalize an agreed-upon strategy and implementation plan, to include key elements: registration of antimalarials, phaseout of monotherapies for treatment of uncomplicated malaria, limiting sulfadoxine-pyrimethamine (SP) use only for intermittent presumptive treatment in pregnancy (IPTp), and strengthening pharmaceutical regulatory procedures and practices.

Expected outcomes of the workshop were—

1. Articulation of the key regulatory actions that must be carried out to support policy implementation.
2. Definition of the role of the NDA in supporting implementation of the new malaria treatment policy.
3. Identification of and exchange of experiences, common challenges, and lessons learned from previous malaria treatment policy change in Uganda as well as from recent policy changes in other countries.
4. Finalized strategy and implementation plan, with key elements of pharmaceutical registration, ACT deregulation/scheduling of ACTs for different levels within the EDL, local manufacture of ACTs, phaseout of monotherapies, limiting SP for IPTp use only, and plans for strengthening medicine regulatory procedures and practices.

WORKSHOP OPENING

Twenty-eight technical experts and six support staff attended the workshop, including representatives from the Ministry of Health (MOH); NDA; Rational Pharmaceutical Management (RPM) Plus Program of Management Sciences for Health (MSH); Global Fund to Fight AIDS, Tuberculosis and Malaria; the Malaria Consortium; the Uganda Malaria Control Programme (MCP); Office of the District Director of Health Services, Wakiso district; National Medical Stores (NMS); and the World Health Organization (WHO). Also attending was a visiting Dr. John L. Graham, Assistant Vice President for International Affairs at Delaware State University, United States. A complete list of participants and contact information can be found in Annex 1.

The workshop began October 4 at 9:30 a.m., and the opening session was chaired by Mr. Saul Kidde from MSH/RPM Plus. The chairman told participants that the malaria policy had been changed from chloroquine (CQ) + SP to ACT, presenting a need for a forum—the workshop—to discuss the implementation process. The chairman welcomed participants and asked that they introduce themselves.

The focal person for malaria case management at the MOH, Dr. Frederick Kato, outlined the strategies used by the ministry in management of malaria and the recent change in treatment policy. He then introduced the Executive Secretary/Registrar of the NDA, who was the guest of honor.

KEYNOTE ADDRESS

Mr. Apollo Muhairwe, the Executive Secretary/Registrar of NDA, thanked RPM Plus for organizing the workshop so that participants could discuss how best to implement the new policy with minimal disruptions in health care delivery. He explained that NDA was mandated by law to regulate medicines in the country and also to act as an adviser to the MOH on issues related to the national medicine policy. NDA had realized that the new antimalarial policy would affect the availability of medicines listed on the National Drug Register. Concern had also been raised in some of the committees of the NDA, such as the Committee on the National Formulary (CNF), about the speed of implementation of the policy and about the government's intention to distribute the ACTs, which are relatively new products, at the grass-roots level using community medicine distributors. He noted that such a move would require an effective pharmacovigilance system covering both the public and private sectors.

Consequently, these issues were discussed by the Technical Committee of the NDA Secretariat, which decided to approach this and other policy changes in a scientific and systematic way. An Advisory Committee on New Policies, comprised of five members, was therefore formed to advise the secretariat on implementation of and regulatory issues related to new health care policies. It was under the auspices of this committee that the workshop was convened.

The Executive Secretary/Registrar noted that, although artemisinin has a long history of use in China and has also more recently been used in other countries as a monotherapy, WHO currently recommends combination therapy. He said that the NDA expected guidance from the workshop on how to implement the new policy, and that workshop members were expected to outline regulatory actions in support of policy implementation and to identify possible challenges.

The Executive Secretary/Registrar declared the workshop officially opened and thereafter left to attend a function at the National Drug Quality Control Laboratory organized by the United States Pharmacopeia in conjunction with NDA.

PRESENTATIONS

Current Malaria Treatment Policy, Presented by Dr. Frederick Kato, Senior Medical Officer, MOH, Malaria Control Programme

Dr. Kato's presentation was followed by a discussion period, in which participants provided feedback.

Presentation

Dr. Kato informed workshop members of the general objective of the national Malaria Control Programme (MCP): to reduce malaria morbidity, mortality, and disability and to minimize related economic losses and adverse social effects.

He informed participants that the new malaria treatment policy was launched April 25, 2006, in line with the objectives of the MCP and the Health Strategic Plan II (2006–2010).

Highlights of the presentation included—

- The intervention and enabling strategies
- The five malaria control targets for the Health Sector Strategic Plan II (2006–2010)
- The change from CQ monotherapy to CQ + SP combination therapy
- The change from CQ + SP to ACT
- The current malaria treatment policy in relation to—
 - Uncomplicated malaria (artemether/lumefantrine)
 - Severe malaria (quinine)
 - IPTp (SP)
 - Uncomplicated malaria in special groups (quinine for children weighing less than five kilograms or less than four months of age)

The full details of the presentation are attached in Annex 2.

Reactions and Questions

It was noted that malaria treatment policy is dynamic because malaria parasites develop resistance. The NDA was urged to enforce proper dispensing practices to ensure that medicines are dispensed in the right doses and not in incomplete doses, which were found to be one of the causes of resistance. Therefore, there was a need to be vigilant to ensure that malaria treatment is effective; scientists should be able to think beyond the new policy. Participants were informed that malaria treatment was being actively monitored through eight sentinel sites using the WHO protocol. Members were encouraged to familiarize themselves with this protocol and its

recommendations on how to assess reinfection, recrudescence, and efficacy in relation to parasitology and clinical cure.

The need for an alternative to quinine, especially in children weighing less than 5 kg, was highlighted.

It was recommended that—

- Before registration, the NDA should consider clinical data from local research studies or studies done in regions with similar disease intensity and transmission.
- In the absence of this data, there should be a requirement for a local phase IV or operational study within one year of registration.
- The NDA should also develop linkages with local researchers and sentinel sites to access data for establishing and monitoring drug efficacy and to enable changing the policy from time to time.

It was clarified that severe malaria is defined as malaria with complications and that health workers had been trained throughout the country on how to recognize severe malaria. It was also noted that books and charts are available on management of complicated malaria. Every health worker who had attended the training had received a copy of the documents and MCP would also distribute them for posting in the clinics. District leaders and health workers had been sensitized and informed about the new policy, and the activity was ongoing. It was noted that sensitization was budgeted for with funding from the Global Fund and that sensitization required follow-up to ensure that health workers were practicing what they had been trained.

It was stated that the MCP had adopted a strategy of home-based management of malaria (HBMM), which aims to increase access to an effective first-line medicine within 24 hours of symptom onset. This had been achieved by training pharmaceutical distributors and giving them CQ and SP (HOMAPAK[®]) to administer to children. The intention was to continue HBMM using Coartem[®] (brand name for artemether/lumefantrine [AL]). Currently, no ACT (Coartem/AL) is classified as an over-the-counter (OTC) medicine. Workshop members were informed that a pilot study was being conducted in Iganga and Bugiri districts on the feasibility of use of ACT (Coartem/AL) in HBMM. The NDA had also allowed the use of AL in internally displaced person (IDP) camps in Pader and Kitgum.

It was noted that Uganda has a strategic plan and policy for malaria control. Participants were advised to consult the National Health Policy and Health Sector Strategic Plan II (2006–2010) as a reference for strategies and targets in management of malaria.

Regulatory Issues in the Implementation of the New Antimalarial Drug Policy, Presented by Mr. Deusdedit K. Mubangizi, Chief Inspector of Drugs, NDA

Mr. Mubangizi's presentation was a collection of views from the NDA Committee on New Policies, comprised of the following members—

Mr. Deus Mubangizi, chairman
Mr. Gabriel Kaddu, secretary
Mr. Moses Oгаа, member
Mr. David Nahamya, member
Mr. Samuel Kasozi, member
Ms. Huldah Nassali, member
Mr. Chris Ntege, member

The presentation (provided in full in Annex 3) highlighted the quality assurance measures used by NDA, including medicine registration; Good Manufacturing Practices (GMP) inspection and licensing of local and foreign manufacturing sites; inspection and licensing of medicine outlets (pharmacies and drug shops); inspection of other institutions where medicines are handled (hospitals, clinics, maternity homes, etc.); licensing and inspection of imports; quality control (testing of medicine samples); pharmacovigilance; postmarketing surveillance; regulation of pharmaceutical promotion and advertising; and regulation of medicine-related clinical trials. All these areas are applicable to antimalarial medicines.

It was explained that clinical-trial or bioequivalence data to prove efficacy, plus GMP inspection, are required before medicine registration and, thereafter, every three years. There is mandatory analysis of each batch of imported antimalarial medicines, anti-TB medicines, antiretroviral medicines (ARVs), and condoms.

Methods used to control importation of medicines were outlined. Every importer requires an annual import permit and a Verification Certificate per consignment. Importation is only through gazetted entry ports, and the consignments are inspected at the port of entry. Samples are picked for analysis if necessary—or mandatory, as in the case of antimalarial medicines, anti-TB medicines, ARVs, condoms, and screening of injectable products for particulate matter.

The role of pharmacovigilance in the new policy was outlined as informing regulatory decisions and filling any gaps in information on ACTs. It was discussed that tests in laboratory animals are not predictive of human safety and that clinical trials are carried out with a limited number of patients, over a limited time duration, and in conditions different from clinical practice. ACTs are relatively new medicines in our setting, and there is limited experience and knowledge on their use. Pharmacovigilance would provide information on possible medicine interactions, adverse drug reactions (ADRs) due to poor patient compliance (different dosage regimen, side effects, properties [no antipyretic/analgesic properties compared to CQ]). It was reported that since pharmacovigilance forms were distributed, the total number of ADR reports received was 78 and ADR reports due to Coartem totaled five, but were all expected.

It was stated that the new antimalarial medicine policy specifies Coartem, which promotes use of a brand-name product, contrary to the provisions of the National Drug Policy and Authority Act (NDP/A), which promotes generics. It was further stated that because of Uganda's status as a least-developed country (LDC), it was not bound by patents until the year 2016:

Further to Paragraph 7 of the Declaration on the TRIPS Agreement and Public Health adopted by the WTO Ministerial Conference on 14 November 2001

(WT/MIN(01)/DEC/2), the WTO Council for TRIPS decided on 27 June 2002 (IP/C/25) that least developed Members of the WTO need not enforce patents and data protection with respect to pharmaceutical products at least until 1 January 2016.

In light of this policy, the NDA registers any medicine with proof of safety, efficacy, and quality. It was recommended that the policy should refer to the generic name and not a brand name. Members were asked, however, to deliberate on whether efficacy data should be based on studies conducted in Uganda, East Africa, Africa, or internationally—and how to factor in different drug resistance patterns and disease intensity and transmission patterns.

These ACTs were registered for use in Uganda at the time of the workshop—

- Amodiaquine/artesunate tablets
- AL tablets
- Artemisinin/naphthoquine phosphate tablets
- Artesunate/SP tablets
- Artesunate/mefloquine tablets
- Beta-AL powder for reconstitution
- Dihydroartemisinin/piperaquine phosphate tablets

It was stated that the NDA was concerned with the high cost of Coartem (15,000–20,000 Uganda shillings [UGX] per dose) and the limited number of suppliers (i.e., Novartis). There was inadequate supply of Coartem in the private sector because its free availability in the public sector raised concerns about possible losses through expiry at private outlets. This problem, together with inadequate controls/accountability in the public sector, had led to some leakage from the public to the private sector. To curb this leakage, the following recommendations were made—

- Increase controls and accountability in the public sector.
- Increase inspection and surveillance in the private sector.
- Increase supplies to the private sector (through accredited centers, subsidies, social marketing).

Implications of the New Policy for Monotherapies

These implications were outlined as follows—

1. Chloroquine (CQ)—
 - Reserve oral CQ for sickle cell prophylaxis and management of rheumatoid arthritis.
 - Halt registration and importation of injectable CQ.
 - Manufacture only locally, on an order basis, for MOH and accredited centers in the private sector.

- Reclassify/reschedule CQ to prescription-only medicine (POM) or pharmacist-initiated medicine (PIM) status.
 - Issues:
 - What quantities of CQ are needed for sickle cell prophylaxis and rheumatoid arthritis?
2. Sulfadoxine/pyrimethamine (SP)—
- Reserve SP tablets for IPTp.
 - Halt registration and importation.
 - Manufacture only locally, on an order basis, for MOH and accredited centers in the private sector.
 - Reclassify/reschedule SP to POM or PIM status.
 - Issues—
 - What is the role of injectable SP?
 - Is there a role for any combination therapy with SP and co-trimoxazole in Uganda?
 - What quantities of SP are needed for IPTp?
3. Quinine—
- Both oral and injectable forms remain as second-line treatment, in pregnancy, and in children weighing less than five kilograms or below four months of age.
4. Primaquine—
- Reserve for treatment of *P. ovale* and *P. vivax*.
5. Mefloquine—
- Reserve for prophylaxis.
6. Proguanil—
- Reserve for prophylaxis.

7. Artemether/artesunate—
 - Tablet: discontinue.
 - Rectal: reserve for emergencies at level 2 health centers.
 - Injections: reserve for emergencies.
 - Syrup: reserve for children weighing less than five kilograms or less than four months old.
8. Amodiaquine—
 - Tablet: discontinue.
 - Syrup: reserve for children weighing less than five kilograms or less than four months of age.
9. Malarone—
 - Reserve for prophylaxis.
10. Lapdap—
 - Reserve for treatment and prophylaxis for malaria.
11. Pyrimethamine—
 - Reserve for use in combination with other antimalarial medicines.

