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Chloroquine Efficacy Study in Zambia
1995-1996

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PREFACE

Activity Report No. 15 was first published by EHP in November 1995. It described the initial studies of antimalarial drug resistance in Zambia, conducted in early summer, 1995. Under that activity, EHP/CDC consultants, in collaboration with a team from WHO and the staff of the Zambian Ministry of Health, designed a national drug efficacy study to measure resistance to chloroquine in children under five who visited clinics with non-severe malaria. The EHP/CDC team was involved in conducting efficacy studies at two clinics in Chipata District, while the WHO team worked in another district, Katete.

In 1996, the EHP/CDC team was asked to continue work on this activity, by testing the protocol designed in 1995 (and refining it, if needed), providing further training for MOH and district health staff, and conducting studies at five additional sites around the country. The report on work undertaken from January through March 1996 gave further evidence of drug resistance in children under five with non-severe malaria. Since the 1996 studies were based on the same methodology used in 1995 and described in Activity Report No. 15, EHP decided to revise and expand that document, adding findings from the five additional sites.

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ACRONYMS

CDC	Centers for Disease Control and Prevention
CFR	case fatality rate
CQ	chloroquine
CRPf	chloroquine-resistant *Plasmodium falciparum*
DHMT	District Health Management Team
EHP	Environmental Health Project (sponsored by USAID, located in Arlington, Va.)
GMPD	geometric parasite density
hct	hematocrit
HMIS	health management information system
JICA	Japanese overseas aid agency
Kw	Kwacha (Kw 850 = US $1)
LTF	lost to follow-up (patients who dropped out of a study)
MCH	Maternal and Child Health
NGO	nongovernmental organization
NMCC	National Malaria Control Centre, Lusaka, Zambia
QN	quinine
SP	sulfadoxine/pyrimethamine or Fansidar™
TDRC	Tropical Disease Research Centre, Ndola, Zambia
USAID	United States Agency for International Development
UTH	University Teaching Hospital, Lusaka, Zambia
WBC	white blood cells
WHO	World Health Organization
ZCH	USAID-funded Zambian Child Health Project

EXECUTIVE SUMMARY

Malaria is the number one cause of morbidity, hospital admissions, and mortality in Zambia. Among all age groups it accounts for one-fourth of both clinic and hospital admission diagnoses, and 21% of all deaths (MOH Bulletin of Health Statistics 1989-1992). The crude incidence rates are high: 355.7 per 1,000 population in 1994. A third of all under 5 year old clinic visits are due to malaria. A child will experience 9-11 episodes before reaching age five with the inherent risks of significant anemia and vulnerability to other diseases. The vast majority of the malaria cases are caused by *Plasmodium falciparum* (86-95%) with associated case fatality rates as high as 43/1,000 cases (MOH 1990). Clearly the burden of malaria on the health care system and for Zambian families in terms of productivity and quality of life is significant.

Reduction of morbidity and mortality is dependent on early diagnosis and adequate treatment; the latter becoming increasingly hampered by what is suspected to be an emerging resistance of *P. falciparum* to chloroquine. This is reflected in the upward trends in both morbidity and mortality seen in Zambia over the last decade. For instance, case fatality rates have jumped more than two fold; from 13/1,000 cases in 1982 to 29.5/1,000 in 1992. Crude incidence has risen from 168/1,000 to 354/1,000 over the same time period. Yet the extent and severity of resistance to chloroquine is not clear because to date there have not been consistent standardized methods to collect data on the problem. The mechanisms to understand the problem come from two sources: the Tropical Disease Research Centre (TDRC) in Ndola which has been conducting drug sensitivity testing over the decade throughout the country in asymptomatic children under age 15, and independent hospital-based studies. Both of these sources use a variety of WHO *in vivo* methodologies yielding inconsistent results. For instance, TDRC reported during the same year (1985) in Lusaka overall resistance at 8% and 48% (NMCC 1994). Many of the sources do not discriminate the severity of the resistance (RI-RIII); rather they report a singular value. This makes it difficult to determine the level of drug resistance and if alternative drugs (e.g., Fansidar™) should be used.

In recognition of this problem, the government of Zambia wishes to establish a sentinel surveillance system to better analyze the efficacy of chloroquine. The critical components for such a system are first to standardize the testing methodologies which will be comparable to those employed in neighboring countries. Sites for testing during peak transmission seasons need to be selected based on epidemiologic data. Further, clinical and laboratory staff will need training on patient selection, standardized methods for testing, and proper reporting. Finally, policymakers will need information and a framework on which to decide how data can inform national malaria policies, specifically, at what point revisions in drug policies should be made for better case management.

In response to these needs and as a bridging activity between development of the project paper and initiation of the USAID-supported Zambia Child Health (ZCH) Project, the Environmental Health Project and the Centers for Disease Control and Prevention carried out chloroquine efficacy studies in Chipata District, Eastern Province, Zambia, together with the National Malaria Control Centre (NMCC) and the TDRC during the period 9 May to 9 July 1995. The purpose of the bridging activity was to develop the capacity of the government of Zambia to monitor chloroquine drug resistance and to use the information to assess national malaria drug policies.

During the course of the activity several tasks were accomplished: a standard protocol for a 14-day test of treatment efficacy was prepared for use by the NMCC and TDRC for routine monitoring; staff from the NMCC, TDRC, Chipata District Health Management Team, and Chipata General Hospital

were trained in the protocol while participating in the studies in Chipata; reports of the findings were prepared and disseminated to relevant persons in the Ministry of Health and other bodies; and recommendations for future development of malaria drug policy were made to USAID/Lusaka and the Ministry of Health.

A total of 558 children under 5 years of age were screened in two clinics in Chipata District. Children with measured fever and moderate parasitemia were enrolled in the study. Of the 70 children treated with chloroquine and adequately followed, 68.5% showed resistance at the RII or RIII level and 41.4% experienced either a clinical failure or needed to be treated with an alternative drug because of unacceptable parasite response to chloroquine. Of the 45 children treated with sulfadoxine-pyrimethamine, 6.7% showed RII response, but all were free of parasites and fever by the fourteenth day.

Differences in response between the two clinics in Chipata District (one semi-rural and one urban) and between the response in Chipata and a neighboring district raise interesting scientific questions which should be addressed by further research.

It is recommended that further development of the monitoring and malaria drug policy framework continue with USAID support and with the close collaboration of WHO and other donor partners. The very significant levels of treatment failure with chloroquine call for urgent reassessment of treatment guidelines, particularly for Eastern Province.

1 BACKGROUND INFORMATION

1.1 History and Context*

The impact of malaria on the health and economic development of human populations is greatest in the tropics and subtropics (Campbell 1991). In Africa alone, the World Health Organization (WHO) has estimated that over one million children under the age of 5 die annually from malaria.

In their efforts to reduce malaria morbidity and mortality, many countries in sub-Saharan Africa have adopted a malaria control policy which relies primarily on prompt and effective treatment. For the past 30 years, chloroquine (CQ) has been the drug of choice for the treatment of malaria throughout Africa, based on its rapid action, efficacy, safety and low cost relative to other antimalarials.

In Africa, chloroquine-resistant *Plasmodium falciparum* (CRPf) was first described in the late 1970s. Since that time, while CRPf was spreading throughout sub-Saharan Africa, resistance was intensifying to intolerable levels in much of eastern Africa. Currently, countries in southern, central, and western Africa may be experiencing declines in chloroquine efficacy that are similar to those that have been occurring in eastern Africa over the last 10 to 15 years. In eastern Africa, recognition of the problem of intensifying resistance and implementation of a response was probably delayed, resulting in otherwise avoidable morbidity and mortality. So that an appropriate response can be made in a timely fashion in other areas of Africa facing declining efficacy, efforts to monitor malaria therapy must become a priority.

Over the past 10 years, many changes have occurred in the way that drug resistance is thought of and measured. Using both *in vivo* and *in vitro* methods, the first studies of drug resistance in Africa collected data only on the persistence of malaria parasites in the face of known quantities of drug. As resistance intensified and persistence of malaria parasites became an increasingly common occurrence, attention shifted to the clinical response of patients. The observation that, even when malaria parasites are not cleared from the blood after treatment with CQ, patients typically respond clinically, with resolution of fever and improvements in activity level and appetite, was used as misleading evidence of continued efficacy.

Many studies have focused on school-aged children, raising concern about the relevance of such data to the age group that carries the greatest burden of malaria-related morbidity and mortality, children under 5 years of age. It is unclear whether initial clinical improvement with incomplete parasitological cure can be considered an adequate therapeutic response in all patients, especially those with little or no acquired immunity.

Of even greater importance is the fact that hematologic recovery among anemic children treated with CQ may be incomplete. Although a causal relationship has not yet been shown, it is possible that much of the severe anemia associated with *P. falciparum* malaria in Africa and the high mortality associated with that anemia is due to repeated, ineffective therapy with CQ.

* The material in this section is excerpted from the ABackground and Rationale@ section of the protocol, which appears in Appendix A.

An additional problem is that because of the ready availability of CQ in the community, many children with febrile illnesses believed to have malaria have been treated before going to a dispensary or health center. As a result, many patients seen at health centers have already used CQ and may, therefore, already have experienced therapy failure or are infected with malaria parasites that have been exposed to subtherapeutic concentrations of CQ.

It is now recognized that *in vitro* assessment of malaria parasite resistance and categorization of resistance levels based on *in vivo* evaluations with short duration follow-up (e.g., 7 days) do not adequately assess malaria therapy efficacy. More emphasis needs to be placed on the clinical status of the patient at the time of treatment and on the chronic effects of malaria parasitemia, particularly anemia.

Malaria in Zambia is recognized as one of the leading causes of morbidity and mortality, especially among young children and pregnant women, and accounts for more outpatient visits and hospital admissions than any other disease. In 1994, over 3 million cases of malaria were reported in Zambia, a rate of 356/1,000 population. The case fatality rate among children under 5 years of age since 1990 has ranged from 21/1,000 to 48/1,000. CQ is currently the drug of choice for the treatment of malaria in Zambia.

Although numerous studies have been conducted in Zambia to document the occurrence and measure the prevalence of CRPf malaria, it is difficult to compare their results because of the lack of a standardized methodology. This may account for the wide ranges of CRPf reported. For example, studies conducted between 1992 and 1994 indicate that between 8% and 39% of *P. falciparum* infections are CQ resistant. Moreover, since these studies were conducted among asymptomatic school-age children, the ability to extrapolate these findings to the population at greatest risk of malaria illness, children under 5 years, is limited.

To address concerns regarding the current therapeutic efficacy of CQ in Zambia, a systematic evaluation has been initiated by the Ministry of Health that will use standardized procedures in multiple sites throughout the country. The findings of these CQ sensitivity trials will allow the Ministry of Health to evaluate and update its current national malaria therapy policy. At the same time, some of the sites selected will be set up to allow ongoing surveillance of CQ efficacy. This will permit the Ministry of Health to recognize rapidly any significant changes in therapy efficacy that occur and to make appropriate adjustments to national therapy policy in a timely fashion. The results of initial studies in this effort are presented here.

1.2 Scope of Work/Objectives of the Activity

To assist the Zambian government in this malaria therapy issue, USAID, through its support of the Zambian Child Health (ZCH) Project, funded specific testing activities at two sentinal sites in 1995 and at five additional sites in 1996. The technical assistance was managed through the USAID-sponsored Environmental Health Project (EHP). The purpose of the activity was to develop the capacity of the government of Zambia to monitor chloroquine drug resistance and to use the information to assess national malaria drug policies.

The 1995 assistance was to consist of seven elements:

1. Development of a standard protocol/method for drug efficacy testing/monitoring;
2. On-site, participatory training of local staff in the protocol;

3. Completion of drug efficacy studies at sites identified by the National Malaria Control Center (NMCC) for routine testing/ monitoring;
4. Analysis, reporting, and dissemination with local partners of findings;
5. Provision of information to policy forming bodies including Ministry Headquarters, National Malaria Advisory Committee, the Director of the NMCC, the Tropical Disease Research Centre (TDRC) in Ndola, and the WHO office;
6. Initial planning for the forthcoming Sub-Regional Meeting on Chloroquine Resistance; and
7. Assistance with development of technical guidelines for malaria control planning.