Proposed Implementation Plan

- Halt immediately receipt of applications for registration for nonrecommended monotherapy formulations.
- Suspend the registration of and stop the verification for importation of monotherapy formulations within three months of final decision.
- Establish deadline for importation of suspended products as three months from suspension date.
- Reschedule CQ and SP to POM/PIM status, through the following process—
 - Stakeholders' resolutions (report).
 - Minutes of the Technical Committee, CNF, and NDA
 - Drafting statutory instrument (SI) (NDA Legal Committee)
 - Review by MOH Legal Committee (PP + SM)
 - Reviewing and drafting of SI by First Parliamentary Council

- Pigeonhole members of parliament (MPs) for 14 days
- Handling any queries from the MPs
- Signing of the SI by MOH
- Publication of the SI in the *Uganda Gazette*

Community Use of the Selected ACT

It was stated that because Coartem is relatively new medicine to our setting and there is limited experience and knowledge on its use, the feasibility of its use in the community is not known. Community use would require rescheduling to OTC status. For a medicine to be rescheduled to OTC status, it should be or have—

- Well-known and good safety profile (long-term use in China)
- For a condition easily recognized by members of the public
- Easy and well-known dosage regimen
- Administration requiring little expertise or no supervision (see p. 15 of *Guide for Health Workers*)
- Known good compliance and acceptability (reinfection or recrudescence)
- Low potential for diversion or abuse (leakage)
- Pharmaceutical properties supporting community use—
 - Dosage form
 - Packaging
 - Stability (moisture)

It was emphasized that the feasibility of Coartem use at the community level needs to be studied. It was reported that a study in Uganda had been started, and the progress report was given as follows—

- Funded by WHO
- Executed by Makerere University Institute of Social Research, MOH, and WHO
- Areas—
 - Iganga district: Namungalwe subcounty
 - Bugiri district: Nankoma subcounty
 - 56 villages, 112 community medicine distributors

- Progress—
 - Medicine deployment: last week, June 2006
 - So far no ADRs observed/reported
 - Uptake is good: based on stock-outs (could this be because of leakage?)
 - 100 percent retention of community medicine distributors
- Issues not yet tackled—
 - Effectiveness of the medicine: blood slide at day 0 and day 28: tests to be done in Ghana
 - Stability in the supply chain—
 - NMS ⇒ district store ⇒ level 4 health center ⇒ community medicine distributor ⇒ patient
 - To start soon—
 - Compliance of community medicine distributors and caregivers: midterm review (December 2006–January 2007)
 - Acceptability of the medicine: midterm review (December 2006–January 2007)
 - Sustainability: costing

Presentation Conclusion

In conclusion, NDA posed the following issues to help shape an implementation plan with ownership by all stakeholders—

- Policy to refer to ACT generic name rather than the brand name
- Basis for efficacy: Uganda, East Africa, regional, or international
- Stopping new registration of monotherapies
- Phasing out importation of monotherapies
- What are the options for children weighing less than five kilograms or below four months of age?
- Restricting supply of CQ and SP to local manufacturers
- Rescheduling of CQ and SP to POM/PIM status

- Feasibility of use of ACT at the community level, and the process
- Controls, accountability, and leakage
- Pharmacovigilance and quality surveillance
- Supply to the private sector

Changing Malaria Treatment Policies: A Guide to Implementation, Presented by Dr. Gladys Tetteh, MSH/RPM Plus Program

Dr. Tetteh gave an overview of the framework for implementation of ACT policy change, which outlined the technical and operational considerations required and the role of the drug regulatory authority, or DRA (in Uganda, the NDA). The phases of change were outlined as (1) policy change decision, (2) transition, (3) implementation, and (4) monitoring and evaluation at each phase. The elements of the implementation framework were identified as—

1. Financing and resource mobilization
2. Planning and coordination
3. Technical considerations
4. Operational considerations
5. Monitoring and evaluation

Involving stakeholders, building partnerships, and using coordination mechanisms are vital steps in the planning stage. Some of the technical considerations identified were regulatory issues, pharmacovigilance, standard treatment guidelines, and information, education, and communication (IEC). Operational considerations identified included procurement and forecasting, prepackaging, distribution and inventory management, phasing out of old medicines, and private sector access.

The following activities were identified as vital for phasing out old medicines—

- Determine pipeline for old medicines through central and peripheral data collection.
- Adjust future procurements of current medicines to avoid accumulation of large pipelines of old medicines when new medicine is procured.
- Develop a plan for phaseout of current medicines from the health system as new medicine becomes available.
- Withdraw old medicines using the plan developed (see above) when change occurs.

For policy change to be effective, it is important to develop a plan for making ACT available in the private sector and to consider appropriate interventions to enable access (e.g., accredited private practitioners, pharmacies/chemical sellers) and to train relevant private sector providers.

A case study of Ghana's policy change to artesunate + amodiaquine was presented. The government ensured registration of the ACT and its reclassification as a malaria program medicine. A quality assurance program for the manufacture of ACTs in Ghana was established (raw materials screening, specifications, specifications for raw material/active pharmaceutical ingredient [API], labeling, safety studies), a system for assessment of antimalarial quality in the public and private sectors was put in place, and an ACT formulation meeting was held to train local manufacturers.

It was decided to phase out monotherapies in Ghana and to limit the use of SP. The rationale for this decision was—

- Partner medicines that comprise Ghana's choice of ACT were individual components (artesunate and amodiaquine) formulated into copackaged dosage forms for simultaneous administration (coadministered therapy).
- Because artesunate and amodiaquine had each previously been used as monotherapies, they were still available on the Ghana market.
- It was agreed among stakeholders that continued use of artesunate and amodiaquine as monotherapies could potentially compromise the value of the artesunate + amodiaquine combination by selecting for drug resistance.
- The recommendation was to withdraw from the market artemisinins (artesunate and its derivatives) and other antimalarial monotherapies (such as chloroquine, amodiaquine, and SP and their derivatives).

In phasing out any group of medicines from a supply chain, the existing pipelines of the medicines must be determined and future procurements of current medicines adjusted to avoid accumulation of large pipelines of "old" medicines. In November 2005, the Ghana Food and Drugs Board undertook an assessment of the existing pipeline of antimalarials within the outgoing malaria treatment policy, with the aim of—

- Determining approximate quantities of antimalarial monotherapies on the market
- Determining the quantities of raw materials in the warehouses of the local pharmaceutical manufacturers capable of being used for the production of monotherapies
- Determining stocks of finished products of antimalarial monotherapies in the warehouses of importers of such products
- Determining stocks of monotherapy antimalarials in the Central and Regional Medical Stores

The assessment was designed to cover the following products—

- All the different dosage forms of chloroquine and their raw materials
- All the different dosage forms of amodiaquine and their raw materials

- All the different dosage forms of artesunate and other artemisinin derivatives and their raw materials

The following were the key findings of the assessment—

- It was observed that within the six months following the assessment, all stocks in the public sector would be exhausted if no new supplies were received in this period.
- In the private sector, companies assessed had already made huge investments in raw materials, packaging materials, and finished products.

In view of these findings, the following recommendations were made—

- The Food and Drugs Board recommended that a period of six months to one year should be allowed for phasing out the existing antimalarial monotherapies.
- The immediate discontinuation of chloroquine was recommended, whereas amodiaquine + artesunate and its derivative products were allowed to be prescribed and used simultaneously during the transition period.
- The Food and Drugs Board implemented the phaseout plan by—
 - Immediate discontinuation of registration of new antimalarial monotherapies
 - Immediate discontinuation of renewal of antimalarial monotherapies whose market authorization has expired
 - Immediate discontinuation of issuance of new permits for importation of chloroquine powder
 - SP stocks manufactured and procured were limited by Central Medical Stores and manufacturers for IPTp use only

The full details of the presentation are provided in Annex 4.

The example of Ghana highlighted the need to involve the DRA during the early stages of policy change, as well as the value of proper planning and a phased implementation approach.

The Role of Monotherapies in the Treatment of Malaria, Presented by Dr. Ambrose Talisuna, Assistant Commissioner, Epidemiology and Surveillance, MOH

Dr. Talisuna's presentation included these highlights—

- History of the development of antimalarial medicines from as early as 1632
- Available monotherapies

- Chronology of CQ resistance to *P. falciparum*, 1960–1984
- Loss of monotherapy to resistance in Southeast Asia

As a result of resistance, there was a paradigm shift from monotherapy to combination therapy. Combination therapy was defined as the simultaneous use of two or more blood schizonticidal medicines with independent modes of action and different biochemical targets in the parasite. Two types of combination therapy were discussed—

- NACT: non-artemisinin-based combination therapy
 - AQ + SP (use where amodiaquine and SP are still effective, and possibly for IPTp)
- ACT, including—
 - Artemether/lumefantrine (AL)
 - Artesunate/amodiaquine (AS/AQ)
 - AS + SP (where efficacy of SP is still optimal)
 - Artesunate/mefloquine (AS/MQ) for areas of low transmission—e.g., Southeast Asia

The main issues in combination therapy were identified as compliance and choice of partner medicines in the combination. The pill burden in coadministered medicines affected compliance, whereas fixed-dose combinations were linked with better compliance. The pharmacokinetics and pharmacodynamics of the medicines must be considered when deciding which partner medicines to include in the combination.

It was discussed that, whereas intravenous quinine monotherapy is a mainstay of treatment for severe malaria, new evidence in Southeast Asia suggests that intravenous artesunate as monotherapy is probably better than quinine. Rectal artemether is useful as prereferral treatment for severe malaria in areas with poor access to parenteral treatment. SP “monotherapy” is the only option for IPTp presently. Products considered safe but not effective for treatment of malaria in pregnancy (MIP) include CQ sulfonamides (SP, DDS, proguanil), whereas quinine is considered effective and safe for treatment of MIP. Other potential medicines for treatment of MIP and IPTp include amodiaquine, mefloquine, chlorproguanil-dapsone, and artemisinin derivatives or ACTs.

Other issues covered included—

- Special groups: severe malaria, malaria/HIV, and MIP
- Medicines that could soon be on the WHO recommended list
- HIV/antimalarial medicines interactions
- New medicines under development

The presenter highlighted the following critical issues for the NDA to note—

- Careful registration of new products (limit registration of monotherapies)

- Limited use of monotherapies (dialogue with importers to limit importation of monotherapies)
- Fake medicines/counterfeits (drug quality monitoring and safety surveillance)
- Government sector (limit leakage)
- Nonformal health sector–private sector: nonpremium and premium
- Deregulation of ACTs

The full details of the presentation are provided in Annex 5.

Change of Malaria Treatment Policy from Chloroquine Monotherapy to CQ-SP Combination Therapy as First Line: Lessons Learnt, Presented by Mr. Deo Kimera, Pharmacist, AXIOS International

Mr. Kimera's gave a background on national malaria treatment policy changing from CQ monotherapy as first-line treatment to the CQ/SP combination in June 2000. It was observed that the change was implemented through a consultative process with various stakeholders and that extensive policy dissemination was carried out. However, the study done by Mr. Kimera may not necessarily be used to generalize about practices in Uganda, because it covered two districts (Kampala and Rakai) out of 56. The objectives of the study were—

- To understand the basis of change in malaria treatment policy in Uganda and define steps that had been taken to ensure efficient implementation of the new policy.
- To review treatment (prescribing) practices for uncomplicated malaria in public and private, not-for-profit (PFNP) health facilities in Rakai and Kampala districts as a measure of level of adherence to the national antimalarial medicine policy.
- To identify factors that influence adherence to national malaria treatment guidelines.

The study used both quantitative and qualitative data collection methods. Data was obtained from both primary and secondary sources. Quantitative data on prescribing practice was collected by records review of patient/prescription registers, while qualitative methods were used to collect data from prescribers, heads of health facilities, and key stakeholders at the national level.

The general findings were—

- Of prescribers interviewed, 72.7 percent correctly stated the content of the new policy.
- Of health facilities visited, 83 percent had a copy of the policy in place.
- Support supervision rated higher in promoting adherence than workshop-based training.

Factors that influenced prescribers' practice included medicine availability and efficacy, patient affordability, treatment guidelines, previous medication, patient preference, and medicine side effects.

Factors believed to promote adherence are support supervision, politician sensitization, public mobilization through media campaigns, effective dissemination of treatment guidelines, and medication efficacy. Reasons for deviating from policy were identified as—

- Recommended treatment not continuously available
- Perception that patients respond faster to second-line medicines
- Assumption that patients have taken CQ + SP under home-based management program before visiting facility
- Fear of serious ADR from using SP-based combination
- Historically known position of CQ as first-line medicine for management of uncomplicated malaria

Lessons learned from this policy change were discussed. It was observed that the choice of CQ + SP took into consideration the efficacy, safety, affordability, and ease of administration of the medicines, whereas less consideration was given to the potential for delaying development of resistance.

The process of policy change was effective in terms of involving multiple stakeholders, ensuring availability of treatment guidelines, and equipping prescribers with knowledge about policy change, but these achievements were not directly translated into prescribing recommended therapy (39 percent adherence level).

On prescribing practice, it was observed that—

- There was a significant difference between public (55.8 percent adherence) and private not-for-profit (PNFP) (22.2 percent adherence) prescribing practice ($P < 0.000$).
- PNFP staff prescribed more quinine monotherapy (34.3 percent) than recommended therapy (22.2 percent).
- No significant difference was noted between rural and urban prescribing practice.
- Level 4 health facilities least adhered to policy change (17.8 percent) as compared to level 2 and 3 health centers ($P < 0.0001$).
- A reasonable proportion of chloroquine monotherapy was still being prescribed, especially in the public sector.
- Lower cadre staff adhered more to the policy than licensed practitioners of facilities with medical officers.

- Medicine availability was a major factor influencing prescribing practice.

The discussion observed that multiple factors are involved in general practitioners' decisions to change their prescribing habits, including the volume and authority of evidence, cost pressures, and dramatic clinical events. Experienced prescribers may believe that the principles of rational prescribing or prescribing according to guidelines limit their choice of therapy.

The following recommendations were made—

1. Including an indicator for measuring the level of adherence to the national antimalarial medicine policy among those monitored by MCP and the Quality Assurance (QA) section of the MOH
2. On changing policy, provide assurance for sustainable availability of the recommended antimalarials
3. On changing policy, design special strategies for the PNFP sector, where cost recovery of treatment is an issue
4. Consider allocating more resources to support supervision/on-the-job-orientation than workshop-based training

The full details of the presentation are provided in Annex 6.

The Impact of the New Antimalaria Policy on Access to Antimalarial Medicines in the Private Sector, Presented by Mr. James Tamale, Secretary, Pharmaceutical Society of Uganda

The presenter noted that the policy on treatment of uncomplicated malaria, severe malaria, IPTp, and malaria case management in special cases applied to both the public and private sectors.

The presenter observed that an increase in imports of ACTs had occurred this year (2006) as compared with 2005. In the private sector, the uptake of ACTs by patients was price dependent—and ACTs are costly, compared to preexisting therapies. As a result, practitioners provide what clients can afford. Affordability of ACTs in rural areas (upcountry) was still a challenge, and it was doubted whether practitioners would be willing to stock these medicines if patients are unable to afford them. There was a noticeable lack of awareness and knowledge of ACTs among a number of health practitioners, the presenter noted, asking: Whose role is it to undertake behavior change management in the private sector?

The importance of availability in the private sector was discussed. It was important to determine what percentage of the ACTs required are actually imported by the government into the country whether the quantities meet demand. It was proposed that alternative means be put in place to fill the gap in availability should demand exceed supply, and the potential role of the private sector was noted.

The presentation also noted other issues to be addressed, including—

- Patient power: The problem of patients' insisting on using therapies (monotherapies) they have used before. It is the role of practitioners to curb this rather than condone it.
- Smugglers may try to fill the supply gap: This is likely to result in counterfeits reaching the market.

The need to put in place effective and efficient monitoring mechanisms to nullify these threats was emphasized. It was therefore recommended that—

- Importation of monotherapies should be stopped.
- Special groups and their medication needs should be taken into consideration.
- There should be monitoring to ensure compliance to new policy.
- Implementation of the new policy should be phased in to take into account idiosyncrasies of the rural community (upcountry areas).

The full presentation is provided in Annex 7.

Challenges of Procurement, Storage, and Distribution of ACTs: Impact of NAMTP on Activities of NMS, Presented by Mr. Benjamin Oryema on Behalf of Mr. Paul Tenywa, NMS

Mr. Benjamin Oryema from NMS, presenting on behalf of his colleague Dr. Paul Tenywa, highlighted NMS activities, including—

- Receipt of medicines
- Storage/warehousing
- Documentation/picking/packaging/loading
- Distribution
- Follow-up on payments

Inventory of antimalarials at NMS as of October 2006 was described as composed of 23 percent NMS stock (including CQ, quinine, etc.) and 77 percent program stocks (including HOMAPAK). The implementation of the NAMTP has been associated with the following impact on and challenges to NMS—

- Change in procurement plan
- Increase in workload: more orders processed (70/day to 100/day), packaging, loading
- New districts: more distribution points, time
- High demand for ACTs: failure to fit into the NMS cycle
- Strain on storage space
- Lapse on timely distribution due to high demand

- Increasing cost of gasoline: hence reduced attention to emergencies
- Poor road infrastructure leads to delays, hence affecting the cycles
- Movement of stocks from government units to private units (leakage)
- Accumulation of old stock

To address these challenges, the following proposals were made—

- Involvement of NMS in quantification and procurement of ACTs
- Improving communication between NMS and the health units
- Adhering to the distribution plan
- Recalculating the cost of storage and distribution
- Renting more storage space
- Working with partners (e.g., MSH/RPM Plus)
- Supervisory visits for monitoring and evaluation
- Provision of timely reports and networking with programs

The presentation concluded that NMS must be involved in quantification/procurement, improve its working relationships with programs, sensitize customers about timely ordering, and strengthen the monitoring of ACTs in government health facilities.

The full presentation is available in Annex 8.

RECOMMENDATIONS AND RESOLUTIONS MADE AT THE PLENARY SESSIONS

At the plenary sessions, the following recommendations were made. They supplement those recommended by the small groups.

1. The policy specifies artesunate/lumefantrine (AL) and the brand name Coartem. *The Guidelines for Management of Uncomplicated Malaria* indicate Coartem because it is currently procured for the public sector. A generic name should be adopted in the guidelines in line with the AMTP and the NDP/A Act (cap. 206).
2. The NDA should pay greater attention to efficacy evidence during preregistration dossier evaluation, with respect to the comparability of disease intensity and transmission to that in Uganda. Relevant external experts may be involved in the evaluation if necessary, but care must be taken to avoid conflict of interest.
3. Registration of monotherapies (except those intended for special circumstances as stipulated in the policy) should be stopped.
4. Importation of monotherapies (except those intended for special circumstances as stipulated in the policy) should be phased out.
5. SP + combinations might not be relevant in Uganda in light of available data on resistance and are recommended for deregistration.
6. The supply of CQ and SP will be restricted to local manufacturers. Although the NDA assures the quality of products manufactured locally and internationally, there is a need to address negative public perception about local industry and its products.
7. SP and CQ should be rescheduled to POM or PIM status.
8. Following favorable results of feasibility studies on the use of ACTs at the community level, they should be rescheduled to OTC status.
9. The respective councils (PSU, Medical Council, Nurses & Midwives Council, and Allied Health) should enforce acceptable standards of practice for professionals through increased inspection of premises and greater vigilance. The NDA and the councils should develop/review sanctions for violations of practice standards and product quality standards.
10. Greater controls need to be instituted on accountability in the public sector to prevent leakage of medicines.
11. Mechanisms should be put in place to improve the supply of AL to and possible delivery of subsidies through the public sector.

SUMMARY OF THE WAY FORWARD/RECOMMENDATIONS BASED ON SMALL GROUP DISCUSSIONS

The meeting split into four groups to discuss the way forward in these specific areas—

Group 1: Rescheduling ACTs for different levels within the DLU

Group 2: Registration of antimalarials

Group 3: Postmarketing activities (phase IV study)

Group 4: Phasing out monotherapies and suboptimal combination therapies

The recommendations of the working groups were adopted as the consensus way forward. Summaries of the presentations made by the discussion groups are presented in Tables 1–4. A complete list of group members can be found in Annex 9.

Table 1. Group 1: Rescheduling ACTS for Different Levels within the DLU

Key Activities	Indicators	Responsible
<ul style="list-style-type: none"> • Sharing of midterm review results of the feasibility study of use of ACTs in the community (WHO/NMCP) • Report writing of the workshop results • Drafting of the statutory instrument (NDA) • MOH evaluation of the statutory instrument (SI) • Parliamentary Council evaluation of the SI • Parliament evaluation of the SI and recommendation to MOH • Signing and gazetting of the SI by the MOH • Dissemination of the SI 	<ul style="list-style-type: none"> • Draft of midterm report • Draft of SI • Forwarding letter from the Minister to Parliament • Report of the first Parliamentary Council to the Parliament/draft SI • Report of Parliament to the Minister • Gazette posting 	<ul style="list-style-type: none"> • Makerere University • Institute of Social Research/WHO • NDA • MOH/DGHS • MOH/MoJCA • Speaker of Parliament • MOH/MoJCA
Information Required	<ul style="list-style-type: none"> • Effectiveness of the medicines • Stability through the supply chain • Compliance by distributors • Safety profile of the medicine • Acceptability to users 	
Financial Requirements (NDA appealed to donors for funding)	<ul style="list-style-type: none"> • Report to Technical Committee of NDA • Report to CNF (NDA) • Report to NDA board • Review of the statutory instrument by MOH Committee on Laws • First Parliamentary Council • Publication of <i>Uganda Gazette</i> • Dissemination 	
Timeline	<ul style="list-style-type: none"> • Dissemination and sharing of results to stakeholders • Report to be discussed by Technical Committee of NDA • Report to CNF (NDA) • Report sent to NDA board • Drafting of SI by NDA • Review of the statutory instrument by MOH Committee on Laws • First Parliamentary Council • Presentation to MPs • Signing by the Minister • Publication in the <i>Uganda Gazette</i> • Dissemination 	<ul style="list-style-type: none"> January 2007 January 2007 January 2007 February 2007 March 2007 March 2007 April 2007 April 2007 May 2007 May 2007 May 2007

Note: It was agreed by the plenary that the recommendations shown in Table 1 will be followed, functioning as guidelines/working document.

Table 2. Group 2: Registration of Antimalarials

No.	Recommendation
1	Efficacy studies should be done in areas with stable malaria transmission.
2	Safety data should be collected among groups with similar genetic profiles (comparable population), including phenotypes.
3	Companies that do not fully meet the above requirements on efficacy and safety data could be given provisional registration for a specified period (one year) as they carry out studies locally through phase IV studies.
4	For new molecules and formulations, the NDA secretariat should seek expertise from relevant experts for an independent scientific opinion on efficacy and safety data. One or two experts with no conflict of interest should be asked to submit a confidential report that can be reviewed by the CNF.
5	Periodically, the NDA should publicize a list of the newly registered medicines in the local gazettes (for transparency, to sensitize the public and health care providers, and to help prevent counterfeits from entering the country).
6	The consultative process highlighted can be used to deregister medicines whose efficacy is failing.

Note: All the above six recommendations were adopted by the plenary.

Table 3. Group 3: Postmarketing Activities (Phase IV Study)

No.	Activity	Recommendation(s)	Indicator(s)
1	Efficacy studies through sentinel sites <i>Note: Participants were informed that there are eight sentinel sites in Uganda for the MOH; however, because of financial constraints, not all were functioning.</i>	<ul style="list-style-type: none"> • Endeavor to do efficacy testing every two to three years, dependent on funding. • However, pharmacovigilance reports should act as a guide. • Studies done in the East African region or areas with similar risk and transmission rates should be valued. 	<ul style="list-style-type: none"> • Efficacy studies done • Results from sentinel sites received
2	Safety through pharmacovigilance <i>Note: Participants were informed that sensitization of both health workers and consumers was inadequate.</i>	<ul style="list-style-type: none"> • More sensitization of both health workers and consumers should be done. • Health workers should inform and encourage patients to report back to health workers in the event of any ADRs. • Improve efficiency of reporting through technology to capture ADR information from patients and health workers (e.g., use cell phones). 	<ul style="list-style-type: none"> • Reports received by NDA from health workers and patients <p><i>Note: It was acknowledged that all recommendations and indicators would require funds and staffing.</i></p>
3	Quality control and postmarketing surveillance <i>Note: Participants were informed that there was 100 percent sampling of all antimalarials, batch for batch, at entry points, and they recommended that this surveillance continue.</i>	<ul style="list-style-type: none"> • Encourage both health workers and patients to identify any changes in the medicines (i.e., start from level 1–4 in pharmacovigilance). • Equip drug inspectors with portable testing equipment (Minilabs) as a second-level quality control method at postmarketing points. 	<ul style="list-style-type: none"> • Tests done on ACTs by NDA's National Drug Quality Control Laboratory
4	Monitoring and distribution <i>Note: It was agreed that distribution and monitoring issues exist at all levels.</i>	<ul style="list-style-type: none"> • Training of current drug monitors. • Train health facility managers on record-keeping and quantification. • Recruit more drug monitors. • NMS should devise alternative methods for emergency distribution of malaria commodities (e.g., allow some health facilities with motor vehicles to pick up their supply whenever they come from upcountry, provided that they inform NMS three to four days prior to arrival). 	<ul style="list-style-type: none"> • Number of health facility managers trained • Number of current drug monitors recruited • Number of drug monitors • Correct record forms verified

Note: All the above recommendations were adopted by the plenary.

Table 4. Group 4: Phasing Out Monotherapies and Suboptimal Combination Therapies

Activity	Timeline	Responsibility	Deliverable
Assessing the pipeline for all listed medicines: <ul style="list-style-type: none"> • Inventory at the NMS • Inventory of local manufacturers and Importers • National stock-taking of tracer medicines and active pharmaceutical ingredient (by brand) 	2 months	NDA	Report
Rescheduling (See details from Group 1)			
Restricting importation of monotherapies subject to availability of adequate quantities of ACTs: <ul style="list-style-type: none"> • Determination of what is in the pipeline • Survey of availability of ACTs • Guarantee supplies of ACTs for the next year • Restrict importation of monotherapies 	1 year from introduction of ACT HBMF	MOH/MCP MOH/MCP NDA	Report
Review of current contracts		MOH/MCP	Revised agreements
Increasing access to ACTs in the private sector:			
<ul style="list-style-type: none"> • Monitoring the development of ACTs and facilitating their registration 	3 months	MOH/MCP/NDA	Regular production of ACTs
<ul style="list-style-type: none"> • Advocacy in the private sector to reassure sellers that free medicines are available to match needs 	4 months	MOH/MCP	
<ul style="list-style-type: none"> • Transparency in prices: resume publication of indicator prices 	4 months		Indicator prices
<ul style="list-style-type: none"> • Raise profile of ACTs in the private sector 		NMS/MOH	Workshop
<ul style="list-style-type: none"> • Reduce the occurrence of counterfeits 			Labels for ACTs

Note: The above recommendations and process proposed by Group 4 were adopted by the plenary.