The seventh element, designed to be carried out in coordination with a consultancy from USAID=s BASICS Project to the Ministry of Health, was postponed due to a delay in the BASICS consultancy.

While the initial activity was being carried out (May 9 to July 9, 1995), a WHO consultant was also working with the NMCC to initiate chloroquine sensitivity testing. Therefore, one of the primary tasks of the USAID consultant team was coordination of activities with the WHO consultant in development of a standard protocol and training.

In the second phase of this efficacy study (January 31-March 30, 1996), EHP and CDC fielded a three-person team to undertake the following activities:

1. Train national staff in *in vivo* antimalarial drug efficacy testing at four sites in Zambia and

2. Conduct *in vivo* antimalarial drug efficacy testing for CQ and sulfadoxine-pyrimethamine at five sites in Zambia.

1.3 How This Report Is Organized

Chapters 2 and 3 of this report present a description of the 1995 activity and recommendations. Those chapters were first published by EHP in November 1995. (The 1995 version of the report also carried the protocol, as developed in 1995, and a detailed description of the methods and findings of the 1995 work.)

Chapter 4 describes activites carried out from January through March 1996. The protocol was tested and revised as a result of the additional studies. The revised protocol is included in its entirety as Appendix A. As in the first version of this report (November 1995), Appendix Bincludes a detailed description of the methods and clinical findings of the 1995 studies in Chipata District. Appendix C covers the findings from the additional studies in 1996. (The same methods and definitions described in Appendix B were employed during the 1996 studies, so they are not repeated in Appendix C.) Appendix C also includes a list of clinic visits by the EHP/CDC team and the principal contacts in 1996.

2 TECHNICAL ASSISTANCE ACTIVITIES IN 1995

In 1995, EHP fielded a two-person team, made up of an independent consultant specializing in malaria and a Centers for Disease Control and Prevention (CDC) epidemiologist (two individuals rotated this slot during the two-month period), to participate in initial chloroquine efficacy testing carried out by the NMCC of Zambia.

2.1 Development of a Standard Protocol

During this activity, a detailed protocol was developed for use in routine testing/ monitoring of efficacy of antimalarial drugs in Zambia. It is a protocol which can be used to test not only CQ, but also other possible first- or second-line drugs for treatment of uncomplicated malaria in outpatient settings. (Minor revisions were made as a result of subsequent trials in 1996, and the final [1996] version of the protocol is found in Appendix A.)

The protocol sets out methods for selecting sites, evaluating the requirements of the study in terms of design and sample size, enrolling and following subjects, determining outcomes, and managing and analyzing data, equipment and supplies, personnel, and time. The protocol allows for variation in study design depending on the drug being studied and the epidemiological particulars of the study site and the season.

Recommendations outlined in the recent report of a WHO consultant suggest the possibility of reducing the efficacy testing to a 7-day rather than a 14-day test. Although this would certainly simplify the testing and reduce costs, many of the important parameters that have been identified and used in evaluating malaria therapy efficacy, such as duration of clinical response and hematologic response, cannot be adequately assessed within 7 days. A shortened follow-up period would limit the results to discussions of purely parasitologic response over 7 days and initial clinical response. Unfortunately, in areas where CQ resistance is prevalent, as is indicated by the recent studies at Katete and Chipata, parasitologic resistance alone has only limited relevance to and is poorly predictive of the clinical experience of children treated with CQ. Additionally, previous studies have shown that initial clinical response (i.e., the proportion of febrile children or children with a history of recent fever who become well 2 or 3 days after initiation of therapy) is almost always high (80 to 90%), even in areas with intolerable levels of drug resistance, because of the antipyretic (fever-reducing) effects of CQ. Compared to the more definitive 28-day test, a 14-day test is itself a concession to logistics and finances, but it can provide adequate information with which to assess malaria therapy efficacy.

It is important that efficacy monitoring activities be conducted during peak transmission season. Not only will this aid in reducing costs by increasing the efficiency of enrollment of parasitemic children, it will also allow assessment of clinically important and potentially seasonal issues such as hematologic response to malaria therapy. While it would be valuable to collect data in both high- and low-transmission seasons (i.e., to

find the predictive value of diagnosis of malaria based on history of fever), conceptually, it makes sense for a malaria therapy policy that will be used throughout the year to be formulated with information collected predominately during the time of year with the highest incidence of malaria illness.

The protocol developed and used by the USAID consultants for training and conducting the studies constitutes Appendix A of this report. It was reviewed by and incorporates the comments of several Zambian counterpart team members, including Dr. Mulenga, Mr. Nkunika, and Mr. Chipipa. Dr. O. Walker, the WHO consultant, also reviewed the draft protocol and made comments. Copies were produced and made available to local colleagues and relevant bodies, e.g., the NMCC, TDRC, the WHO office in Lusaka, and those trained at each site.

2.2 Training Provided

The objective of the training component of the consultancy was to develop technical capacity for monitoring drug efficacy at both the national and district level. A cadre of trained, reliable professionals was to be developed at the central level (i.e., staff of the NMCC, Ministry of Health) to coordinate a monitoring system and offer technical support and training to district teams that would carry out the routine work.

After somewhat brief meetings with NMCC staff, two study sites were identified: Katete and Chipata Districts, both in Eastern Province bordering Mozambique and Malawi, respectively. The USAID consulting team was to work in Chipata with Mr. S. Nkunika of the NMCC and Dr. M. Mulenga from TDRC, and the WHO consultant was to work in adjacent Katete with Dr. H. B. Himonga, Director/Senior Consultant of the NMCC.

After arriving in Chipata, the consultants and colleagues met with the Regional Health Officer and staff of the District Health Office to explain the purpose of the study, identify appropriate outpatient facilities as sites for the study, and facilitate the availability of staff identified as trainees.

Two health centers were selected as sites: Kapata MCH Clinic, an urban clinic near the main market in the town of Chipata, and Prison=s Clinic, located approximately 10 km outside town in a semi-rural setting near a prison.

Work was begun in Kapata Clinic on 23 May. Training was conducted as the work progressed, after an initial explanation of the study purpose and methods. The clinical staff was trained in screening and enrollment of subjects and, later, in follow-up activities. The microscopists received refresher training in preparation of blood smears, staining and drying slides, and the determination of parasite densities. One person was trained in organizing activities of the study and managing data.

After initial training at Kapata Clinic, a second site was opened at Prison=s Clinic, and training was carried out in this second site. Training and supervision were carried out at both sites throughout the study. Particular emphasis was placed on the quality of the microscopy as parasite density is one of the key factors determining the characterization of treatment efficacy. Careful recording and management of information were stressed.

The consultants found that staff members at both clinics already had good basic skills. Refresher training was needed, however, to upgrade those skills to the quality required by the study, the technical elements of which are not complicated but must be executed properly if the findings are to be dependable.

The members of the study team who were trained include:

Mr. Simon Nkunika, Scientific Officer, NMCC
Dr. Modest Mulenga, Clinical Pharmacologist, TDRC
Mr. Mathias Lazao, Microscopist, NMCC
Mr. Delphin Kinkese, Deputy Director, Chipata Health Office
Mr. Kingsley Lapukeni, Laboratory Technician, Chipata General Hospital
Mr. Amos Chilonge, Laboratory Technician, Chipata General Hospital
Mr. Mwale, Clinical Officer, Kapata MCH Centre, Chipata

Mr. Katope, Malaria Assistant, Chipata
Mrs. Phiri, Senior Public Health Nurse, Chipata
Mrs. Banda, Public Health Nurse, Prisons Clinic, Chipata
Mr. Championaire, Laboratory Technician, Chipata General Hospital

In addition, several nurses at each clinic were trained in methods of screening children for enrollment.

As the study progressed, Dr. Mulenga became proficient in data entry and analysis using EPI INFO 6.0 software. Mr. Kinkese also expressed interest in developing his skills in both word processing and data management. Mr. Nkunika was provided with both software and data files so he can begin to develop his computing skills.

The members of the USAID team in Chipata travelled on several occasions to Katete to observe the activity of the WHO team and learn from their experience.

After completion of studies in both districts, members of the team assembled at the NMCC to crosscheck slides and exchange data and analyses. This was another opportunity for informal hands-on training by the CDC consultants. Additional persons involved in this process included:

Mr. J. Chipipa, Parasitologist, TDRC
Mr. M. D. Nguluwe, Microscopist, NMCC

During this period, one of the CDC consultants was able to meet and discuss the study methods with several members of the Department of Pediatrics at the University Teaching Hospital and with two members of the faculty of Chainama Hills College of Medical Sciences who train clinical officers and environmental health technicians in clinical and laboratory skills.

The training was successful in developing three units capable of independently carrying out such studies in the future with only a brief refresher training and intermittent supervision/support. A team from the NMCC can act as trainers/coordinators for expansion to other sites, as can the team from TDRC. The Chipata District team could be used to great advantage as trainers in other districts, such as neighboring Lundazi, as well as for future studies in Chipata District itself.

2.3 Completion of Treatment Efficacy Studies in Chipata

One hundred and twenty-three children with uncomplicated *P. falciparum* malaria were enrolled in treatment efficacy studies in Chipata District. The trial comprised three parts:

- A 14-day study of efficacy of chloroquine as initial treatment;
- A 14-day study of efficacy of SP as second-line treatment after failure of chloroquine; and
- A 14-day study of efficacy of SP as initial treatment.

A comparative trial was not conducted as initial surveys of the children presenting with uncomplicated malaria in Chipata at the time of the study (after the rainy season peak of transmission) did not indicate significant levels of moderate anemia. In the presence of significant rates of moderate anemia, a comparative trial would be conducted in order to examine hematological recovery after treatment for malaria.

High levels of parasitological and clinical failure (68.5%) within 7 days of chloroquine treatment were found in this group of children. Lower levels (2.2%) were found following

treatment with SP. Full details of the study methodology and findings are presented as Appendix B of this report.

It was not possible to carry out studies at additional sites at this time of year and with the logistic and supervisory support available during the consultancy. During peak transmission season, with previously trained personnel and more supplies and vehicles, two or three complete studies could be carried out in an equivalent period of field work (six to eight weeks). In all likelihood, less time would be taken up getting supplies assembled and logistics arranged, now that the study methods and requirements are better known.

All of the original data forms, EPI INFO 6.0 data files and analysis programs, all study slides, and the revised protocol document have been left at the NMCC, along with equipment and supplies provided by EHP as part of the ZCH bridging activity. (Supplies left for future studies include a Polaroid camera, a small hair dryer for drying slides, four electronic thermometers, leftover latex examination gloves, lancets, pediatric urine bags, urine test reagents, pipette tips, and other items.)

2.4 Assistance with Analysis, Reporting, and Dissemination of Results

Several of those trained in the study protocol were involved in analysis and presentation of results, particularly Mr. Nkunika, Dr. Mulenga, and Mr. Kinkese. A full briefing was given in Chipata District on the purpose, methods, and preliminary findings of the study; attendees included the Regional Health Officer, the Acting Director of Chipata General Hospital, representatives from the District Health Management Team, private local practitioners, nursing students, and clinical and laboratory staff of Chipata General Hospital.

Further involvement of colleagues at the national level in reporting and dissemination of information was hampered by travel committments of Mr. Nkunika and Dr. Himonga. Both were out of the country for the final week of the consultancy. Drs. Himonga and Walker were also both quite busy with a WHO workshop on severe and complicated malaria during the penultimate week of the consultancy, which limited their input a bit. However, the consultants were able to meet briefly with Dr. Himonga and more fully with Dr. Walker to discuss the studies and recommend future action.

The protocol and other reports were prepared by the consultants and reviewed by Zambian colleagues. Copies were provided to the NMCC, Ministry Headquarters, UNICEF, WHO Brazzaville, WHO Geneva, WHO Lusaka, TDRC, and USAID/Zambia.

A detailed report has been prepared by the consultants, outlining the results of the studies in Chipata and discussing some of the implications of the findings. As mentioned earlier, this report is attached as Appendix B.

It was not possible to hold a meeting with the Ministry of Health to discuss the findings and to begin to identify other areas which can be strengthened in preparation for a formal review of national policy on antimalarial drugs. A clear view was expressed that such discussion should wait for the results of further CQ sensitivity testing.

3 RECOMMENDATIONS & DISCUSSION FROM 1995 ACTIVITIES

3.1 Consultant=s Recommendations to the Government of Zambia and USAID

The EHP/CDC team arrived at the following recommendations in 1995, based on the two months of technical assistance.