CLOSING OF THE WORKSHOP

Mr. Deus Mubangizi, Chief Inspector of Drugs, NDA, thanked RPM Plus/MSH for funding a timely workshop. He commended participants, MCP, and the experts for their contributions. He expressed NDA's gratitude for WHO's continued support.

He promised the report would be available as soon as possible.

The workshop was officially closed at 2:20 p.m. by Dr. Ambrose Talisuna, Assistant Commissioner, Epidemiology and Surveillance, MOH. He thanked all who thought of the workshop as it was timely and it was going to be very helpful. He thanked members for allowing the visitor from United States to attend.

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ANNEX 2. CURRENT MALARIA TREATMENT POLICY

WORKSHOP ON THE STRATEGIC PLAN FOR IMPLEMENTATION OF THE NEW ANTI- MALARIA POLICY.

CURRENT MALARIA TREATMENT POLICY (Launched on 25th April 2006).

Dr. F. K. Kato
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Malaria Control Policy

2

General Objective of National Malaria Control Programme

The general objective of the Malaria Control Programme is to reduce malaria morbidity, mortality and disability and to minimize related social ill effects and economic losses attributable to malaria .

3

Intervention Strategies

- 1. Effective Malaria Case Management ***
 - Facility-based management of malaria
 - Home-based management of fever (HBMF)
- 2. Selective Vector Control.**
 - Indoors residual-insecticide spraying (IRS)
 - Insecticide-treated nets (ITNs)
 - Environmental management
- 3. IPT for pregnant women***
- 4. Malaria epidemic preparedness and response**

4

Enabling Strategies

1. **IEC/BCC for malaria prevention and control**
2. **Capacity building** (e.g., training, logistical support)
3. **Surveillance & research** (e.g., drug efficacy studies, monitoring & evaluation, KAP studies)
4. **Infrastructure & supplies** (e.g., medicines and other supplies, diagnostic facilities, treatment facilities)
5. **Programme management** (e.g., mobilisation and deployment of resources including transport, support supervision)

5

Malaria Control Targets for 2010

Health Sector Strategic Plan II (2006-2010)

1. To increase proportion of pregnant women who have completed IPT2 from 34% to 80%
2. To increase proportion of households having at least one ITN from 15% to 70%
3. To increase proportion of targeted structures for IRS from 0% to 80%
4. To increase proportion of children under five with malaria getting **correct treatment within 24 hours** from 25% to 80%*
5. To reduce **case fatality rate** among malaria patients under five from 4% to 2%*

6

Malaria Treatment Policy

7

CQ monotherapy to CQ+SP combination therapy

1. Resistance to chloroquine first reported in East Africa in 1979. By 2000 drug efficacy studies showed overall clinical failure of–
 - 30% (range 10-48%) for CQ monotherapy after 14 days follow-up
 - 10% (range 0-19%) for SP monotherapy after 14 days follow up
2. The cutoff point recommended by WHO (when change in policy must be made) was clinical failure of 25%.
3. Before 2000 CQ monotherapy was first-line treatment for uncomplicated malaria; SP was second-line; AQ was alternative second-line; and quinine (QN) was the reserve.
4. In June 2000 MOH reviewed information available and adopted an interim policy of CQ+SP combination instead of CQ monotherapy as the first-line treatment for uncomplicated malaria.

8

Change from CQ+SP to ACT

4. Between 2001 and 2004 drug efficacy studies showed overall clinical failure of:
 - 21.4 % (range 3-45%) for CQ+SP after 14 days of follow up
 - 5.4 % (range 0.6-15.9%) for AQ+SP after 14 days of follow up
 - 1.8% (range 0-4.2%) for AS+AQ after 14 days of follow up
 - 0% (zero) for AL after 28 days of follow-up
5. The cutoff point recommended by WHO (when change in policy must be made) is now clinical failure of 15%.
6. In May 2004 MOH reviewed the information available and changed the national policy on malaria treatment from CQ+SP combination therapy to ACTs for treatment of uncomplicated malaria. AL was the ACT selected as first-line and AS+AQ was selected as alternative first-line

9

Current Malaria Treatment Policy

(Launched 25th April 2006)

1. **Uncomplicated malaria:**
 - First-line: **artemether/lumefantrine.**
 - Alternative first-line: **artesunate + amodiaquine.**
 - Second-line: **quinine**
2. **Severe malaria:**
 - Recommended: **Parenteral quinine**
 - Alternative: **Parenteral artemisinin derivatives**

10

Current Malaria Treatment Policy (continued)

3. Intermittent Preventive Treatment (IPT) in pregnancy:


- Recommended: SP**

4. Uncomplicated malaria in special groups:

- Pregnant women during the first trimester: **quinine** (ACTs contraindicated).
- Pregnant women after the first trimester: **ACTs may be used.**
- Children below 5 kg body weight: **quinine** (ACTs contraindicated).


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ANNEX 3. REGULATORY ISSUES IN THE IMPLEMENTATION OF THE NEW ANTIMALARIAL DRUG POLICY




**REGULATORY ISSUES IN THE
IMPLEMENTATION OF THE NEW
ANTIMALARIAL DRUG POLICY**

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Scope of Presentation

- Mandate/Mission of NDA
- Organization of NDA: Roles of CNF & Board
- QA measures used by NDA
- New Anti-malarial Drug Policy
- Implications of new policy
- Implication on monotherapies
- Implementation plan
- Use of ACTs at the Community
- Requirements for rescheduling: POM ⇒ OTC
- Progress of Feasibility study: Iganga and Bugiri
- Summary of Issues for Discussion.



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Mandate/Mission of NDA

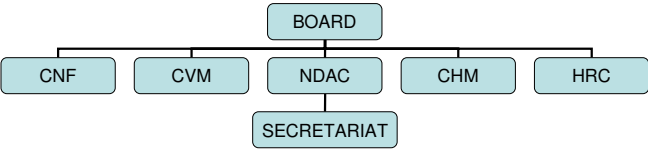
- ❑ To ensure *availability*, at all times, of *essential*, *efficacious* and *cost-effective* drugs to the entire population of Uganda, as a means of providing satisfactory health care and safeguarding the *appropriate use of drugs*.
- ❑ Scope of regulation is in the definition of a drug:

Any substance or preparation used or intended to be used for internal or external application to the human or animal body either in the treatment or prevention of disease or for improving physiological functions, or for agricultural or industrial purposes.

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Organization of NDA (1)



```
graph TD; BOARD[BOARD] --- CNF[CNF]; BOARD --- CVM[CVM]; BOARD --- NDAC[NDAC]; BOARD --- CHM[CHM]; BOARD --- HRC[HRC]; NDAC --- SECRETARIAT[SECRETARIAT];
```

CNF= Committee on the National Formulary
CHM= Committee on Herbal Medicine
CVM= Committee on Veterinary Medicine
HRM= Human Resource Committee
NDAC= National Drug Authority Commission

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Committees of NDA (1)

Committee on the National Formulary

– Composition:

- 12 members representing various disciplines
- Chairman from members of the Board

– Responsibilities:

- Approve Secretariat's recommendations for registration and deregistration of products
- Approve Secretariat's recommendations following GMP inspection
- Approve indications and scheduling of drugs



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Quality Assurance Mechanisms used by NDA

- Drug registration.
- GMP inspection and licensing of local and foreign manufacturing sites.
- Inspection and licensing of drug outlets: Pharmacies and Drug shops.
- Inspection of other institutions where drugs are handled: Hospitals, clinics, Maternity Homes, etc...
- Licensing and inspection of imports.
- Quality control: testing of medicine samples.
- Pharmacovigilance.
- Postmarketing surveillance.
- Regulation of drug promotion and advertising.
- Regulation of drug-related clinical trials.




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QA measures....

- ❑ Registration requires clinical trial or bioequivalence data to prove efficacy.
- ❑ GMP inspection before drugs are registered and thereafter every 3 years.
- ❑ Mandatory analysis of each batch of imported:
 - **Anti-malarials.**
 - Anti-TB medicines.
 - ARVs.
 - Condoms




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Control of Imports

- ❑ Requires annual import permit
- ❑ Verification certificate per consignment
 - Application showing product name, strength, pack size, registration number and **site of manufacture**
 - Comparison with registration details and samples
- ❑ Importation only through gazetted entry ports
- ❑ Inspection at port of entry: Documents including CoA and organoleptic evaluation of consignment & samples.
 - Comparison with registration details and samples.
- ❑ Analysis of samples if necessary: Mandatory for antimalarials, anti-TBs, ARVs, Condoms and screening of Injectable products for particulate matter.





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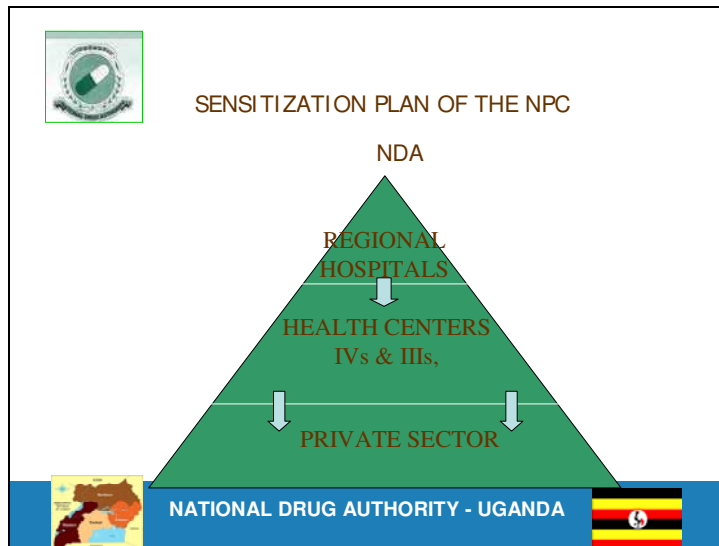





Role of Pharmacovigilance

- ❑ Pharmacovigilance:
 - the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problems
- ❑ Informs regulatory decisions
- ❑ Fills in information gaps; e.g., on ACTs
- ❑ Multiple consultations made by patients with complex illnesses - multiple prescriptions
- ❑ Tests in lab animals not predictive of human safety
- ❑ Clinical trials are carried out on limited no. of patients, in a limited duration of time and in conditions different from clinical practice

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Progress of PV Sensitization

- ❑ Sensitization in the public sector - 120 units
 - Number followed up - 90 units
- ❑ Sensitization in private sector - In Sept 2006

- ❑ Dividends of sensitization
 - Number of ADR reports received- 78
 - ADR reports due to coartem-5 (**all expected**)




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Why PV on ACTs is essential

- ❑ Relatively new drug in our setting, limited experience and knowledge
- ❑ Possible medicine interactions
- ❑ ADRs due to poor patient compliance: different dosage regimen, S/Es, properties (no antipyretic/analgesic properties compared to CQ)



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New Anti-malarial Drug Policy

- ❑ WHO Recommends Artemisinin Combination Therapy (ACTs)
- ❑ First line:
 - Artemether/Lumefantrine (COARTEM®)
- ❑ Alternative First Line:
 - Artesunate/Amodiaquine
 - Artesunate/Sulphadoxine/Pyrimethamine
 - Artesunate/Mefloquine
 - Amodiaquine/Sulphadoxine/Pyrimethamine
- ❑ Second Line:
 - Quinine
- ❑ Treatment in Pregnancy:
 - Quinine
- ❑ Intermittent Preventive Treatment:
 - Sulphadoxine/Pyrimethamine



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Implications of the new Policy (1)



- ❑ Anti-malarial drug policy specifies COARTEM:
 - This promotes brand name Vs NDP/A that promotes Generics.
 - Uganda being LDC, not bound by patents up to 2016:
 - NDA registers any medicine with proof of safety, efficacy and quality.
- ❑ Recommendation:
 - Policy should refer to **Generic Name and not Brand Name**
 - **Efficacy data: Uganda, East Africa, Africa, International (Resistance)???**






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 ACTs Registered for Use in Uganda(1)					
MANUFACTURER	DRUG NAME	REG NO	GENERIC NAME	STRENGTH	DOSAGE FORM
IPCA LABORATORIES LTD	LARIMAL	4631/06/04	AMODIAQUINE/ ARTESUNATE	153.1MG/ 50MG	TABLET
CIPLA LTD	LUMARTEM	5275/06/05	ARTEMETHER/ LUMEFANTRINE	20MG/120MG	TABLET
NORVATIS PHARMA AG	COARTEM	4839/06/05	ARTEMETHER/ LUMEFANTRIN	20MG/120MG	TABLET
AJANTA PHARMACEUTICALS LTD	ARTEFAN 20/120	5360/06/06	ARTEMETHER/ LUMEFANTRINE	20 /120 MG	TABLET
KUNMING PHARMACEUTICAL CORP	ARCO	5436/06/06	ARTEMISININ/ NAPHTHOQUINE PO4	125MG/50MG	TABLET
EFRA NV/SA	CO-ARINATE	4771/06/05	ARTESUNATE/ SP	200MG/ 500MG/25MG	TABLET