1. National policy review

The Ministry of Health should begin now to develop the framework for reviewing its policy on treatment for uncomplicated *P. falciparum* malaria. Data from two sites in Eastern Province suggest significant levels of resistance to the current first-line antimalarial drug, chloroquine. Further studies must be carried out before a change in national policy can be considered; however, planning should start immediately to ensure that the consideration of a change in national policy is taken up by an appropriate policymaking body on the basis of full and accurate information.

Specific actions to this end should include formation of a Malaria Advisory Committee or Working Group, identification of gaps in information needed to review the national policy on antimalarial drugs, development of specific operational and technical research to fill the information gaps, and coordination of resources (from government, external donors and interested parties including WHO and USAID, local NGOs) to carry out the research and the policy review process itself. The review process should include identification of other information (aside from that provided by formal treatment efficacy studies) which will be needed and development of particular operational research projects to provide that information. (Examples of such questions are compliance, cost, self-treatment behavior, parental recognition of malaria and response to severe symptoms, patterns of treatment-seeking, supply of alternative antimalarials, logistics, referral patterns, and the current knowledge of antimalarial drugs among practitioners.)

2. Interim treatment protocol

The consultants feel there is a clear need for an interim local policy in Chipata District to make an alternative antimalarial available at all levels of the health care system, either as a first- or second-line treatment for uncomplicated malaria. If the alternative antimalarial is used as a second-line treatment, the interim policy should establish clear guidelines for routine follow-up and assessment of patients after administration of CQ to identify treatment failures. Treatment protocols for use of the alternative antimalarial should also be developed and widely disseminated. Procurement and logistics systems should be established to provide an adequate supply of the alternative antimalarial.

The consultants base this recommendation not only on results from the initial CQ efficacy studies, in which 68% of children under 5 years of age experienced either a clinical or parasitologic failure of CQ therapy by Day 7, but also on the experiences of local clinicians and the obvious pattern of repeated attendance at health centers for unrelieved symptoms of malaria after CQ therapy. In the face of ineffective CQ therapy, clinicians have apparently devised their own

treatment protocols, many of which involve wasteful and potentially harmful use of antibiotics or suboptimal doses of other antimalarials. Clear guidance from the Ministry of Health would help to rationalize drug use in both public and private facilities in Chipata District.

The interim policy for Chipata District could be applied in other areas where significant CQ resistance is demonstrated over the course of the next several years.

3. Orderly sequence of sentinel site testing

A standard 14-day test of treatment efficacy should be implemented in identified sentinel districts on a defined schedule as part of a national network to test/monitor the efficacy of CQ and any other antimalarial drug selected for first- or second-line treatment of uncomplicated malaria.

4. USAID support

USAID/Zambia through the ZCH Project should continue to support routine testing/monitoring with 14-day antimalarial efficacy studies. The 1995 level of support for this bridging activity from EHP and CDC should be replicated in both 1996 and 1997.

The assistance should support further expansion of the monitoring network to Southern and Lusaka Provinces and to Lundazi District of Eastern Province in January-February 1996, and to Central and Western Provinces in January-February 1997. The technical assistance should include initial training with Zambian colleagues of teams at new sites, brief refresher training of previously trained local teams, provision of supplies and equipment not locally available, partial support for local transport and other expenses, and support for seminars and meetings to discuss issues surrounding antimalarial drug policy.

5. Training

Training priorities should be set to strengthen or improve diagnosis and treatment of uncomplicated malaria as well as identification and appropriate further treament of cases not responsive to CQ. Training priorities also need to be set to incorporate microscopy to a greater degree in the management of uncomplicated malaria.

6. Interagency seminar and collaboration

A national seminar or meeting should be convened as soon as possible to identify and explore the critical issues concerning malaria drug policy outlined below (section 3.2). Participation of relevant Ministry of Health, private sector, NGO and donor partners, including USAID=s ZCH Project, should be assured.

Close cooperation and coordination should be sustained between the WHO, which has a long-standing and important role in malaria control in Zambia, and USAID, which has a new but increasingly significant role in those activities. Lines of communication should remain open both between the two donor partners and between the Ministry of Health and each of the partners.

Similarly, cooperation among all partners active in malaria control in Zambia, including UNICEF, JICA, and the NGOs, should be encouraged. Communication and coordination through an Integrated Malaria Advisory Committee or Working Group is recommended.

7. Alternative drug therapies

One critical issue which must be addressed by the Malaria Advisory Committee or Working Group is regulation of newly available antimalarial drugs, such as artemisinin. Premature or inappropriate use of these drugs

can reduce their future effectiveness. While they should be available for investigation by research institutions such as TDRC and University Teaching Hospital (UTH), Lasaka, wider availability should be decided on scientific and policy grounds rather than through commercial or economic interest. The Malaria Advisory Committee will need to identify the regulatory and financial constraints to implementation of a revised national drug policy on antimalarials and formulate a stratgey to overcome those constraints both in the short-term and in the longer future term.

Additionally, this group should address and advise on issues of the availability of antimalarials at the various levels of the health care system and in the community. For example, it was noted during this consultancy that because sulfadoxine/pyrimethamine was not readily available to health care providers, cotrimoxazole was often used to treat resistant or recurrent malaria infections. While this is a very resourceful response to the lack of a second-line antimalarial drug, overuse or misuse of cotrimoxazole for malaria therapy may, over time, have deleterious effects on both its usefulness for treating pneumonias as well as on the future usefulness of sulfadoxine/ pyrimethamine, a drug with a similar chemical composition.

8. Integration with primary health care policy and practices

Malaria control activities should be more closely integrated with other primary health care elements, particularly at district, health center, and community levels. This integration should be applied to development of technical guidelines for district planning, current efforts to revise the HMIS, integrated preventive and case management strategies, and training. Clearer definition of malaria prevention and treatment at each level is needed within the minimum package of health services. (A strategy for encouraging appropriate household management of uncomplicated malaria should be part of this package.) Explicit reference to diagnostic elements, including microscopy, and therapeutic agents**C**e.g., first- or second-line antimalarials**C**should be included.

9. USAID=s role through the Zambian Child Health Project

The support of the ZCH Project for pre-service and in-service training of health center staff should explicitly address the need to upgrade skills in malaria microscopy, clinical diagnosis of malaria, and outpatient management of uncomplicated malaria. Technical assistance to the drug efficacy monitoring system could offer some upgrading of these skills through interaction with key instructors at Chainama Hills College of Medical Sciences and UTH and during the training in testing methodology. However, the training component of the ZCH Project should develop a more systematic and integrated approach to ugrading these important skills.

3.2 Discussion: A Rational Approach to National Malaria Treatment Guidelines

A rational approach needs to be used in conducting a complete evaluation of national malaria treatment guidelines. A conceptual model for such an approach is being developed for use by sub-Saharan African countries that are or soon may be facing the need for revision of malaria treatment policy. The process begins with recognition at the national level that there is a problem with the current guidelines, frequently exhibited by a growing impression by medical practitioners and patients of an increasing frequency of treatment failures. Countries with well-developed health information systems may recognize increases in admissions or deaths attributed to malaria or increases in pediatric blood transfusions. This is followed by the

collection of baseline information using established, standardized methods with which to verify this impression.

Very early in this process, a meeting should take place involving national policymakers, practicing physicians or clinical officers, university or research center staff who are working on malaria within the country, representatives of governmental and nongovernmental agencies involved with the health sector, and appropriate members of the private sector (such as representatives of pharmaceutical concerns). The primary purpose of this meeting would be to review the existing data and define as specifically as possible the goals of malaria therapy (i.e., what is expected on a national, regional, or individual level of malaria therapy with regard to resolution of the acute illness, duration of clinical response, ability to resolve malaria-associated anemia, ability to interrupt the progression of illness towards severe disease or death). The usefulness of these goals of therapy would lie in their ability to provide an objective measure by which to judge existing therapy guidelines; without such a measure, the decision of whether a particular therapy option does or does not Awork@ becomes problematic and prone to either belated or premature changes. Once these goals of therapy are articulated and agreed upon, the assembled experts can identify what additional information is needed for decision making, decide on standardized methodologies to be used to collect that information, allocate responsibility for the collection of the information, define the time-line for data collection, and coordinate resources.

A period of data collection and operational research should follow such a meeting. Using the new data and information collected, the current malaria treatment guidelines would be reevaluated against the previously defined goals of therapy (i.e., does the currently recommended first-line malaria therapy meet or exceed the stated standards and goals of therapy or not). Rational, informed decisions can then be made about the appropriate response and actions to be taken.

Experience in other countries suggests that, even when a less formal approach is taken, it can take several years to decide upon and implement a change in malaria treatment policy. Conducting the required operational research, training medical staff and developing the necessary training materials, organizing the logistics of purchase and distribution for the new drug, and patient education, for example, all take considerable time. If a change in therapy policy is anticipated, a minimum of two to three years before complete implementation must be expected.

A number of options for addressing increasing chloroquine resistance stop short of total nation-wide abandonment of CQ. If research indicates that CQ resistance is approaching, but not yet exceeding, tolerable limits, operational improvements in early identification of chloroquine failures can be made. Although most countries have written policies concerning the proper use of second-line malaria therapy, frequently patients with believable histories of repeated CQ treatment failure are placed yet again on CQ, often due to lack of available therapeutic alternatives or lack of understanding or initiative on the part of the health care provider. In areas of subcritical CQ resistance, improved patient access to second-line therapy might decrease the burden of illness due to CRPf while still making CQ available as a first-line therapy. This latter approach, however, must be implemented in a way that assures the proper training of staff and the ready availability of and access to the the second-line drug at all levels of health care; realistically, anything less than this would be equivalent to no change at all.

If research suggests that intolerable levels of CRPf are associated with geographically defined areas, a targeted approach can be applied in which first-line therapy is changed only in those areas that need it. Continued surveillance of CRPf could then be used to monitor the needs in other areas, and changes in first-line therapy phased in to other areas of the country when and if needed.

This might be an appropriate response to the situation in Chipata, if further research suggests that that district is more the exception than the rule with regard to CRPf.

Finally, whether a total change in first-line malaria therapy is required or not, continued monitoring of malaria therapy efficacy, using standardized methodology and rigorous quality control, is essential. Whatever the first-line therapy, whether it is continued use of CQ, targeted use of SP, or total switch to SP, there will be a continued need to assess its efficacy periodically and judge it against defined goals of therapy. The reality of the malaria situation in most of the world today is that it is highly unlikely that any antimalarial drug will have an unlimited useful lifespan. If CQ is replaced by SP as the first-line therapy for malaria, there will be a continued need to monitor the efficacy of SP in order to recognize and address in a timely fashion the advent and intensification of SP resistance. Although many are concerned with what seems to be a future of constantly switching from one drug to another in the face of developing resistance, the only alternative at present is to continue using a drug of known inefficacy and face a future of increasing incidence of illness and death associated with treatment failures due to CRPf.

In summary, this first of a number of investigations into the efficacy of malaria therapy in Zambia has identified a serious problem at one site in Eastern Province. While more data are clearly needed to ascertain the national distribution of CRPf and the intensity of resistance in other regions of the country, the information derived from this study supports the need to begin the process of formally addressing CQ resistance and moving toward replacing CQ as the drug of choice for nonsevere malaria, at least locally, if not nationally.

4 TECHNICAL ASSISTANCE ACTIVITIES IN 1996

4.1 Background

As mentioned in earlier chapters, initial steps in monitoring antimalarial drug efficacy were taken during 1995. WHO and USAID agreed to provide funding for baseline data collection. Sites were selected in 11 geographically distinct regions of the country (see map and Table 1) for such testing. During May-July 1995, testing for CQ and SP efficacy was conducted in Chipata (Eastern Province) and testing for CQ alone was conducted in Katete (Eastern Province) using a modified WHO, 14-day *in vivo* test. A full description of the methods and findings is given in Appendix B. In brief, these studies demonstrated 68% RII/RIII resistance to CQ in Chipata and approximately 25% RII/RIII resistance to CQ in Katete. Clinical failure rates to were 24% in Chipata and 23% in Katete. Additional testing was carried out during January 1996 in Mpongwe (Copperbelt Province) by a team from the NMCC and TDRC. As of the writing of this report (August 1996), results of the testing were not yet available.