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 ACTs Registered for Use in Uganda (2)					
EFRA NV/SA	CO-ARINATE JUNIOR	4770/06/05	ARTESUNATE/ SP	100MG/ 250MG/12.5MG	TABLET
CIPLA LIMITED	FALCIMON KIT	5099/06/05	ARTESUNATE/ AMODIAQUINE	50MG/200MG	TABLET
MARPHAR LABS	ARSUCAM TABLETS	5451/06/06	ARTESUNATE/ AMODIAQUINE	50MG/200MG	TABLET
CIPLA LIMITED	FALCIMON KIT (FOR CHILDREN)	4764/06/05	ARTESUNATE/ AMODIAQUINE	200MG/50MG	TABLET
CIPLA LIMITED	FALCIMON KIT (FOR ADULTS)	4763/06/05	ARTESUNATE/ AMODIAQUINE	200MG/50MG	TABLET
ERFA NV/SA	AMONATE JUNIOR	5259/06/05	ARTESUNATE/ AMODIAQUINE	100MG/200MG	TABLET
MEPHA LTD	ARTEQUIN 600/1500	4642/06/04	ARTESUNATE/ MEFLOQUINE	200MG/250MG	TABLET


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ACTs Registered for Use in Uganda (3)

MEPHA LTD	ARTEQUINE 600/ 750 LACTAB	4544/06/04	ARTESUNATE/ MEFLOQUINE	200MG/50MG	TABLET
MEPHA LTD	ARTEQUIN 300/375	4828/06/05	ARTESUNATE/ MEFLOQUINE	300MG/375MG	TABLET
PHARMAMED LTD.	ARIPUS	4513/06/04	ARTESUNATE/ SP	100MG/500MG/ 25MG	TABLET
ERFA NV/SA	AMONATE	5118/06/05	ARTESUNATE/ AMODIAQUINE	200MG/200MG	TABLET
COSMOS LTD	AMQUNATE	4917/06/05	ARTESUNATE AMODIAQUINE	50MG/150MG	TABLET
ERFA SA	AMONATE ADULT	5390/06/06	ARTESUNATE+ AMODIAQUINE	200MG/153.1MG	TABLET
FARMACIA APPELHOF OUDEHASK	CO-ARTESIANE	5281/06/05	BETA- ARTEMETHER/ LUMEFANTRINE	180MG/60ML/ 1080MG /60ML	POWDER FOR RECONS- TITUTION
JIAXING NANHU PHARMACEUTICAL	DUO-COTECXIN	5271/06/05	DIHYDRO ARTEMISININE/ PIPERAQUINE PHOSPHATE	40MG/320MG	TABLET
AJANTA PHARMA	COMBISUNATE FORTE	5362/06/06	SP/ARTESUNATE	500MG/25MG/ 100MG	TABLET


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Implications of the new Policy (2)

❑ Issue related to drug and distribution policy:

- Expensive drug – 15,000 – 20,000 Uganda shillings per dose
- limited suppliers – Novartis
- inadequate supply in the private sector – fear of loss through expiry because available free in public sector.
- Inadequate controls/accountability in public sector

⇒ **Leakage from public to private sector**

❑ **Recommendations:**

- ⇒ Increase controls and accountability in public sector
- ⇒ Increase inspection and surveillance in the private sector
- ⇒ Increase supplies to the private sector (Accredited Centres, Subsidies, Social marketing)


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Implications on monotherapy (1)

- ❑ Chloroquine:
 - Reserve Oral CQ for Sickle Cell Prophylaxis and mng't of Rheumatoid Arthritis.
 - Halt registration and importation of Inj. CQ.
 - To be manufactured only **locally** on order basis for **MOH** and **accredited centers in the private sector**.
 - **Reclassify/Reschedule CQ to POM or PIM.**
- ❑ Issues:
 - **Need to quantify CQ needed for SS and RA.**



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Implications on monotherapy (2)

- ❑ S/P:
 - Reserve SP Tablets for IPT
 - Halt registration and importation
 - To be manufactured only **locally** on order basis for **MOH** and **accredited centers in the private sector**.
 - **Reclassify/Reschedule SP to POM or PIM.**
- ❑ Issues:
 - **What is the role of Injection SP?**
 - **Is there a role of any combination therapy with SP/SMP in Uganda??**
 - **Need to quantify SP needed for IPT.**





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Implications on monotherapy (3)



- ❑ Quinine:
 - Both Oral and Injection remain as second line, in Pregnancy and in children < 5kg or <4m???
- ❑ Primaquine:
 - Remain for Txt of P. Ovale and P. Vivax
- ❑ Mefloquine:
 - Remain for prophylaxis
- ❑ Proguanil:
 - Remain for prophylaxis

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Implications on monotherapy (4)

- ❑ Artemether/Artesunate:
 - Tablet – discontinue
 - Rectal – remain for emergencies at HC2
 - Injections – remain for emergencies
 - Syrup – remain for children < 5kg or <4m???
- ❑ Amodiaquine:
 - Tablet – discontinue
 - Syrup – remain for children < 5kg or <4m???

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Implications on monotherapy (5)

- Malarone:
 - Remain for prophylaxis
- Lapdap:
 - To remain for Txt and prophylaxis in PFP
- Pyrimethamine:
 - To remain but for use in combination with???



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Implementation Plan (1)

- Halt immediately receipt of applications for registration for non-recommended monotherapy formulations.
- Suspend the registration and stop the verification for importation of monotherapy formulations 3 months of final decision.
- Deadline for importation of suspended products, 3 months from suspension date.



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Implementation Plan (2)

- Rescheduling of CQ and SP to POM/PIM
 - Stakeholders resolutions (Report).
 - Minutes of the TC, CNF and Authority
 - Drafting Statutory Instrument (NDA Legal Committee)
 - Review by MOH Legal Committee (PP + SM)
 - Review and Drafting of SI by First Parliamentary Counsel
 - Pigeon hole of MPs for 14 days
 - Handling any queries from MPs
 - Signing of SI by MOH
 - Publication of the SI in the Uganda Gazette.



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Use of ACTs at Community

- Relatively new drug in our setting,
limited experience and knowledge:
 - **Feasibility of use at community not known.**
- Requires rescheduling to OTC.





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Requirements for Rescheduling to OTC



- Drug should be/have:
 - ? Well know and good safety profile (*Long use in China*)
 - ✓ For a condition easily diagnosed by public
 - ? Easy and well known dosage regiment
 - ? Administration requires little expertise or no supervision. (*See page 15 of Guide to HW*)
 - ? Known good compliance and acceptability (*Re-infection or recrudescence*)
 - ? Low potential for diversion or abuse (*Leakage*)
 - ? Pharmaceutical properties support community use:
 - ✓ dosage form
 - ✓ Packaging
 - ? Stability (moisture)
- Feasibility needs to be studied

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Progress of Feasibility study in Uganda

- Funded by WHO-TDR
- Executed by MUK-SS + MoH + WHO
- Area:
 - Iganga - Namungalwe Sub-county
 - Bugiri – Nankoma Sub-county
 - 56 village, 112 Community Medicine distributors (CMDs)
- Progress:
 - Drug deployment – Last week, June 2006
 - So far no ADR observed/reported
 - Uptake is good: based on blue stock outs (*Leakage??*)
 - 100% retention of CMDs


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Feasibility: Issues not yet tackled



- Effectiveness** of the drug: blood slide at day0 and day28: tests to be done in Ghana
- Stability** in the chain:
 - NMS ⇒ District store ⇒ HCIV ⇒ CMD ⇒ Patient
 - To start soon.
- Compliance** of CMDs and Care Givers: mid-term review (Dec'06 – Jan'07)
- Acceptability** of the drug: Mid term review (Dec'06 – Jan'07).
- Sustainability**: Costing

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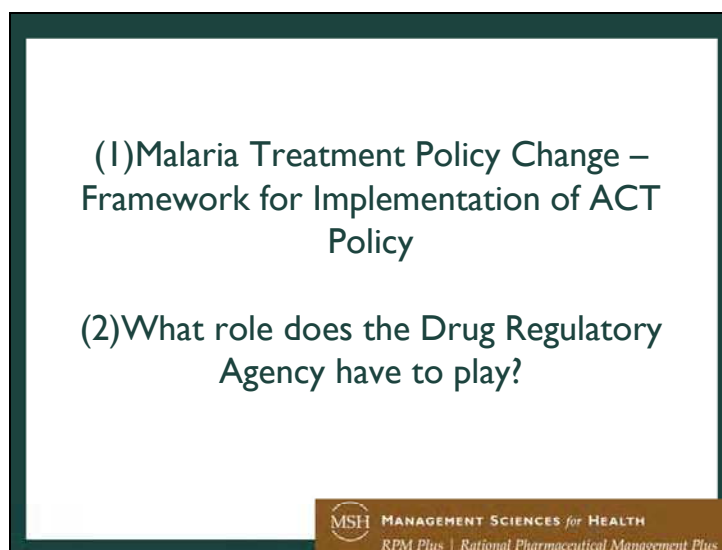


Summary of Issues

- Policy to refer to ACT generic name and not brand name
- Basis for efficacy: Uganda, E. Africa, Regional or International (Resistance)
- Stop new registration of monotherapy
- Phase out importation of monotherapy
- Options for **children < 5kg or <4m???**
- Supply of CQ and SP restricted to local manufacturers
- Rescheduling of CQ and SP to POM or PIM
- Feasibility of use of ACT at community and process
- Controls, accountability and leakage
- Pharmacovigilance and quality surveillance
- Supply to the private sector

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ANNEX 4. CHANGING MALARIA TREATMENT POLICIES: A GUIDE TO IMPLEMENTATION



Background

- Documented evidence of growing parasite resistance (*P. falciparum*) to commonly used therapies
- **WHO Recommendation** - All countries needing to change their first-line treatments for *P. falciparum* malaria should change to artemisinin-based combination therapies (ACTs)
- Therapeutic options currently recommended by WHO:
 - Artemether/lumefantrine (FDC)
 - Artesunate plus amodiaquine
 - Artesunate plus sulfadoxine/pyrimethamine (S/P) (in areas where S/P efficacy remains high)
 - Artesunate plus mefloquine (areas of low transmission)



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Uganda's current AMDP outline (I)

Treatment of uncomplicated malaria:

- The recommended first line medicine is **Artemether/Lumefantrine**. This medicine (Artemether/Lumefantrine) is not recommended for children below 4 months of age or 5 kg body weight and pregnant women in the first trimester. Artesunate + Amodiaquine is the alternative when Artemether/Lumefantrine is not available.
- The recommended second line medicine is oral quinine for all patients.

Treatment of severe and complicated malaria:

- Parenteral quinine is the recommended treatment for the management of severe malaria for all patients. Parenteral artemisinin derivatives may be used if quinine is contraindicated or not available.

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Uganda's current AMDP outline (2)

Intermittent Preventive Treatment of malaria in pregnancy:

- Sulfadoxine/Pyrimethamine (SP) is the recommended medicine.

Treatment of uncomplicated malaria for special groups:

- **Pregnant women:**

- During the first trimester quinine should be used instead of ACTs. After the first trimester, ACTs may be used.

- **Children below 4 months of age:**

- ACTs are not recommended for children below 4 months of age or 5 kg body weight. Such children should be treated with quinine

Framework for the Malaria Treatment Policy Change process

- Decision to change the antimalarial treatment policy and the subsequent implementation of the policy brings with it challenges and complexities at every level involving a variety of stakeholders
- Phases of change – Policy change decision, Transition, Implementation with M&E running throughout phases
- Framework for implementation – five elements
 - Financing and resource mobilization
 - Planning & coordination
 - Technical considerations
 - Operational considerations
 - Monitoring & Evaluation

Framework for implementation of ACT policy (1)

- Financing
- Planning & coordination
 - Identify stakeholders
 - Establishment of committees
- Technical considerations
 - Drug regulatory considerations
 - Pharmacovigilance
 - Quality Assurance
 - ADR monitoring
 - STGs and other guidelines

Framework for implementation of ACT policy (2)

- Technical considerations (cont.)
 - Communication
 - IEC/BCC
 - Training

Framework for implementation of ACT policy (3)

- Operational considerations
 - Procurement
 - Forecasting
 - Prepackaging
 - Distribution
 - Inventory management
 - Phasing out of old drug
 - Private sector access
- Monitoring & Evaluation

Financing and resource mobilization

- Before beginning policy implementation process, critical to ensure that financing issues have been addressed
- Effective transition and implementation likely to require a time-limited investment of additional resources
- Costs should be and in Uganda's case have been budgeted for at the planning stage
 - Commitment from departments within country and from donors need to be sought before beginning the implementation process

Planning and coordination

- Identify stakeholders
- Determine their roles and responsibilities
- Establish transition committee and other working groups/task forces with responsibilities such as:
 - Program planning
 - Implementation plan development
 - M & Eand determine persons responsible for execution of implementation plan and M&E plan
- Establish TORs for working groups/ taskforces and develop mode of work and frequency of meetings

Technical considerations

- Drug regulatory considerations
 - Registration of ACT in country of use
 - Promulgate regulations for appropriate prescribing and dispensing of ACT (level of care for use)
 - Evaluate regulatory enforcement capacity and develop plan for strengthening
 - Promulgate regulations to facilitate phasing out of old drug and/or monotherapies if needed
 - Review diagnostic criteria for treatment [clinical, biological (microscopic/RDTs)]
 - Consider policy for pregnant women (1st trimester)

Technical considerations (contd)