The objectives of the 1996 consultancy were to continue the training of staff at NMCC and selected District Health Management Teams (DHMTs) in the conduct of antimalarial drug efficacy testing and to carry out testing at four additional sites: Lundazi (Eastern Province); Choma (Southern Province) and two sites in Lusaka Province. The reason for selecting two sites in Lusaka Province was to compare CQ efficacy in a rural and an urban setting.

In the course of the work in 1996, the urban Lusaka site (Chipata Clinic, Chipata Compound) was dropped because of insufficient numbers of locally acquired malaria infections, and two additional sites were added for testing and training: Mansa District (Luapula province) and Isoka District (Northern Province).

In total, testing at five sites was completed during the EHP/CDC 1996 activity (see Table 1). Together with the sites studied in 1995, there are now data on the efficacy of CQ in most areas of Zambia. The NMCC, with WHO support, hopes to complete further studies in Sesheke (Western Province) and in Mwinilunga (Northwestern Province) in the coming months (anticipated as the end of 1996). With these two sites, testing will have been completed in a total of 10 sites in 8provinces of Zambia by mid-1996.

4.2 Training Provided

All of the following persons have been trained in the conduct of antimalarial drug efficacy testing and have sufficient first-hand experience at one or more sites in Zambia that they could conduct such studies with minimal supervision:

Mr. Simon Nkunika, Scientific Officer, NMCC
Mr. Wambiji Kapelwa, Scientific Officer, NMCC
Mr. Matias Lazao, Microscopist, NMCC
Mr. Daka Nguluwe, Microscopist, NMCC

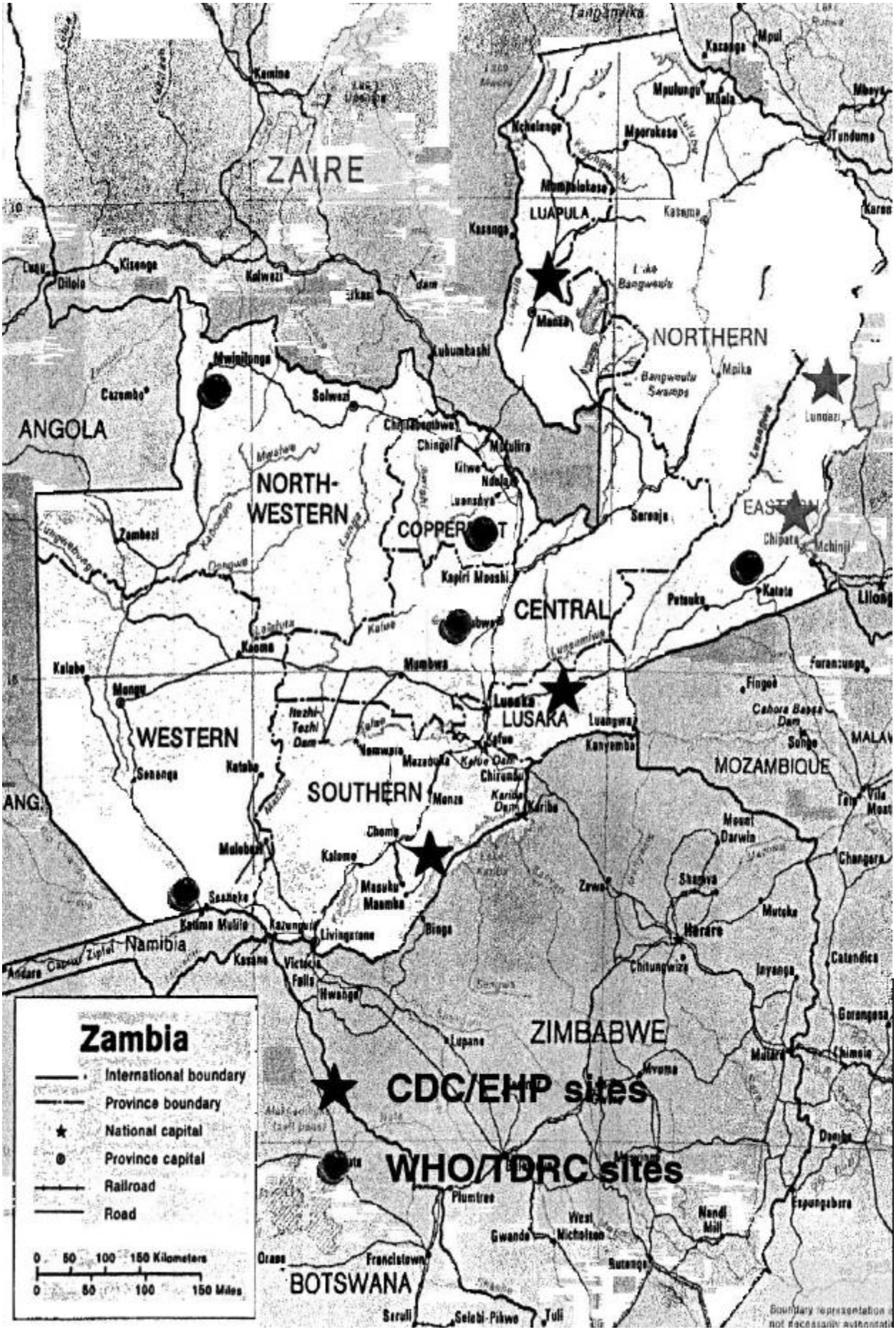
ZAIRE
ANGOLA
ZIMBABWE
BOTSWANA
Namibia
MOZAMBIQUE
MALAWI
NORTHERN
LUAPULA
NORTH-WESTERN
COPPERBELT
CENTRAL
LUSAKA
WESTERN
SOUTHERN
EASTERN
Zambia
International boundary
Province boundary
National capital
Province capital
Railroad
Road
0 50 100 150 Kilometers
0 50 100 150 Miles
CDC/EHP sites
WHO/TDRC sites

TABLE 1
Choloroquine Testing Sites

Province	Sites	Status
Eastern Province	Katete District	CQ testing alone, conducted by NMCC/WHO team in 1995
	Chipata District B Kapata Clinic B Prison=s Clinic	CQ and SP testing completed in 1995 by EHP/CDC team
Copperbelt Province	Mpongwe	NMCC/WHO team conducted tests Jan. 1996
Eastern Province	Lundazi	testing in 1996 by EHP/CDC team - completed
Southern Province	Choma	testing in 1996 by EHP/CDC team - completed
Lusaka Province	1) Chipata Clinic (urban)	Study dropped - insufficient numbers
	2) Chongwe (rural)	testing in 1996 by EHP/CDC team - completed
Laupula Province	Mansa District	testing in 1996 by EHP/CDC team - completed
Northern Province	Isoka District	testing in 1996 by EHP/CDC team - completed
Western Province	Sesheke	testing by NMCC and WHO pending (as of late 1996)
Northwestern Prov.	Mwinilunga	testing by NMCC and WHO - completed

Mr. Kingsley Lapukeni, Laboratory Technician, Chipata General Hospital
Ms. Charity Malwamba, Environmental Health Inspector, Lundazi
Dr. C. Sichone, Choma General Hospital
Mr. James Chipipa, Scientific Officer, Tropical Disease Research Centre, Ndola
Dr. Petra Wiersma, UTH
Mr. Gordon Kakubo, Senior Clinical Officer, Chongwe District Health Mgmt. Team
Mrs. Frida Chaava, Laboratory Technician, Chongwe Health Center
Mr. Wilson Manda, Clinical Officer, Mansa General Hospital
Mr. J. Serenge, Laboratory Technician, Mansa General Hospital

Given the field experience gained during this trip and 1995 testing at Chipata and Katete, at least three very experienced teams can be formed of staff at the NMCC and TDRC. These teams would consist of Mr. Nkunika, Mr. Kapelwa, Mr. Lazao, and Mr. Nguluwe (NMCC) and Dr. Modest Mulenga and Mr. Chipipa (TDRC).

4.3 Discussion of Findings from 1996 Study

With the completion of antimalarial drug efficacy testing in Chipata, Katete, Mpongwe, Lundazi, Choma, Chongwe, Mansa,and Isoka, it is now possible to map CQ resistance in almost all areas of Zambia. When data from Sesheke and Mwinilunga in Western and Northwestern Provinces are available, a complete picture will emerge. Considering that testing began only in 1995, this is a remarkable achievement for the NMCC and its colleagues at TDRC together with donor partners. The standardized protocol as well as the training and experience gained by this work will enable the development of a surveillance and monitoring network to examine the efficacy of both current and future first-line antimalarial drugs. In addition, this information will form a strong foundation for antimalarial drug policy discussions.

Rates of moderate to high-level (RII/RIII) parasitologic failures and clinical failures after treatment with CQ have now been documented at all sites studied in Zambia. From one-third to one-half of children treated with CQ demonstrated RIII (high level) or RII (moderate) parasitologic resistance. Most sites had rates of RIII/RII failures of approximately 50%, including sites in Eastern, Copperbelt, Lusaka, Northern, and Southern provinces. Although fever resolved over the first three days in the majority of children treated with CQ, this response did not correlate with ultimate clinical outcomes. From one-quarter to one-half of children treated with CQ were classified as clinical failures, that is, children with persistent or recurrent fever and parasitemia after treatment during the 14-day follow-up period.

In Chipata District (1995) and Lundazi District (1996) where SP was also evaluated, findings indicate the superior antimalarial efficacy of this drug. Only one child at each site failed clinically to SP. In contrast, clinical failure rates wtih CQ were 24% in Chipata and 33% in Lundazi. All but one child treated with SP in Chipata and two children treated in Lundazi had negative blood smears by the fourteenth day after treatment.

Based on these findings, consideration should be given to modifying the current national antimalarial drug policy for the outpatient treatment of *P. falciparum* infection. There are several possible options for how the Zambian Ministry of Health (MOH) might implement such a change. CQ could be continued as the first-line agent and SP used for children who fail initial therapy. Alternatively, CQ could be replaced by SP as the first-line agent for children and pregnant women. The Ministry of Health could also consider a phased-in change to SP in certain provinces or districts, based on the level of failures in each area. Finally, a nationwide change to SP as the first-line agent for treatment of all uncomplicated malaria infections in Zambia could be implemented.

Although parasitologic responses to SP were superior to those with CQ, the mothers of some of the children treated with SP expressed concern about the apparently slower clinical response, as manifested by persistance of fever up to 48 hours after treatment. This suggests that appropriate educational messages for mothers should be developed so that they will be prepared for a slower clinical reponse to SP and that the use of antipyretics along with SP be considered by health care providers.

With the exception of Chipata District where studies were carried out in the dry season of 1995 and urban Lusaka (Chipata Clinic, Chipata Compound), high rates of parasitemia (> 70%)

were demonstrated in febrile children under five presenting to outpatient facilities. These findings have significant implications for implementation of Integrated Case Management protocols in Zambia. Even children presenting with other possible reasons for fever were often parasitemic and required antimalarial treatment in addition to treatment for other conditions.

Although anemia was not formally assessed as part of these studies, a review of hospital records from both Lundazi and Mansa Hospitals indicates that about four or five children with hemoglobins less than 5 mg/dl are admitted for transfusion daily. Current or recent malaria infection is often implicated as an underlying cause of severe anemia in these children. Additional information is needed on the prevalence of severe anemia in Zambia and on the impact of different antimalarial regimens on the resolution of anemia.

Several practical outcomes related to these studies should be noted. First, Zambia now has two teams at the NMCC and one at TDRC capable of independently carrying out drug efficacy studies. Each of the district-level study sites also has several staff members trained to work with the national team. These trained personnel at the national and district level can form the nucleus of a surveillance network. Second, conducting the 1996 studies during the rainy season, when transmission of malaria is higher, was a much more efficient use of resources and personnel, compared to the timing of the 1995 studies. Third, the use of small incentives for mothers (e.g. a Polaroid photo, a bag of sugar, and a bar of soap) is clearly an effective and inexpensive way to increase compliance with scheduled follow-up visits. Few patients required follow-up in their homes in 1996, resulting in a significant savings of fuel and time. The study team recommends use of such incentives in future drug efficacy studies requiring multiple return trips to the clinic. Finally, the presence of the study teams in the participating health facilities over the course of the drug efficacy testing has led to improvements in several skills of health care workers related to the diagnosis and treatment of fever, including malaria microscopy and more accurate measurement of temperature and respiratory rates.

4.4 Follow-on Activities

Copies of the primary data, both paper and electronic, have been left with NMCC staff, who were trained in statistical analysis using EPI INFO 6.0 in 1995.

Dr. Himonga, Director, NMCC will be convening a meeting of Ministry of Health staff, technical advisors from WHO, CDC, and EHP, and other interested parties to discuss the complete findings from the 10 study sites and consider options for changes in national antimalarial drug policy in late July 1996. Another product of this meeting should be a detailed plan for ongoing routine monitoring of malaria drug efficacy in Zambia.

The 1996 work revealed several minor clarifications and improvements which were needed in the study protocol. These were discussed with EHP and a revised protocol produced. (This version appears as Appendix A.) Revisions included altering the daily task charts to flow charts, clearer language in the definitions of parasitologic and clinical failures, and additions to the daily task list for Day 3.

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APPENDIX A

A STANDARD PROTOCOL FOR ASSESSING AND MONITORING MALARIA THERAPY EFFICACY IN ZAMBIA

Revised 30 August 1996

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Annexes

I Criteria for Diagnosis of Severe Malaria (from WHO 1986)
II Checklist of Daily Activities and Decision Points
III Definitions
IV Informed Consent
V List of Minimum Necessary Inputs per 60 Patients Enrolled: Supplies and Equipment
VI Patient Record Form
VII Wall Charts

I. SUMMARY

A standardized protocol has been developed to assess the efficacy of antimalarial therapy in Zambia and to provide the basis for establishing a network of sentinel sites to monitor changes in malaria therapy efficacy over time. The purpose of this protocol is to allow the collection of standardized data which can be compared between geographic areas and over successive years. Although the protocol has been developed specifically to test chloroquine (CQ) and sulfadoxine/ pyrimethamine [SP or Fansidar**7**] therapy efficacy, it can easily be modified to assess any antimalarial drug which might be used as first- or second-line therapy in Zambia.

In brief, children less than 5 years of age will be randomly assigned to be treated with either CQ or a highly effective, alternative antimalarial (e.g. sulfadoxine/pyrimethamine or quinine). Clinical, parasitologic, and hematologic parameters will be monitored over a 14-day follow-up period and will be used to evaluate drug efficacy.

II. BACKGROUND AND RATIONALE

The impact of malaria on the health and economic development of human populations is greatest in the tropics and sub-tropics (1). In Africa alone, the World Health Organization (WHO) has estimated that more than one million children under the age of five die annually from malaria.

In their efforts to reduce malaria morbidity and mortality, many countries in sub-Saharan Africa have adopted a malaria control policy that relies primarily on prompt and effective treatment. For the past 30 years, CQ has been the drug of choice for the treatment of malaria throughout Africa, based upon its rapid action, efficacy, safety and low cost relative to other antimalarials.

Chloroquine-resistant *Plasmodium falciparum* (CRPf) malaria was first reported from Kenya and Tanzania in 1978/79. Since then, it has spread from east to west throughout most of sub-Saharan Africa. In most areas of East Africa, high levels of resistance to CQ are common. A recent study conducted at a district hospital in western Kenya showed that, among children less than 3 years of age treated with CQ at a dose of 25 mg/kg, 50% had an RII parasitologic response and 25% had an RIII parasitologic response. Similar rates of resistance were observed in studies conducted in Malawi during the same period (Bloland et al, Bloland unpublished data). The prevalence and distribution of CRPf has not been well characterized in other areas of sub-Saharan Africa, but this information is essential for developing treatment policies aimed at preventing severe disease and death.

Even when malaria parasites are not cleared from the blood after treatment with CQ, patients typically respond clinically, with resolution of fever and improvements in activity level and appetite. It is unclear, however, whether clinical improvement with incomplete parasitological cure can be considered an adequate therapeutic response in all patients. Studies conducted in coastal areas of Kenya have shown that in spite of an initial clinical improvement, about 20% of children treated with CQ returned with a malarial illness within 2 to 3 weeks and required further therapy. In western Kenya, it was found that while 83% of febrile, parasitemic children improved clinically within 48 hours of treatment with CQ (as measured by a decrease in axillary temperature to $< 37.5^{o}C$), 60% experienced a reappearance of symptoms within 14 days of therapy, and 90% failed clinically within 28 days. Similar results have been obtained in studies conducted in Malawi.

Of great concern is the fact that hematologic recovery among anemic children treated with CQ may be incomplete. The previously mentioned studies in Malawi and Kenya have demonstrated that the increase in hemoglobin concentration among anemic children treated with an effective antimalarial drug, such as sulfadoxine- pyrimethamine (SP or Fansidar**7**) was greater and occurred earlier when compared to increases experienced by anemic children treated with CQ. Although a causal relationship has not yet been shown, it is possible that much of the severe anemia associated with *P. falciparum* malaria in Africa and the high mortality associated with that anemia is due to repeated, ineffective therapy with CQ. Unpublished data from a study of malaria and anemia in early childhood in western Kenya indicate that mean hemoglobin concentrations associated with persistent malaria infections, such as might occur with inadequate therapy, were significantly lower than the mean hemoglobin levels associated with either recently cleared infections or new infections (Bloland, unpublished data).

An additional problem is that, because of the ready availability of CQ in the community, many children with febrile illnesses believed to have malaria have been treated before going to a dispensary or health center. As a result, many patients seen at health centers have already used CQ and may, therefore, already have experienced therapy failure or are infected with malaria parasites that have been exposed to sub-therapeutic concentrations of CQ.

These observations raise concern about the continued use and efficacy of CQ for the treatment of malaria in sub-Saharan Africa. Although most of this information has been obtained in equatorial regions of East Africa, where drug resistance is known to be intense, similar concerns have been raised regarding the efficacy of CQ in areas where CRPf appears to be intensifying, as well as in areas where relevant data are too limited to resolve this issue.

It is now recognized that in vitro assessment of malaria parasite resistance and categorization of resistance levels based on in vivo evaluations with short duration follow-up (e.g. 7 days) do not adequately assess malaria therapy efficacy. More emphasis needs to be placed on the clinical status of the patient at the time of treatment and on the chronic effects of malaria parasitemia, particularly anemia.

Relevant parameters that have been used to assess malaria therapy efficacy include initial clinical response among febrile patients, parasitologic response, duration of clinical improvement, and hematologic response among anemic children. Initial clinical response is measured as the proportion of initially febrile patients who are afebrile within 48 to 72 hours after treatment. Measurement of parasitologic response follows the modified WHO classification scheme of RIII/RII/RI/S. By extending the follow-up period to 14 days post-treatment, the duration of clinical response (the proportion of patients responding initially that become ill again within 14 days) can also be assessed. In the context of assessing antimalarial therapy efficacy, hematologic response is best measured using a comparative trial; the change in hematologic status after CQ therapy compared to the change after treatment with an antimalarial known to be effective, such as SP.

Malaria in Zambia is recognized as one of the leading causes of morbidity and mortality, especially among young children and pregnant women, and accounts for more outpatient visits and hospital admissions than any other disease. In 1994, over 3 million cases of malaria were reported in Zambia, a rate of 356 per 1000 population. The case fatality rate among children < 5 years of age since 1990 has ranged from 21/1000 to 48/1000. CQ is currently the drug of choice for the treatment of malaria in Zambia.

Although numerous studies to document the occurrence and measure the prevalence of CRPf malaria have been conducted in Zambia, it is difficult to compare their results because of the lack of a standardized methodology. This may account for the wide ranges of CRPf reported. For example, studies conducted between 1992 and 1994 indicate that between 8% and 39% of *P. falciparum* infections are CQ resistant. Moreover, since these studies were conducted among asymptomatic school-age children, the ability to extrapolate these findings to the population at greatest risk of malaria illness, children < 5 years, is limited.

To address concerns regarding the current therapeutic efficacy of CQ in Zambia, a systematic evaluation using standardized procedures was initiated by the Ministry of Health in 1995 in multiple sites throughout the country. The findings of these CQ efficacy trials will allow the Ministry of Health to evaluate and update their current national antimalarial treatment policy. At the same time, some of the sites will be selected for the implementation of ongoing surveillance of CQ efficacy. This will permit the Ministry of Health to rapidly identify any significant changes in drug efficacy that occur and to make appropriate adjustments to national antimalarial drug policy in a timely fashion.

This document describes in detail the procedures to be used in assessing the therapeutic efficacy of CQ at sites throughout Zambia. Since some degree of CQ resistance is expected, procedures are also included for comparing the efficacy of CQ with SP, the most suitable alternative drug.

III. OBJECTIVES

1. To assess, at selected sites throughout Zambia, the therapeutic efficacy of CQ and SP for uncomplicated *P. falciparum* infections among children, based on parasitologic, clinical, and hematologic parameters.

2. To develop standardized procedures that can be applied by the Ministry of Health to assess the efficacy of antimalarial chemotherapeutic agents in patients with non-severe disease attending health facilities.

IV. METHODS

A. Selection of Study Sites

Study sites should be selected on the basis of the criteria outlined below:

1. Geographic distribution. Sites should be selected representing the major geographic regions of the country**C**eastern, northern, central, southern, and western. Since CQ resistance has been spreading from east to west in sub-Saharan Africa during the last 15 years, it is likely that the highest levels of resistance will be found in the eastern region.

2. Availability of adequate numbers of children < 5 years of age with symptomatic, uncomplicated *P. falciparum* malaria. This is dependent upon local factors such as the seasonality of malaria transmission and the size of the patient population attending the health facility where the study will be conducted. Because most information regarding malaria seen at health facilities is based upon clinical diagnosis, which can greatly overestimate the true incidence of malarial illnesses, final site and health facility selection should be based on blood smear and hematocrit (or hemoglobin) surveys conducted at the

potential site during appropriate times of the year. In most cases, this can also be accomplished by spending 1-2 days conducting blood smear and hematocrit surveys in 25-50 children in several prospective facilities in the selected areas immediately before choosing the best site and beginning the formal drug efficacy testing. Besides ensuring that the best possible sites and facilities are selected, such preliminary work will allow more reliable estimates of the time needed to conduct the study, as well as the anticipated cost. For example, if a clinic can provide 10 patients meeting the inclusion criteria per day, enrollment will take 10 days for the full protocol (including SP comparison) or 5 days for the partial protocol (chloroquine only). If, however, a clinic can only provide 5 patients meeting inclusion criteria per day, the enrollment period will be doubled and the overall length and cost of the activity increased.

3. Willingness of the District Health Management Team and the health facility staff to participate in the trial and to support the work with laboratory space, access to the patient population, and availability of staff members who can participate in and take responsibility for conducting the trial. This will be especially important if the site is to become part of a permanent sentinel surveillance system for antimalarial drug efficacy in Zambia.

B. Clinical Team

A minimum of three clinical staff are needed to conduct the trial: a physician or clinical officer to obtain clinical histories and carry out examinations; a nurse to administer the study medications and provide patient instructions; and a laboratory technician to take blood smears and blood samples for hematocrit (or hemoglobin) determinations, and to examine and count the blood smears. A fourth person, who has prior experience with the protocol, is needed to serve as study site supervisor. This person=s role would be to monitor patient flow to ensure that processes are running smoothly and to assist with clinical tasks when necessary.

Since the clinical team will almost always be made up of members who have not had previous experience with antimalarial drug efficacy testing, it is a good practice to provide the clinical team and other interested health facility staff with an overview of the rationale, goals, and logistics of the study. To ensure standardization of data collection, it is best to maintain the same team members throughout the course of the trial.

C. Criteria for Enrolling Patients

Patients to be enrolled in the trial must meet the following criteria:

1. They must be < 5 years of age.

2. They must have a documented fever (axillary temperature $37.5^{o}C) in the absence of another obvious cause of fever (such as pneumonia, measles, otitis media) or other serious or chronic medical condition (heart failure, sickle cell disease).

3. They must have an unmixed infection with *P. falciparum* of between 2,000 and 250,000 asexual parasites/mm^3 as determined by microscopic examination of thick, or thick and thin peripheral blood smears. Both thick and thin blood smears are useful in sites where non-falciparum malaria is common to aid in identifying pure *P. falciparum* infections.