- National treatment guideline development /revision
 - Publish and disseminate new guidelines to HW (pub/prv)
- Training and Supervision
 - Revise pre-service and in-service training curricula to incorporate new guidelines incl diagnostic criteria
 - Develop/review packages and plans for training of health workers (Medical side/PMM-quant, inv cont)
 - Convene training workshops immediately after
- IEC/BCC
 - Develop/review BCC strategies
 - Develop/review IEC materials and strategies
 - Develop/review plan for implementation of BCC strategy

Technical considerations (contd)

- Quality Assurance systems
 - Develop/review systems for QA during procurement
 - Develop/review systems for violations against drug quality standards
 - Develop/review plan for post-marketing product quality surveillance
- Pharmacovigilance/ADR monitoring
 - Develop/review system for monitoring of adverse events
- Establish mechanism to coordinate the surveillance systems (efficacy, product quality, ADR)

Operational considerations

- Developing a phase-in plan
 - Phased implementation
 - Nationwide roll-out
- Procurement
 - Quantification dependent on phase-in plan
 - Initiate and manage procurement process
- Pre-packaging
 - Identify manufacturer for pre-packaging of combination if needed
 - Develop weight/dosage schedules and appropriate pre-packaging for children
 - Determine if same packaging should be used in public and private sectors



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Operational considerations

- Distribution and Inventory Management
 - Develop/review distribution plan
 - Review/develop inventory management systems to improve management of ACTs in peripheral health facilities
 - Develop/review strategies to prevent leakage to private sector
 - Develop/review distribution systems to remove expired stocks
 - Review storage systems



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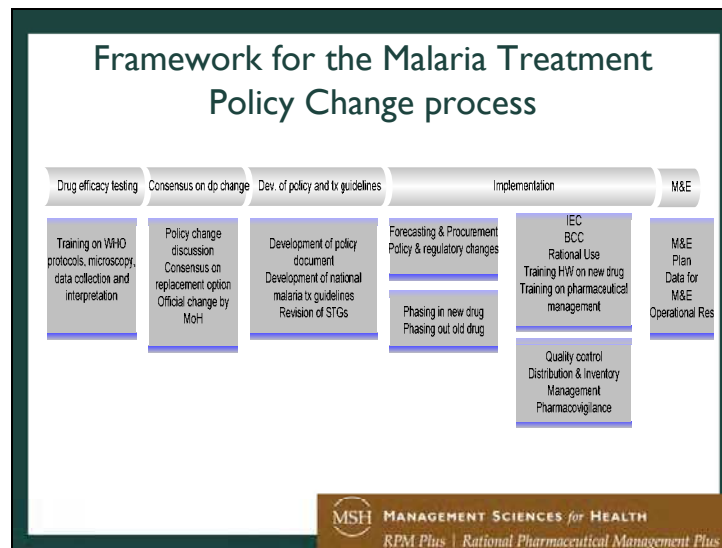
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Operations considerations

- Phase out old medicines
 - Determine pipeline for old medicines through central and peripheral data collection
 - Adjust future procurements of current medicines to avoid accumulation of large pipelines of old medicine when new medicine is procured
 - Develop plan for phase out of current medicine from health system as new medicines becomes available
 - Withdraw old medicines using plan developed above when change occurs

Operational considerations

- Private sector
 - Develop plan for making ACT available in private sector
 - Consider appropriate interventions to enable access (e.g. accredited private practitioners /pharmacies/ chemical sellers)
 - Train relevant private sector providers
- Monitoring & Evaluation



- ### Summarized Role of the Drug Regulatory Agency (NDA)
- Large role in ACT Policy Implementation
 - Involvement in early planning and coordination for policy change
 - Development of Strategic Plan of Action to provide guidance on actions needed to implement national malaria treatment policy change to ACT
 - Costing of Strategic Plan and determination of sources of funding to achieve activity implementation (GOU, GFATM, PMI)
 - Implementation of planned activities and M&E
 - Regular reporting and cataloging of activities
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Summarized Role of the Drug Regulatory Agency (NDA)

- Drug Regulatory changes must be implemented by National Drug Authority on behalf of NMCP and established committee of stakeholders
 - Registration of ACT in country of use
 - Establishment of regulations for appropriate prescribing and dispensing of ACT (level of care for use, public – HC, Disp:private – pharmacies, clinics, OTC, HBM) [changes in medicine scheduling to ensure availability of 1st & 2nd line]
 - Development of plan and regulations (e.g. legislation/rescheduling to POM) to facilitate phasing out of old medicines and/or monotherapies if needed

Summarized Role of the Drug Regulatory Agency (NDA)

Other Roles -

- Evaluation of regulatory enforcement capacity and develop plan for strengthening
 - Ensure enforcement of regulations regarding IEC materials and strategies, pre-packaging, prevention of leakage to private sector
- Ensure that Quality Assurance systems are in place and can coordinate the surveillance systems (efficacy, product quality, ADR)
 - Systematically deal with violations against drug quality standards
 - Achieve post-marketing product quality surveillance
 - Accommodate malaria indicators within its Pharmacovigilance/ADR monitoring system

Country Example – Ghana FDB (2004 Policy change to AS/AQ)

- Ensured registration of ACT & reclassification as program medicine
- Established quality assurance program for manufacture of ACT in Ghana (raw materials screening, specifications, specifications for raw material API, labeling, Safety studies)
 - Assessment of quality of antimalarials in pub/priv. sectors
 - ACT formulation meeting
- Phasing out of Monotherapies and Limiting SP

Ghana Case Study: Phasing out Monotherapies and Limiting SP (I)

Rationale:

- Partner medicines that comprise Ghana's choice of ACT are individual components (AS and AQ) formulated into co-packaged dosage forms for simultaneous administration (co-administered therapy)
- Because AS and AQ have each been previously used as monotherapies, they were still available on the Ghana market.
- It was agreed among stakeholders that continued use of AS and AQ as monotherapies could potentially compromise the value of the AS/AQ combination by selecting for drug resistance
- Action - withdrawal from the market of artemisinins (AS and its derivatives) and other antimalarial monotherapies (such as chloroquine, amodiaquine, SP and its derivatives) was recommended.

Ghana Case Study: Phasing out Monotherapies and Limiting SP (2)

Methodology – principles used

- In phasing out any group of medicines from a supply chain, the existing pipelines of the medicines must be determined and future procurements of current medicines adjusted to avoid accumulation of large pipelines of “old” medicines. In November 2005, the Food and Drugs Board undertook an assessment of the existing pipeline of antimalarials within the outgoing malaria treatment policy, with the aim of—
 - Determining approximate quantities of antimalarial monotherapies on the market
 - Determining the quantities of raw materials in the warehouses of the local pharmaceutical manufacturers capable of being used for the production of monotherapies
 - Determining stocks of finished products of antimalarial monotherapies in the warehouses of importers of such products
 - Determining stocks of monotherapy antimalarials in the Central and Regional Medical Stores

Ghana Case Study: Phasing out Monotherapies and Limiting SP (3)

Methodology

- The assessment was designed to cover the following products—
 - All the different dosage forms of chloroquine and their raw materials
 - All the different dosage forms of amodiaquine and their raw materials
 - All the different dosage forms of artesunate and other artemisinin derivatives and their raw materials

Findings

- The interpretation of the assessment findings indicates that within the six months following the assessment, all stocks in the public sector will be exhausted if no new supplies are received within the period. The same could not be assumed of the private sector, where companies assessed have already made huge investments in raw and packaging materials as well as finished products.

Ghana Case Study: Phasing out Monotherapies and Limiting SP (4)

Recommendation

- The recommendation of the FDB, was that a period of 6 months to 1 year should be allowed for phasing out existing antimalarial monotherapies. The immediate discontinuation of CQ was recommended whereas AS & AQ and ivermectin products were allowed to be prescribed and used simultaneously during the transition period.
- As a follow-up to this assessment, the FDB has implemented the phaseout plan by—
 - Immediate discontinuation of the registration of new antimalarial monotherapies
 - Immediate discontinuation of the renewal of antimalarial monotherapies whose market authorization has expired
 - Immediate discontinuation of the issuance of new permits for importation of chloroquine powder
 - SP stocks manufactured and procured have been limited by CMS and Manufacturers for IPT use only

ANNEX 5. THE ROLE OF MONOTHERAPIES IN THE TREATMENT OF MALARIA

Role of monotherapies in the treatment of malaria

Dr. Ambrose Talisuna, PhD
Assistant Commissioner
Epidemiology and Surveillance, MoH

History of malaria drug development -1

- Quinine
 - Extracted from cinchona bark, used as early as 1632
 - By the 19th century was the only known antimalarial agent

- WW-1 → research: Germany (Bayer)
 - 1926: Plasmochine (Pamaquine®)
 - 1932: Quinacrine, mepacrine (Atabrine®)
 - 1934: Resochin, **sontochin** (3-methyl CQ)

→ abandoned due to side effects

→ formula to U.S. (end 1930s)

History of malaria drug development-2

- WW-II→ research: UK and U.S.
 - Sontochin adapted to chloroquine®= Resochin (4-amino quinolones)
 - 1941: Amodiaquine (4-amino quinolone)
 - 1944: Proguanil (paludrine)
 - 1950: Primaquine (8-amino quinolone)
 - 1952: Pyrimethamine
 - 1967: Sulfadoxine-pyrimethamine

History of malaria drug development-3

- Later
 - Late 1970s: mefloquine and halofantrine (arylaminoalcohol)
 - 1971: Artemisine
 - 1998: Malarone (proguanil-atovaquone)

Summary of available monotherapies-1

Chemical class		Mode of action	Use
Arylaminoalcohols	-Quinine -Quinidine -Mefloquine -Halofantrine	Inhibit polymerization of toxic haem into insoluble heamazoin	Malaria treatment and prophylaxis
4-Aminoquinolines	-Chloroquine -Amodiaquine	Inhibit polymerization of toxic haem into insoluble heamazoin	Treatment and prophylaxis (SCD)
8-Aminoquinolines	Primaquine	Active against non growing stages- hypnozoites and gametocytes	Gametocytocidal for <i>P. falciparum</i> , hypnozoitocidal (antirelapse for <i>P. vivax</i> and <i>P. ovale</i>)

Summary of available monotherapies-2

Chemical class		Mode of action	Use
Type 1 antifolates	-Sulphonamides -Suphones	Inhibit the parasite enzyme DHPS	Treatment and prophylaxis but only in synergistic combination with type 2 antifolates
Type 2 antifolates	Pyrimethamine Biguanides	Inhibit the parasite enzyme DHFR	-Treatment but only in synergistic combination with type 1 antifolates -Biguanides used alone in prophylaxis

Summary of available monotherapies-3

Chemical class		Mode of action	Use
Naphthoquinones	-Atovaquone	Inhibit electron transport	Treatment and prophylaxis in combination with proguanil (Malarone)
Artemisinins	-Artemisinin and its product DHA -Artemether -Artesunate	Probably inhibit polymerization of toxic haem into insoluble heamazoin? -Other mechanisms under investigation	Only useful for treatment

Summary of available monotherapies-4

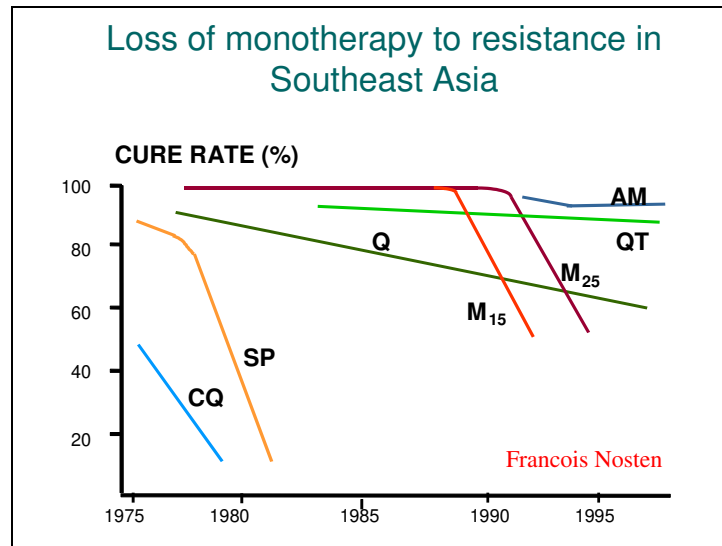
Chemical class		Mode of action	Use
Antibiotics	·Tetracycline ·Doxycycline ·Clindamycin ·Fluoroquinolone	Inhibit ribosomal protein synthesis	-Second line or sometimes last resort for treatment, e.g., QNN+ Tetra -Prophylaxis

Drug resistance (*P. falciparum*)

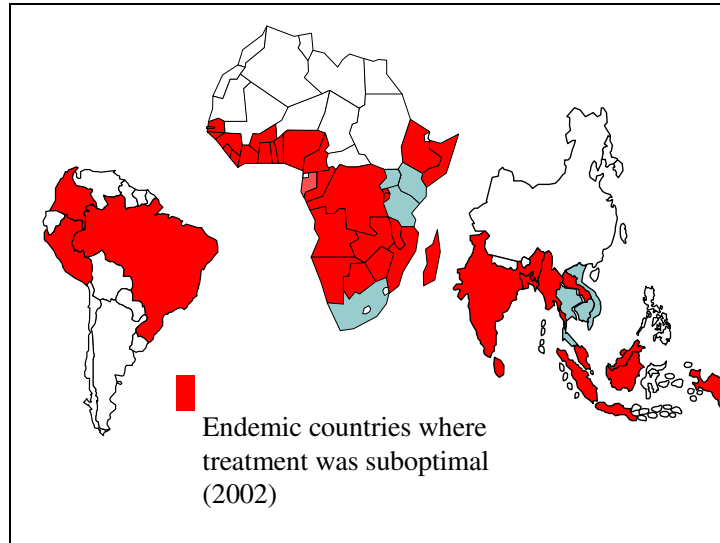
Chemical	Year of development	Year of first report of resistance	Time lag to resistance
Chloroquine	1934	1957	Over 20 years
Pyrimethamine	1953	1955	1-2 years
Proguanil	1944	1947	1-3 years

Drug resistance (*P. falciparum*)

Chemical	Year of development	Year of first report of resistance	Time lag to resistance
SP	1967	1967	0 years
Mefloquine	Late 1970s	1982	5 years
Atovaquone	1996	1996	0 years
Artemisinins	Been used for long	No confirmed resistance yet	--



At the beginning of the third millennium, drug resistance is a major concern in malaria treatment and control.