4. They must have a hemoglobin concentration between 5 g/dl and 8.0 g/dl inclusive (hematocrit between 15% and 24%). (NOTE: If anemia does not appear to be prevalent in the population at the time of the trial {less than about 40% of children with hematocrit or hemoglobin levels fulfilling the above criteria}, this criterium for enrollment should be dropped).

5. They must not have any evidence of severe or complicated malaria (e.g., cerebral malaria) that would require hospitalization for treatment.

6. The parent=s or guardian=s informed consent and willingness to participate in the study must be obtained.

NOTE: Previous use of CQ for the child=s current illness or a positive urine test for CQ are NOT reasons for eliminating the child from enrollment.

D. Number of Patients to Be Enrolled (Sample Size)

An adequate number of children should be enrolled to ensure 50 patients in each of the two drug arms (CQ and SP) at the completion of the trial. In most cases a 10%-15% drop-out rate can be expected during the course of the trial, so 60-65 patients should be enrolled per arm. This number should be sufficient to estimate the prevalence and intensity of CQ resistance, as well as to observe a difference between CQ and SP with regard to changes in hemoglobin level (based on data from previous studies of this type and a 5% level of significance with 80% power). If anemia is not a common complication of malaria infection in the area (such as in areas where malaria transmission is not intense or during low transmission season), it may be best to drop the SP comparative treatment group, thereby reducing the number of patients required for the study. Additionally, the sample size should be adjusted to meet the local epidemiologic situation, if initial data suggest that a sample size of 50 in each treatment group will be inadequate, or if a larger number than usual of losses to follow-up are anticipated.

E. Screening Procedures Before Enrollment (see Annex II)

Since many of the children who come to the health facility for medical care will not be suitable for enrollment into the trial (afebrile, no parasites in the blood, etc.), a rapid screening procedure is needed to identify those children who will be eligible for enrollment. This should be done in the following fashion:

1. For all children < 5 years of age who come to the health facility, an axillary temperature should first be obtained. To obtain an accurate reading, the thermometer should be placed well up in the axilla and the child=s arm held against his/her chest. (NOTE: TEMPERATURES LESS THAN 36.0°C SHOULD BE REPEATED).

2. If the temperature is $37.5°C, the child should be assigned a consecutive screening number (beginning with 001). If the child meets the enrollment criteria and takes part in the trial, this screening number will become the patient=s study number and should be used to identify all forms and blood samples from that child. If more than one site is used in the same district (e.g. in order for the sample size requirements to be met, two health clinics are enrolling patients), then the study number should be preceded by a single letter to identify at which site the child was enrolled. For example, a child enrolled at Clinic A might have a study number of A103, while a child enrolled at Clinic B might have a study number of B012. This will allow both district-level as well as site-specific analyses.

3. For each febrile child a card should be filled out containing the screening number, date, and the patient=s name, age, sex, and measured axillary temperature. This will allow appropriate tracking of each patient though the screening procedure. If the patient is enrolled, this card will also serve as an appointment card, to be brought by the mother to each follow-up visit.

4. A thick blood smear and a blood sample for hemoglobin or hematocrit determination (if the hematologic response to therapy is to be assessed) should be obtained by fingerprick. All specimens should be labeled with the study number and the date of the test.

5. Screening blood smear: This blood smear should be stained rapidly with 10% Giemsa stain for 10 to 15 minutes. The slide should be quickly assessed for the presence of malaria parasitemia and an estimate of the parasite density made by counting the number of asexual parasites and the number of white blood cells in a limited number of fields. Adequate parasitemia for enrollment requires at least 1 parasite for every 4 white blood cells (approximately 2,000 asexual parasites/mm^3). NOTE: Smear preparation and staining quality are extremely important technical aspects; reliable parasite counts ***cannot*** be made from poorly prepared or stained blood films. Common problems include grease and/or debris from poorly cleaned slides and fingers, stain debris from unfiltered Giemsa, thick smears that are too thick and wash off in the stain, unruptured red blood cells from being fixed either by alcohol left on the finger or overheating while drying, and over- or under-staining. Staining times and concentrations given in this protocol should be considered as guidelines and should be altered as needed to consistently produce well stained blood films.

6. If anemia is to be studied, the hemoglobin or hematocrit measurement should be carried out at the same time as the initial screening blood smear. Enrollment requires a hemoglobin of 5.0 g/dl - 8.0 g/dl or a hematocrit of 15% - 24%.

7. If the child meets ALL of the enrollment criteria (see Section IV B), his or her parent/guardian should be asked for consent to participate in the trial.

If more than enough children who meet the enrollment criteria attend the health facility each day, it may be best to limit screening to those children who come from villages within 15-20 minutes drive of the health facility. This will reduce the time and expense of follow-up of patients who live in distant villages.

F. Enrollment Procedures (Day 0)

Once consent to participate in the trial is obtained from the child=s parent or guardian, the following steps should be followed:

1. A standardized 2-page case record form (Annex VI) should be completed on each patient. The first page of this form has spaces for the patient=s name and study number, the date, general information about the patient and his/her family, the patient=s primary symptoms, history of medication use, and physical examination and laboratory findings. (NOTE: The location of the family=s house is particularly important in case a patient misses a scheduled appointment, he/she will have to be

followed up in his/her home village). The second page of the case record form has spaces for the patient=s study number and weight, a table for recording the responses to daily clinical questions, temperature, respiratory rate, hematocrit or hemoglobin, parasite density, and daily dosages of CQ or SP. Once the child is enrolled in the trial, his/her study number should be used on all forms and blood samples from that patient.

2. The child=s body weight should be measured, using a Salter scale or some other hanging scale for weighing young children, and recorded on both pages of the case record form.

3. A repeat thick smear should be obtained from the patient to verify the presence of parasites and to conduct a formal parasite count. This smear should be stained with 2-3% Giemsa for 45 to 60 minutes. To obtain the final calculation of parasite density, the number of asexual parasites (excluding gametocytes) and the number of white blood cells (WBCs) in successive fields are counted until either 300 WBCs are counted or 1000 parasites. The following formula is then used to obtain the parasite density per cubic millimeter of blood:

$$\frac{\text{(No. of asexual parasites)} \times 8000}{\text{(No. of WBCs)}}$$

where 8000 is an estimate of the number of WBCs per mm^3.

It is good practice for two people to review and count independently each blood smear, at least until it is clear that all microscopists on the clinical team are uniform and consistent in their counts. It is also recommended that a second blood smear be obtained, which can be left unstained in case there are problems with the initial smear or the staining technique. See note on staining in section IV.E.5.

If the final Day 0 parasite count is less than 2000 (i.e., less than the preliminary count on the screening blood smear), the patient should be dropped from the trial after receiving his/her full course of antimalarial therapy.

4. Antimalarial Therapy: If CQ and SP are to be compared, a coin (or some similar two-sided object) should be tossed to determine which of the two drugs the patient will receive. If heads, the patient should be treated with CQ; if tails, with SP. If CQ alone is to be used, there is no need to randomize the patients.

CQ or SP should be administered orally in the following dosages:

a. CQ: 25mg base/kg body weight divided into single daily doses over 3 days: (10 mg/kg on the first day; 10 mg/kg on the second day; and 5 mg/kg on the third day). CQ syrup should be used if possible because it facilitates calculation of pediatric dosages.

b. SP: 25 mg/kg body weight of the sulfadoxine component (maximum 3 tablets) as a single dose. Alternatively, an age-based treatment scheme can be used, which reflects the way SP is generally used in practice (**3** tablet for children <1 year, **2** tablet for children 1 to 3 years, and 1 tablet for children $\geq$ 4 years of age). The tablets should be crushed in a small amount of water and the suspension agitated frequently during administration to the patient to be sure that the child ingests the entire dose.

ALL MEDICATION SHOULD BE ADMINISTERED UNDER OBSERVATION BY A MEMBER OF THE CLINICAL TEAM.

Medication should be administered slowly to ensure that the child swallows the entire dose. If the child vomits, a note should be made on the case record form for Day 0 and the medication readminstered after waiting for 20 to 30 minutes. Children who repeatedly vomit (more than twice) should be dropped from the study because proper dosing cannot be assured. An alternative agent must be given to children dropped from the study. On each child=s follow-up form, it should be noted whether or not each dose was successfully given.

NOTE: Special attention should be given to fever control, especially among patients being treated with SP (SP lacks the antipyretic effects normally seen with CQ treatment). Parents/guardians should be instructed in the use and application of tepid sponging, and patients should be given appropriate antipyretics (e.g. Panadol®) if judged necessary by the clinical staff. Failure to discuss this issue with parents/guardians and to adequately control fever during the initial 24 to 48 hours frequently cause parents/guardians to believe that the treatment is not working and can lead them to seek alternative treatment which may interfere with the study.

5. The parent/guardian should be given an appointment for the next day (Day 1) if the child is receiving CQ and for Day 3 if the child is receiving SP. Parents/guardians should also be reminded that they should return to the clinical team at any time during follow-up that the child=s clinical condition is perceived to be worsening or not showing signs of improvement.

Screening and enrollment of children should continue using the procedures described above until the required sample size is obtained. This will generally require 7-14 days for 60-65 patients. Since follow-up of those children who are already enrolled will be going on at the same time that new children are being enrolled, the clinical team must work closely together to avoid mistakes and complete activities in the most efficient manner possible. It has generally been found most efficient to enroll children every day of the week (including Saturdays, Sundays, and holidays) since some children will require follow-up on these days and the clinical team has to be available for them. This will also allow a greater number of children to be enrolled in a shorter period of time.

G. Follow-up Procedures

Ideally, parents/guardians will return to the health facility for each scheduled appointment. Patients receiving CQ should return on Days 1, 2, 3, 7, and 14. Patients receiving SP should return on Days 3, 7, and 14. A checklist of activities and decision points at these follow-up visits is given in Annex II and flow diagrams of the same activities in Annex VII. (NOTE: In areas where, based on Day 7 slide positivity rates, a high degree of drug resistance is suspected, then an extra visit for clinical evaluation on Day 11 can be added to provide a measure of patient safety. If there is little resistance indicated, then Day 11 visits can be omitted).

Small incentives, such as a bar of laundry soap, biscuits, or a packet of sugar, can be given to those families who return on Days 3, 7, and 14 to improve compliance for all follow-up visits. A particularly attractive incentive is a Polaroid® photograph taken of the mother and child on Day 0 that is promised to the

mother if she returns for all scheduled follow-up visits. The cost of most of these incentives is quite small and can result in considerable savings in time, petrol, and wear and tear on the clinical team and the study vehicle. If the patient does not return on the scheduled day, he/she will have to be followed up THAT SAME DAY in his/her village.

Day 1: The following should be done:

1. Obtain an axillary temperature and record result on case record form (Annex VI).

2. Complete Day 1 exam and questions and record results.

3. Administer Day 1 dose of CQ (10 mg/kg) under direct observation and record dose on case record form.

4. Check to see that all data have been correctly entered on the case record form.

5. Give parent/guardian appointment for next day (Day 2).

Day 2: The following should be done:

1. Obtain an axillary temperature and record result on case record form (Annex VI).

2. Complete Day 2 exam and questions and record results.

3. Take two thick blood smears; stain one rapidly, examine immediately, and calculate the parasite density. Based on the parasite density and temperature, the following decisions should be made:

   i. If the patient=s Day 2 parasite density $ his/her Day 0 density, the patient should be classified as a parasitologic failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

   ii. If the patient=s Day 2 parasite density $ 25% but < 100% of his/her Day 0 density **AND** the patient has a temperature $\geq$ 37.5°C **AND** the impression of the clinical staff is that the patient=s condition ***does not*** warrant immediate treatment with an alternate therapy, he/she should be treated with the final dose of CQ (if he/she is in the CQ group) and seen on Day 3. If the patient=s Day 2 parasite density $ 25% but < 100% of his/her Day 0 density **AND** the patient has a temperature $\geq$ 37.5°C **AND** the impression of the clinical staff is that the patient=s condition ***does*** warrant immediate treatment with an alternate therapy, the patient is classified as a clinical failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

   iii. All other patients should remain in the trial and the parent/ guardian given an appointment for the next day (Day 3).

3. Administer Day 2 dose of CQ (5 mg/kg) under direct observation and record dose on case record form.

4. Check to see that all data have been correctly entered on the case record form.
5. Stain the second blood smear slowly and recount parasites/WBCs and calculate parasite density. Enter result on case record form for Day 2.

Day 3: The following should be done:

1. Obtain an axillary temperature and record result on case record form.

2. Complete Day 3 exam and questions and record results.

3. Take two thick blood smears; stain one rapidly, examine immediately, and calculate the parasite density. Based on the parasite density and the temperature, the following decisions should be made:

   i. If the patient=s Day 3 parasite density $ 25% of his/her Day 0 density, the patient should be classified as a parasitologic failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

   ii. If the patient=s Day 3 parasite density < 25% of his/her Day 0 density **BUT** the patient=s temperature $ 37.5°C, the patient should be classified as a clinical failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

   iii. All other patients should remain in the trial and the parent/guardian given an appointment for Day 7.

4. Check to see that all data have been correctly entered on the case record form.

5. Stain the second blood smear slowly and recount parasites/WBCs and calculate parasite density. Record parasite density on case record form for Day 3.

Day 7: The following should be done:

1. Obtain an axillary temperature and record result on case record form.

2. Complete Day 7 exam and questions and record results.

3. Take two thick blood smears; stain one rapidly and examine immediately. Based on the blood smear result and the temperature, the following decisions should be made:

   i. If the patient=s Day 7 blood smear is positive **AND** the child=s temperature $ 37.5°C, the patient should be classified as a clinical failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

   ii. If the patient=s Day 7 blood smear is positive **AND** the child=s temperature ! 37.5°C, the patient should remain in the trial. No additional antimalarial treatment should be given. Parent/guardian should be given an appointment for Day 11.

   iii. If the patient=s Day 7 blood smear is negative **BUT** the child=s temperature $ 37.5°C, the patient should be examined by the clinical staff for signs of other illnesses **BUT** should remain in the trial. No additional antimalarial treatment should be given. Parent/guardian should be given an appointment for Day 11.

iv. If the patient=s Day 7 blood smear is negative **AND** the child=s temperature ! 37.5°C, the patient should remain in the trial. Parent/guardian should be given an appointment for Day 14.

v. The above patient (3.ii.) and all other patients should remain in the trial and continue with the following steps:

4. Check to see that all data have been correctly entered on the case record form.

5. Stain the second blood smear slowly and recount parasites/WBCs and calculate parasite density. Record parasite density on case record form for Day 7.

Day 11 (see Note, section IV.G.): The following should be done:

1. Obtain an axillary temperature and record result on case record form.

2. Complete Day 11 exam and questions and record results.

3. If the patient has an axillary temperature ! 37.5°C, take two thick blood smears; stain one rapidly and examine immediately. Based on the blood smear result and the temperature, the following decisions should be made:

   i. If the patient=s Day 11 blood smear is positive **AND** the child=s temperature $ 37.5°C, the patient should be classified as a clinical failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

   ii. If the patient=s Day 11 blood smear is negative **BUT** his/her temperature $ 37.5°C, the patient should be examined by the clinical staff for other illnesses **BUT** should remain in the trial. No antimalarial should be given.

   iii. The above patients (3.ii.) and all other patients should remain in the trial and continue with the following steps:

4. Check to see that all data have been correctly entered on the case record form.

5. Give parent/guardian an appointment for Day 14.

6. Stain the second blood smear slowly and recount parasites/WBCs and calculate parasite density. Record parasite density on case record form for Day 11.

Day 14: The following should be done:

1. Obtain an axillary temperature and record result on case record form.

2. Complete Day 14 exam and questions and record results.

3. Take a blood sample for hemoglobin/hematocrit, measure hemoglobin/hematocrit level, and record results.

4. Take two thick blood smears; stain one rapidly and examine immediately. Based on the blood smear result and the temperature, the following decisions should be made:

    i. If the patient=s Day 14 blood smear is positive (regardless of the patient=s temperature) he/she should be classified as a parasitologic failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

    ii. If the patient=s Day 14 blood smear is negative **BUT** his/her temperature $ 37.5°C, the patient should be examined by the clinical staff for other illnesses. This patient has now completed the trial.

    iii. If the patient=s Day 14 blood smear is negative and he/she does not have an elevated temperature, nothing further needs to be done. This patient has now completed the trial.

4. Check to see that all data have been correctly entered on the case record form.

5. Thank the parent/guardian for his/her cooperation and tell him/her that the trial has been completed.

6. Stain the second blood smear slowly and recount parasites/WBCs and calculate parasite density. Record parasite density on case record form for Day 14.

Any unscheduled day: On any other day, after Day 3, that the patient returns because the parents/guardians feel the child is ill, the following should be done:

1. Obtain an axillary temperature and record result on case record form.

2. Complete an exam and questions for that day and record results.

3. If the patient has an axillary temperature $\geq$ 37.5°C, take two thick blood smears; stain one rapidly and examine immediately. Based on the blood smear result and the temperature, the following decisions should be made:

    i. If the patient=s blood smear is positive **AND** his/her temperature $ 37.5°C, the patient should be classified as a clinical failure and treated with SP (if he/she is in the CQ group) or quinine (if in the SP group). This patient has now completed the trial.

    ii. If the patient=s blood smear is negative **BUT** his/her temperature $ 37.5°C, the patient should be examined by the clinical staff for other illnesses **BUT** should remain in the trial. No antimalarial should be given.

    iii. The above patient (3.ii.) and all other patients should remain in the trial and continue with the following steps:

4. Check to see that all data have been correctly entered on the case record form.

5. Give parent/guardian an appointment for the next regularly scheduled visit.

6. Stain the second blood smear slowly and recount parasites/WBCs and calculate parasite density. Record parasite density on case record form for that day.

Note: If a patient treated with SP returns on Days 1 or 2, he/she should be managed in a similar fashion to children treated with CQ. Unless he/she meets the criteria for a clincial or parasitologic failure, he/she should be given an appointment for Day 3.

Child returning with symptoms or signs of severe or complicated malaria: If a parent/guardian returns with a child reporting any of the following symptoms:

- Seizures
- Persistent lethargy or coma
- Respiratory distress
- Severe pallor
- Jaundice

the following should be done:

1. Obtain an axillary temperature and record results on case record form.

2. Complete exam and questions and record results.

3. Take a blood sample for hemoglobin/hematocrit, measure hemoglobin/hematocrit level, and record results.

4. Take two thick blood smears; stain one rapidly and examine immediately.

   i. If the blood smear is positive and it is the determination that the child has severe or complicated malaria (see criteria in Annex I), the patient should be classified as a clinical failure and referred for admission for therapy with quinine. This patient has now completed the trial.

   ii. If severe or complicated malaria is ruled out, follow procedures for the appropriate follow up day.

   If time permits, the clinical team may choose to enroll those patients who have had a clinical or parasitological failure on CQ in a subsequent trial of SP efficacy. This will require following those patients for an additional 14 days after their CQ failure and they are started on SP.

G. Concomitant Treatment

If, during the course of the trial, the patient develops any concomitant illnesses or side effects of the CQ or SP, he/she should be treated as needed. If it becomes necessary to use drugs that have antimalarial properties (such as cotrimoxazole for respiratory infections) or if the patient has an illness which would

interfere with the ability to evaluate the clinical response to malaria therapy, the patient should be dropped from the trial.

NOTE: If the child does not have severe or complicated malaria **BUT** requires hospitalization for another condition, he/she may be continued in the study **IF** the patient does not require transfusion, does not receive any medication with antimalarial activity (e.g., cotrimoxazole), and follow-up is logistically feasible.

	Blood Smear	Hemato-crit	Axillary Temper-ature	History/ Exam	Treatment	
					CQ	SP
Day 0	+	+	+	+	+	+
Day 1			+	+	+	
Day 2	+		+	+	+	
Day 3	+		+	+		
Day 7	+		+	+		
Day 11*			+	+		
Day 14	+	+	+			
Any other day (after Day 3)	+ (if fever)		+	+		

*See Note, section IV.G.

H. Indicators of Therapy Failure and Need for Withdrawal from Trial after Enrollment:

The following patients should receive appropriate antimalarial therapy and be dropped from the trial. If a patient is receiving CQ, he/she should be treated with SP; if a patient is receiving SP, he/she should be treated with quinine.

1. Patients who have no change or an increase in parasite density on Day 2 when compared to Day 0. Patients who have no change or only a minimal change in parasite density on Day 3 (i.e. $\geq$25% of Day 0 parasite density). This is referred to as an RIII parasitologic failure (see Annex III).

2. Patients who have an axillary temperature $\geq$37.5^{o}C and malaria parasitemia on Day 3 or later (clinical failure - see Annex III).

3. Patients who experience a decrease in hemoglobin concentration to < 5.0 g/dl during follow-up (hematologic failure - see Annex III).

4. Patients who develop complicated/severe malaria (WHO definition - Annex I).

5. Patients who need or receive a blood transfusion.

Additionally, patients should be considered lost to follow-up (LTF) and dropped from the study for the following reasons:

1. Patient misses a critical follow-up day e.g. patient does not return for one or more of the treatment days (Days 0, 1, and 2) for CQ, Day 3 (a potential defining day for RIII response), or Day 7 (the defining day for RII responses). **NOTE:** Patients who have a defined end-point prior to a critical day are not considered LTF (e.g. a patient having an RIII response on Day 3 would not normally be seen on Day 7, and would not be considered LTF because of missing the Day 7 visit).

2. Patient receives additional antimalarial drugs during the course of follow-up for any reason.

V. DATA MANAGEMENT

It is good practice to review the case record forms on a regular basis to ensure that the data are being correctly entered as patients are seen. The EPI-INFO 6.0 software package should be used for data management and analysis. Forms should be double-entered or checked against a printout of the data and any corrections made before analysis. Reasons for LTF should be noted on the case record forms.

VI. STATISTICAL ANALYSIS

After eliminating from analysis all patients who did not complete their course of antimalarial therapy or who were not studied for a sufficient number of days to classify their parasitological/ clinical response to CQ/SP, drug efficacy should be assessed according to the following parameters:

1. ***Parasitologic response:*** the number and percentage of patients who have Sensitive, RI, RII, and RIII responses, as defined in Annex III;

2. ***Initial clinical response:*** number and percentage of febrile patients on Day 0 who are afebrile on Day 3 (see Annex III);

3. ***Duration of clinical response:*** among children exhibiting a favorable initial clinical response (i.e. temperature < 37.5°C on Day 3) mean number of days between Day 3 and the reappearance of fever (see Annex III); and

4. ***Hematologic response:*** mean change in hemoglobin concentration from Day 0 to Day 14 in patients treated with CQ compared with those treated with SP.

Risk factors (age, prior CQ therapy, initial parasite density, age, etc.) will be assessed for association with probability of clinical, hematologic or parasitologic failure, time to clinical failure, and magnitude of hematologic response.

VII. ETHICAL CONSIDERATIONS

Parents or guardians of children who fulfill the entry criteria will be asked for their informed consent. Details about the trial and its benefits and potential risk will be explained to the patients in the language in which they are most fluent (Annex IV). All information regarding the patients will remain confidential.

VIII. SELECTED REFERENCES

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ANNEX I

Criteria for Diagnosis of Severe Malaria (from WHO 1986).

Any patient with one or more of the following will be considered to have severe malaria.

1. Cerebral malaria (Bangkok definition): Unarousable coma with *P. falciparum* parasitemia and no other cause of encephalopathy.
2. Jaundice.
3. Fluid, electrolyte, or acid/base disturbance; vomiting and diarrhoea.
4. Complicating and associated infections.
5. Pulmonary edema.
6. Hypoglycemia.
7. Hypotension.
8. Bleeding or clotting disturbances.
9. Hemoglobinuria, blackwater fever, or renal failure.

ANNEX II

Checklist of Daily Activities and Decision Points

NOTE: The following sections describing daily activities and decision points can be printed in a larger font on separate pages for each day and placed on the wall of the health facility so that all team members can follow the procedures.