Paradigm shift: From monotherapy to combination therapy

- New paradigm: Combination therapy
- Develop new drugs (MMV, WAIR, DNDi)
- Regular efficacy monitoring, postmarketing surveillance, and pharmacovigilance
- Improve performance of providers and clients
 - Parasite-based diagnosis where necessary

Combination therapy

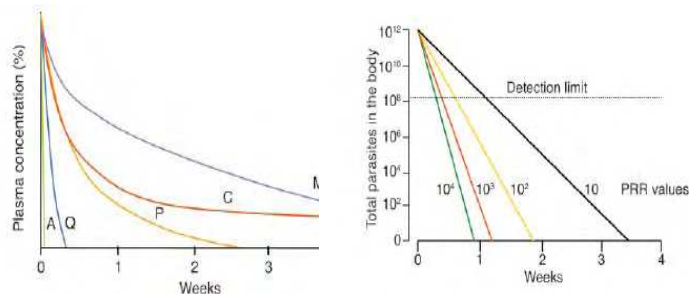
Simultaneous use of two or more blood schizonticidal drugs with independent modes of action and different biochemical targets in the parasite

WHO-recommended combination therapy

- NACT: Non-artemisinin-based combination therapy
 - Amodiaquine-SP (treatment where AQ and SP still effective and possibly IPT[i])
- ACT: Artemisinin-based CT
 - Artemether/lumefantrine (AL)
 - Artesunate/amodiaquine (AS/AQ)
 - Artesunate + SP Artesunate/mefloquine (AS/MQ) - For areas of low transmission—Southeast Asia

Combination therapy: issues

- Compliance
 - Fixed-dose combinations better
 - Pill burden in co-administered
- Which partner drugs in the combination?
 - Pharmacokinetics and pharmacodynamics



Special groups: Severe malaria

- I.V. quinine monotherapy is mainstay of treatment for severe malaria.
- New evidence (Southeast Asia) suggests that I.V artesunate as monotherapy is probably better than quinine.
- Rectal artemether is useful as prereferral treatment for severe malaria in areas with poor access to parenteral treatment.

Special groups: Malaria in Pregnancy (MiP)

- SP “monotherapy” only option for IPTp presently
- Safe but not effective for Rx of MiP
 - CQ, sulfonamides (SP, DDS, PG)
- Effective and safe for Rx of MiP
 - Quinine
- Potential drugs for RX of MiP and IPTp
 - Amodiaquine –IPTp?
 - Mefloquine-IPTp
 - Chlorproguanil-dapsone,
 - Artemisinin derivatives or ACTs

Special groups: Prophylaxis

- Malarone
- Proguanil
- Mefloquine
- Chloroquine for SCD?
- Primaquine for *P. vivax*
- Lapdap for *P. vivax*?

Special groups: Malaria/HIV

Any interaction between malaria and HIV can have enormous public health consequences (treatment failure, drug reactions) where the two diseases coexist.

HIV/malaria interactions

Type of interaction	Pregnant women	Children	Adult men and non-pregnant women
The effect of HIV on Malaria			
- Increased risk of infection with malaria	+	?	+
- Increased malaria parasite density	+	?	+
- Decreased response to standard antimalarial treatment	+	?	+
The effect of Malaria on HIV			
- Increased HIV viral load	+	?	+
- Increased risk of HIV transmission	? ⁽¹⁾	+ ⁽²⁾	?
Effects of dual infection			
- Increased risk of illness	+	+	+
- Increased risk of anaemia	+	+	+
- Increased risk of low birth weight	+	-	-

Drugs that could soon be on the WHO recommended list (1)

Product	Indication	Phase of development
Lapdap (CD)	Uncomplicated malaria, IPTp?	Registered in UK, Kenya, Tanzania, Uganda?
DHA/PPQ	Uncomplicated malaria	Registered in China, Uganda as Duocotexin International development for European registration under way-2007 (Eurartecin)

Drugs that could soon be on the WHO recommended list (2)

Product	Indication	Phase of development
FDC AS/AQ	Uncomplicated malaria	Undergoing phase III (registration possible in 2007)
FDC AS/MQ	Uncomplicated malaria	Phase II/III FDC underway
Paediatric AL	Uncomplicated malaria	Phase III completed

Drugs that could soon be on the WHO recommended list (3)

Product	Indication	Phase of development
CDA	Uncomplicated malaria, ? IPTp	Phase II FDC completed Phase III FDC ongoing (registration possible in 2007)
AS/pyronaridine	Uncomplicated malaria	Phase II FDC ongoing Phase III FDC planned (registration possible in 2008)

Drugs that could soon be on the WHO recommended list

Product	Indication	Phase of development
Rectal artesunate	Moderate/severe malaria	Undergoing regulatory review
IV artesunate	Severe malaria	Clinical trials completed in Asia, ongoing in Africa On WHO list for severe malaria mainly for SEA and if quinine is contra-indicated in Africa

New drugs under development (1)

Product	Indication	Phase of development
Azythromycin combinations	Uncomplicated malaria	Phase III
Tafenoquine	Prophylaxis	Phase II
Fosmidomycin/ clindamycin	Uncomplicated malaria	Non FDC Phase II
DB289 (improved pentamidine)	Uncomplicated malaria	Proof of concept

New drugs under development (2)

Product	Indication	Phase of development
Short-chain CQ	Uncomplicated malaria	<i>In development</i>
Artemisone	Uncomplicated malaria	Preclinical
Isoquine –OZ277 (synthetic trioxane)	Uncomplicated malaria	Preclinical
NPC 1161B(8-aminoquinoline)	Uncomplicated malaria	Preclinical

Critical issues for NDA

- Careful Registration of new products
 - Limit registration of monotherapies
- Limit use of Monotherapies
 - Dialogue with importers to limit importation of monotherapies and flood ACTs
- Fake drugs/counterfeits
 - Drug quality monitoring and safety surveillance
- Governmental sector
 - Limit leakage
- Nonformal health sector-private sector-nonpremium and premium, HBMF
 - Deregulation of ACTs

ANNEX 6. CHANGE OF MALARIA TREATMENT POLICY FROM CHLOROQUINE MONOTHERAPY TO CQ-SP COMBINATION THERAPY AS FIRST LINE: LESSONS LEARNT

	<p>Change of malaria treatment policy from chloroquine monotherapy to CQ-SP combination therapy as first line:</p> <p>“Lessons Learnt”</p> <p>Deo Kimera B. Pharm; MPH/Health Economics</p> <p>October 2006</p>
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	<p>Study done in partial fulfillment of the requirement for a Masters of Public Health in Health Economics, UCT</p> <p>Data collected in April/May 2003</p>
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Background

- National Malaria Treatment Policy Changed from CQ monotherapy as 1st line to CQ-SP combination in June 2000
- Policy change was through a consultative process with various stakeholders
- Extensive policy dissemination was carried out

Designing rational and appropriate antimalarial drug policy does not necessarily guarantee proper use of antimalarials by providers, dispensers or consumers
(Williams et al., 2004)

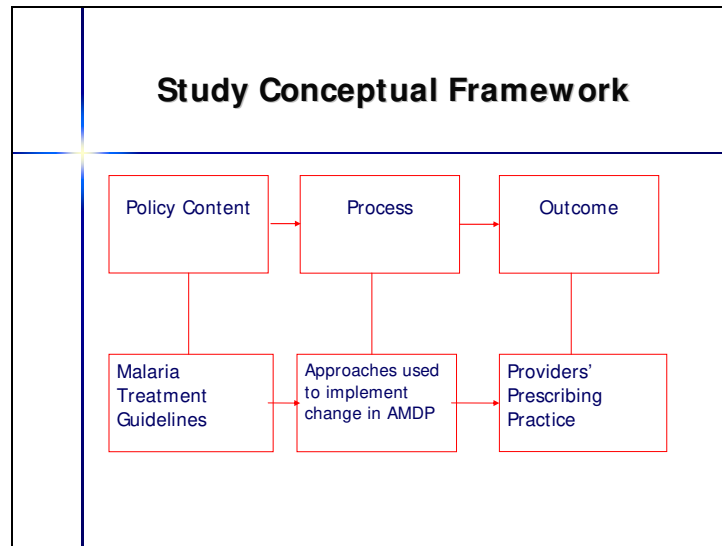
Aim was to examine the extent of implementation of the change in antimalarial drug policy (AMDP) in Uganda, from CQ monotherapy to CQ-SP combination therapy for management of uncomplicated malaria

Study Objectives

- To understand the basis of change in malaria treatment policy in Uganda and define steps that had been taken to ensure efficient implementation of the new policy.
- To review treatment (prescribing) practices for uncomplicated malaria in public and PNFP health facilities in Rakai and Kampala districts of Uganda
 - as a measure of level of adherence to the national AMDP.
- To find out factors that influence adherence to national malaria treatment guidelines

Study Design

- The study involved both quantitative and qualitative data collection methods
- Data was obtained from both primary and secondary sources
- Quantitative data on prescribing practice was collected by records review method from patient / prescriptions registers
- Qualitative methods were used to collect data from prescribers, heads of HF and Key Stakeholders at National level



Study Area

Level of Care	KAMPALA DISTRICT		RAKAI DISTRICT		Total number of Health Facilities
	Public	PNFP	Public	PNFP	
Level II	KCC staff Clinic	Katwe Dispensary	Kabuwoko H/C	St. Elizabeth Kijjukizo Disp.	4
Level III	Kampala Dispensary	Joy Medical Centre	Mutukula H/C	Lyantonde Muslim	4
Level IV	Naguru Health Centre	Namungoona H/C	Lyantonde H/C	Biikira H/C	4
Total	3	3	3	3	12

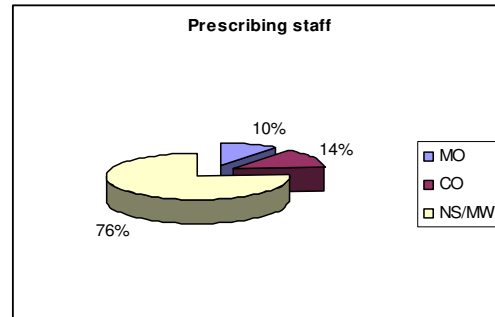
Sampling Method	
	<ul style="list-style-type: none"> ■ Multistage stratified random sampling was used to select HF involved in the study <ul style="list-style-type: none"> - Urban Versus Rural - Public Versus PNFP - Health care levels (II, III & IV) ■ Systematic random sampling at varying intervals used to select malaria cases from prescription register <ul style="list-style-type: none"> - Interval was determined by number of cases recorded in previous 6 months targeting 100 per facility

Number of Malaria Cases Reviewed					
Level of HC	Kampala District (Urban)		Rakai District (Rural)		Total
	Public	PNFP	Public	PNFP	
Level II	100	100	100	100	400
Level III	100	100	100	100	400
Level IV	100	100	100	100	400
Total	300	300	300	300	1200

	<h2>Study Limitation</h2>
	<ul style="list-style-type: none">■ Not able to segregate prescription for pregnant mothers■ Study only done in 2 districts out of then 56, therefore, finding may not necessarily be used to generalize practice in Uganda■ Study was initially designed to include PFP but due to difficulty in accessing prescription records this category was excluded

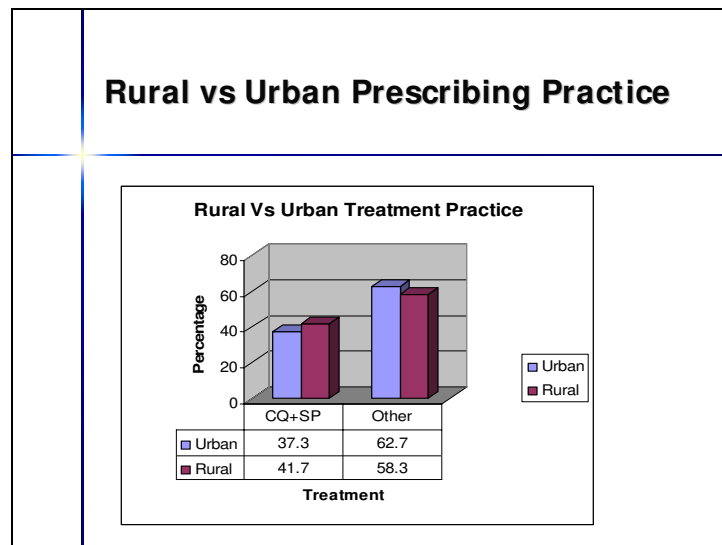
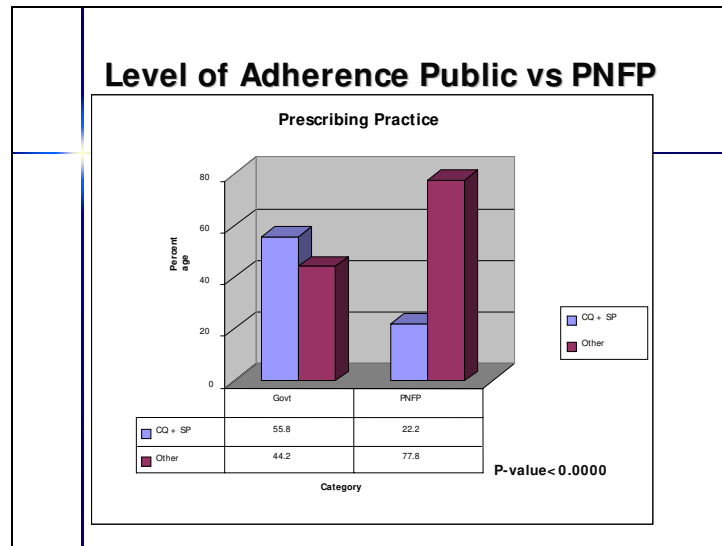
	<h2>Study Results</h2>

Description of prescribing staff

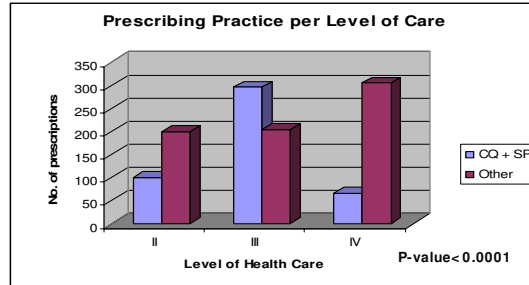


General Findings

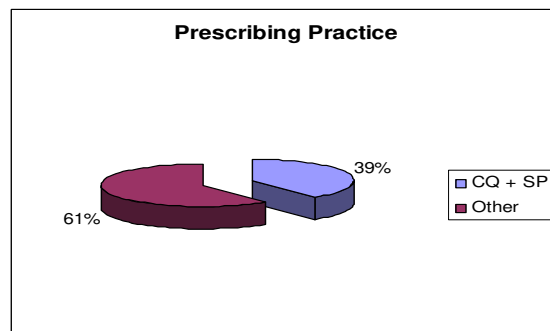
- 72.7% of prescribers interviewed correctly stated the content of the new policy
- 83% of health facilities visited had a copy of policy in place
- Support supervision rated higher in promoting adherence than workshop based training



Prescribing Practice by level of care

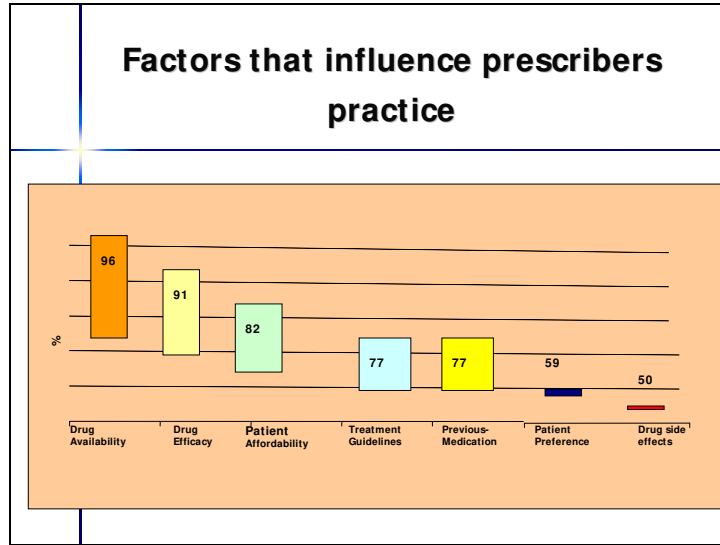


Level of Adherence (Public & PNFP)



Prescribing Practice and Level of qualification						
Facility with at least one MO	Number of HFs	CQ+SP		OTHER		p-value
		n	%	n	%	
Yes	6	160	26.7	440	73.3	0.0000
No	6	302	52.9	269	47.1	

Range of Prescribed Antimalarials														
Category	CQ+SP		SP + QNN		CQ only		SP only		QNN only		Other		Total	
	n	%	N	%	n	%	n	%	n	%	n	%	n	%
Public	3355	55.8	6	1	147	24.5	35	5.8	37	6.2	40	6.7	600	100
PNFP	127	22.2	4	5	85	14.9	70	12.3	196	34.3	48	8.4	571	100
Total	462	39.5	5	1	232	19.8	105	9	233	19.9	88	7.5	1171	100



- ### Factors considered to promote adherence: *Policy Maker perspective*
- Support supervision
 - Politician sensitization
 - Public mobilization through media campaigns
 - Effective dissemination of treatment guidelines
 - Drug efficacy

	Reasons for deviating from policy
	<ul style="list-style-type: none">■ Recommended treatment not continuously available■ Perception that patients responds faster to second line drugs■ Assumption pts take CQ-SP under home based management program before visiting facility■ Fear for SAE on using SP based combination■ Historically known position of CQ as first line drug for management of uncomplicated malaria

	Lessons Learnt

	Process of CQ-SP Choice
	<ul style="list-style-type: none">■ Took into consideration issues related to:<ul style="list-style-type: none">– efficacy– safety– affordability– ease to administer■ But less consideration made on potential for delaying development of resistance

	Process of Policy Change
	<ul style="list-style-type: none">■ Was effective in terms of<ul style="list-style-type: none">– Involving multiple stakeholders– ensuring availability of treatment guidelines– Equipping prescribers with knowledge about change in policy■ But this was not directly translated into prescribing recommended therapy (39% level of adherence)

Prescribing Practice

- There was a significant difference between public (55.8% adherence) and PNFP (22.2% adherence) prescribing practice ($P < 0.000$)
- PNFP staff prescribed more Quinine monotherapy (34.3%) than recommended therapy (22.2%)
- No significant difference noted between rural and urban prescribing practice
- Level IV health facility least adhered to policy change (17.8%) as compared to HCIII & II ($P\text{-value} < 0.0001$)

Prescribing Practice

- A reasonable proportion of chloroquine monotherapy was still being prescribed especially in public sector
- Lower cadre staff adhered more to the policy than prescribing practice of facilities with Medical Officers
- Drug availability was a major factor influencing prescribing practice

	Prescribers' Behaviour
	<ul style="list-style-type: none">■ Multiple factors are involved in general practitioners' decisions to change their prescribing habits- Armstrong et al. (1996)<ul style="list-style-type: none">– Volume and authority of evidence obtained– Cost pressures– Dramatic clinical event■ Experienced prescribers believe that the principals of rational prescribing or prescribing according to guidelines limits their choice of therapy-Waller (2005)

	Policy Recommendations
	<ul style="list-style-type: none">■ Include an indicator for measuring level of adherence to AMDP among those monitored by MCP/QA■ On changing policy, provide assurance for sustainable availability of recommended antimalarials■ On changing policy, design special strategies for PNFP sector where treatment cost recovery is an issue■ Consider putting more resources in support supervision/on job-orientation than workshop based training

ANNEX 7. THE IMPACT OF THE NEW ANTIMALARIA POLICY ON ACCESS TO ANTIMALARIAL MEDICINES IN THE PRIVATE SECTOR

The Impact of the new antimalarial policy on access of antimalarial medicines in the private sector

James William Tamale
Secretary, Pharmaceutical Society
of Uganda

Why change to ACT's?

- Clear evidence of the need for change
- Rising failure rates for both CQ and SP
- WHO recommendation for artemisinin-based combination therapies (ACTs) adopted as global strategy
- Decision taken by MoH-Uganda to change policy in 2004

Treatment of uncomplicated malaria

- First-line treatment is artemether-lumefantrine (AL): currently the only fixed-dose ACT
- Alternative first-line is artesunate+amodiaquine (AS+AQ)
- When artemether-lumefantrine is not available
- This combination can be given when the artemether/lumefantrine is not contraindicated because of the lumefantrine component
- Second-line medicine is oral quinine for all patients



Treatment of severe malaria

- Parenteral quinine remains the recommended treatment for the management of severe malaria in all patients.
- Parenteral artemisinin derivatives may be used if quinine is contraindicated or not available.



Intermittent preventive treatment in pregnancy (IPT)

- Sulfadoxine/pyrimethamine is the recommended medicine
- Is given in the 2nd and 3rd trimesters as directly observed therapy
- Each dose must be given at least one month apart
- Women who are living with HIV should receive three doses of IPT, i.e., one in each trimester, instead of two.
- There is no alternative for pregnant mothers who cannot take SP because of adverse reactions.



Malaria case management in special cases (1)

- Malaria and sickle cell disease
- There is no change in policy regarding the chemoprophylaxis of malaria among children with sickle cell disease.



Malaria case management in special cases (2)

Congenital malaria

- Children who weigh less than 5 kg (or children aged less than 4 months) should not be given ACTs
- In this group, quinine remains the drug of choice given orally



Accessibility (1)

- NDA has recorded an increase in imports of ACTs this year (2006) as compared to 2005.
- In private sector uptake of ACTs by patients is price dependent. ACTs are costly as compared to already existing therapies.
- Practitioners provide what the clients can afford.
- Affordability in rural areas (upcountry). Will practitioners be willing to stock if patients can't afford?



Accessibility (2)

- Need to improve awareness of and compliance to new policy among practitioners and patients
- A noticeable lack of awareness and knowledge of ACTs by a number of health practitioners. (Behavior change management needed--whose role?)



Availability (1)

- How much of required ACTs are actually imported into the country to cater for population needs?
- Do quantities meet demand?
- How can gap be filled if demand exceeds supply? E.g., in case of delays (if any) in importation.
- Patient issues (patient power): Patients insisting to use therapies (monotherapies) they have used before. Role of practitioners in curbing this.



Availability (2)

- Will smugglers try to fill the supply-demand gap? Issue of fakes hitting the market?
- What monitoring mechanisms are in place to nullify these threats?
- Who stocks what? What do drug shops currently stock? What will they be required to stock?



Way forward

- Stop importation of monotherapies
- Take into consideration special groups and their medication needs
- Monitoring to ensure compliance to new policy
- Phased implementation? Is it the way to go to cater for peculiarities of the rural community (upcountry areas)?



ANNEX 8. CHALLENGES OF PROCUREMENT, STORAGE, AND DISTRIBUTION OF ACTS: IMPACT OF NAMTP ON ACTIVITIES OF NMS

CHALLENGES OF PROCUREMENT, STORAGE, AND DISTRIBUTION OF ACTs/IMPACT OF NAMTP ON ACTIVITIES OF NMS



By Benjamin Oryema
5th October 2006

Structure



- A- Activities of NMS
- B- Stocks at NMS
- C- Impact of NAMTP
- D- Challenges
- E- Managing the challenges
- Conclusion

A- Activities of NMS



- Receipt of medicines
- Storage/warehousing
- Documentation/picking/packaging/loading
- Distribution
- Follow-up on payments

B- Stocks at NMS



- NMS stock (23%)
 - CQ, quinine etc
- Program stocks (77%)
 - HOMAPAK

C- Impact of NAMTP



- Change in procurement plan
- Increase in workload--more orders processed (from 70/day to 100/day)/packaging/loading
- New districts--more distribution points--time
- High demand for ACTs--failure to fit into the NMS cycle
- Strain on storage space

D-Challenges



- Timely distribution due to high demand
- Big no. of districts, indirectly affecting the distribution of ACTs
- Increasing cost of gasoline—hence reduced response to emergencies
- Poor road infrastructure--leads to delays, hence affecting the cycles
- Movement of stocks from gov. units to private units (leakage)
- Accumulation of old stocks

E- Managing the challenges



(1)

- Involvement of NMS in quantification and procurement of ACTs
- Improving communication: NMS and health units
- Sticking to distribution plan
- Revising the cost of storage and distribution
- Hiring more storage space
- Working with partners, e.g., MSH

E- Managing the challenges



(2)

- Making customer visits (evaluations)
- Provision of timely reports and networking with programs

Conclusion



- NMS involvement in quantification/procurement
- Improve working relationships with programs
- Need to sensitize customers on timely ordering
- Strengthen the monitoring of ACTs in gov. facilities

ANNEX 9. GROUP DISCUSSION PARTICIPANTS

Group 1: Rescheduling ACTs for Different Levels within the EDL

- Mr. Benjamin Oryema
- Mr. Joseph Mwoga
- Mr. Sunday Erisa
- Mr. Samuel Kasozi
- Mr. David Nahamya
- Mr. Deus K. Mubangizi

Group 2: Registration of Antimalarials

- Ms Jean Zikusooka
- Mr. Gidoen Kisuule M
- Mr. Michael Mutyaba
- Mr. James Tibenderana

Group 3: Postmarketing Activities (Phase IV Study)

- Gwoktho Cephas
- Ms. Stella Watya
- Dr. Myers Lugemwa
- Ms Nassali Huldah
- Mr. Chris Ntege

Group 4: Phasing out Monotherapies and Suboptimal Combination Therapies

- Dr. Kato
- Mr. Saul Kidde
- Dr. Talisuna Ambrose
- Mr. Peter Mbabazi
- Ms Annette Nsubuga
- Dr. Gladys Tetteth
- Mr. Apollo Angole
- Mr. Deus K. Mubangizi