SCREENING (DAY 0)

Enrollment criteria
a. Less than 5 years old
b. Axillary temperature $\geq$ 37.5°C
c. $\geq$ 2,000 *P. falciparum* parasites/mm^3
d. Hemoglobin 5.0 g/dl - 8.0 g/dl or hematocrit 15% - 23% (if relevant to study)
e. Parental consent

ENROLLMENT (DAY 0)

a. Explain study to parent/guardian (informed consent)
b. Exam and questionnaire (Annex VI)
c. Second blood smear for final parasite density calculation
d. Treatment:
    i. If SP comparison used, flip coin:
        if heads, then treat with CQ 10 mg/kg; if tails, treat with SP (25 mg/kg based on sulfa component.
    ii. If SP comparison not used:
        treat all children with CQ 10mg/kg.
e. Appointment to come on following day (Day 1).

DAY 1

a. Temperature
b. Follow-up exam and questionnaire (Annex VI)
c. Treatment (CQ group only) CQ 10 mg/kg
d. Appointment to come on following day (Day 2).

DAY 2

a. Temperature
b. Blood smear
c. Follow-up exam and questionnaire (Annex VI)

d. Calculate parasite density:

i. If Day 2 density $\geq$ Day 0 density, classify as a parasitological failure and treat with SP (if CQ group) or quinine (if SP group).

ii. If Day 2 density $\geq$ 25% but < 100% of Day 0 density, treat with CQ 5 mg/kg (CQ group only) and make appointment to see on Day 3.

iii. If Day 2 density < 25% of Day 0 density and temperature < 37.5°C, treat with CQ 5 mg/kg (CQ group only) and make appointment to see on Day 3.

DAY 3

a. Temperature
b. Follow-up exam and questionnaire (Annex VI)
c. Blood smear
d. Calculate parasite density:

i. If Day 3 density $\geq$ 25% of Day 0 density, classify as parasitological failure and treat with SP (if CQ group) or quinine (if SP group).

ii. If Day 3 density < 25% of Day 0 density but temperature $\geq$ 37.5°C, classify as a clinical failure and treat with SP (if CQ group) or quinine (if SP group).

iii. If Day 3 density < 25% of Day 0 density and temperature < 37.5°C, make appointment to see on Day 7.

DAY 7

a. Temperature
b. Blood smear
c. Follow-up exam and questionnaire (Annex VI)
d. Calculate parasite density:

i. If blood smear is positive and the temperature < 37.5°C, make appointment to see on Day 11.

ii. If temperature $\geq$ 37.5°C and blood smear is positive, classify as clinical failure and treat with SP (if CQ group) or quinine (if SP group).

iii. If temperature $\geq$ 37.5°C and blood smear is negative, have clinical staff examine patient and make appointment to see on Day 11.

iv. If blood smear is negative and the temperature < 37.5°C, make appointment to see on Day 14.

DAY 11

a. Follow-up exam and questionnaire (Annex VI)
b. Temperature:

i. If temperature < 37.5°C, make appointment to see on Day 14.

ii. If temperature $ 37.5°C, take blood smear. If blood smear is positive, classify as clinical failure and treat with SP (if CQ group) or quinine (if SP group).

iii. If temperature $ 37.5°C and blood smear is negative, have clinical staff examine patient and make appointment to see on Day 14.

DAY 14

a. Temperature
b. Blood smear
c. Hemoglobin/hematocrit
d. Follow-up exam and questionnaire (Annex VI)
e. Calculate parasite density:

i. If temperature < 37.5°C and blood smear is negative, patient has completed trial.

ii. If temperature < 37.5°C and blood smear is positive, treat with SP (if CQ group) or quinine (if SP group).

iii. If temperature $ 37.5°C and blood smear is positive, classify as clinical failure and treat with SP (if CQ group) or quinine (if SP group).

iv. If temperature $ 37.5°C and blood smear is negative, have clinical staff examine patient.

ANY NON-SCHEDULED DAY (AFTER DAY 3)

a. Temperature
b. Follow-up exam and questionnaire (Annex VI):

i. If temperature < 37.5°C, make appointment to see on next scheduled day.

ii. If temperature $ 37.5°C, take blood smear. If blood smear is positive, classify as clinical failure and treat with SP (if CQ group) or quinine (if SP group).

iii. If temperature $ 37.5°C and blood smear is negative, have clinical staff examine patient and make appointment to see on next scheduled day.

SYMPTOMS OF SEVERE OR COMPLICATED MALARIA ON ANY VISIT

a. Temperature
b. Blood smear
c. Hemoglobin/hematocrit
d. Follow-up exam and questionnaire (Annex VI)
e. Calculate parasite density:

i. If blood smear is positive and child had findings of severe or complicated malaria, classify as a clinical failure and refer for admission for treatment with quinine.

ii. If severe or complicated malaria are ruled out, follow procedures for the appropriate follow-up day.

ANNEX III

Definitions

A. PARASITOLOGIC OUTCOMES:

These are outcome measures based solely on changes in the patient=s parasite density in response to a standard dose of an antimalarial drug.

1. ***Parasitologic Response***:

Parasitologic response refers to the change in parasite density in response to a standard dose of an antimalarial drug. All patients are seen on Days 0, 1, and 2 for treatment. Blood smears are taken on Days 0, 2, and 3. IF THE DAY 2 PARASITE DENSITY IS $100% OF THE DAY 0 DENSITY, THE PATIENT WILL BE CONSIDERED A PARASITOLOGIC FAILURE AND BE GIVEN AN ALTERNATE THERAPY. Additional blood smears are scheduled for Days 7 and 14, as well as any day in between that the patient presents with fever. The parasitologic response is categorized using the following scheme:

a. **RIII**: a Day 3 parasite density that is $25% of the Day 0 parasite density.

b. **RII**: a positive Day 3 blood smear with a parasite density that is < 25% of the Day 0 density and a positive Day 7 blood smear.

c. **Early RI**: ***EITHER***
a negative Day 3 blood smear with a positive blood smear on any day between Day 4 and Day 14
OR
a positive Day 3 blood smear with a parasite density that is <25% of Day 0, a negative Day 7 blood smear, and a positive blood smear on any day between Day 8 and Day 14.

d. **Sensitive/Late RI**: a Day 3 parasite density that is <25% of the Day 0 density and negative blood smears on every follow-up examination between Day 7 and Day 14. Because follow-up lasts only 14 days, it is not possible to distinguish sensitive responses from late recrudescences, and these responses are combined in the RI/S category.

2. ***Parasitologic Failure***:

Parasitologic failure is defined as the presence of any parasitemia on or after Day 7. Parasitologic failure in the absence of documented fever will NOT be an indication for treatment with a second drug and removal from the trial, unless other clinical indicators warrant removal (e.g., worsening clinical condition, altered mental status, significant deterioration of hematologic status).

B. CLINICAL OUTCOMES:

These are outcome measures based on changes in the patient=s clinical condition in response to a standard dose of an antimalarial drug.

1. ***Initial Clinical Response***:

The proportion of febrile patients (measured as an axillary temperature $ 37.5EC) on Day 0 who are afebrile (axillary temperature < 37.5°C) on Day 2.

2. ***Duration of Clinical Response***:

The number of days between Day 3 and the reappearance of fever among patients with a favorable Initial Clinical Response.

3. ***Hematologic Response***:

The change in hemoglobin/hematocrit between Day 0 and Day 14.

4. ***Clinical Failure***:

After Day 2, fever in the presence of any parasitemia will be defined as a clinical failure. Prior to day 2, any malaria-associated condition requiring a change in malaria therapy will ALSO be defined as a clinical failure (including unresponsive malaria parasitemia on Day 2 or a significant deterioration in hematologic status). Clinical failures will be treated with a second drug and the patient removed from the study.

ANNEX IV

Informed Consent

The Ministry of Health is interested in finding out how well the current treatment for malaria in Zambia is working. To do this, we are carrying out a study in which we are treating a group of children for malaria and then following them for 14 days to see if their infection is cured and if they have any problems with anemia, a common complication of malaria.

If you agree for your child to participate in this study, we would like to take another small amount of blood from a fingerprick in order to confirm that your child has malaria and anemia. All participating children will be assigned at random (by tossing a coin) into one of two groups: one group will receive chloroquine, the standard treatment for malaria in Zambia; the other group will receive a drug called Fansidar, which is very good at treating malaria infections. The reason for treating some children with Fansidar is so that we can compare the effectiveness of chloroquine to Fansidar.

We would like you to bring your child back to the clinic 5 more times over the next 2 weeks so that we can monitor the progress of the treatment. It is very important that we see your child on these days, so if you feel that you will not be able to return on these days, please let us know now. On 3 or 4 of these visits we will take another blood smear from a fingerprick to see if your child still has malaria parasites.

Your participation is completely voluntary. If you do not want your child to participate in this study, he/she will still be able to receive treatment as usual at this clinic. Participation in this study will not cost you or your family anything. You may also withdraw your child from the study at any time and for any reason.

Your child will benefit from participating in this study because he/she will be closely followed over the next 14 days. If your child continues to suffer with malaria, he/she will receive an alternative treatment which will cure the illness. There will be someone here at the clinic every day so that even on days between scheduled visits and on weekends you may bring your child in for a checkup if you feel that he/she is ill.

Do you have any questions about the study?

ANNEX V

List of Minimum Necessary Inputs per 60 Patients Enrolled: Supplies and Equipment

Stationery:	Amount
logbooks	2
notebooks (small, lined)	2
paper (for data forms)	3 reams
indelible pens for marking slides (sharpies)	6 black
ball point pens	20
scissors	1
binder	1
folder (envelope style)	3
ruler	1
stapler	1
staples	1 box
hole punch	1
clipboard	2
packing tape	1 roll
packing boxes	2
electrical convertor	2
pocket calculator	1
plastic document covers	10
Laboratory supplies:	
slides 30/subject (includes screening)	50 1/2 gross boxes
lancets 10/subject (includes screening)	1 box
large slide boxes	2
small slide boxes for outreach follow-up	2
sharps container	3
10 ml pipettes for mixing stain	1 box
staining jars	2
slide drying rack	1
hair dryer (with cool setting)	1
examination gloves (various sizes)	2- boxes (1M, 1L)
tally counters (hand held, egg style)	4
microscopes	2
spare microscope bulbs	2
Giemsa stain and stock buffer	500 ml
methylated spirits	1 liter
cotton wool	1 bag
paper towels or wipes	1 case
toilet paper for wrapping slides	1 case
dropper bottles	1
immersion oil	1 bottle
extension cord- 220 volt	1
multiplug- 220 volt	1
xylene	

Laboratory supplies (cont=d.)

lens paper	1 pad
concentrated dishwashing soap	1 bottle
plastic basins	2
Hemocue cuvettes (if hemoglobin testing to be done)	1 box
Hemocue machine (if hemoglobin testing to be done)	1

Screening/ clinical evaluation:

electronic thermometers, centigrade	4
salter scales	1
count-down timer (2 for clinical evaluation, 2 for lab)	4
spoons	4
brown glass jars	2

Incentives:

Polaroid camera	1
film 1/subject plus 15 (includes drop outs)	13 boxes of 10
sugar	120 one kilo bags
laundry soap	120 bars
hard candies	1000 pieces

Urine testing:

Selectapette pipetter (Clay-Adams)	1
Selectapette tips	1 box of 1000
15 ml. conical centrifuge tubes	20
centrifuge tube rack	1
reagents for urine testing	
pediatric urine bags or cups	1 box

Travel:

four-wheel drive vehicle	1
fuel	500 liters + travel to and from field site

Drugs:

chloroquine liquid (25 mg/kg base total dose/child)	2- 5 liter bottles OR 500- 150 mg (base) tablets
sulfadoxine-pyrimethamine (25 mg/kg sulfadoxine total dose)	1- 1000 pill tin

ANNEX VI

Patient Record Form

CASE RECORD FORM

DATE: _____

STUDY NUMBER: _____

PATIENT'S NAME: _____

MOTHER'S AND FATHER'S NAME: _____

DIRECTIONS TO HOME: _____

A. HISTORY OF CHILDS ILLNESS (ASK PARENT/GUARDIAN):

1. WHAT SYMPTOMS DOES YOUR CHILD HAVE?

1. _____ DURATION _____ DAYS

2. _____ DURATION _____ DAYS

3. _____ DURATION _____ DAYS

2. WHAT OTHER SYMPTOMS HAS THE CHILD HAD DURING THIS ILLNESS? (Circle all that apply)

1.FEVER	4. CHILLS OR SHAKES	7. EXCESSIVE SWEATING
2. NAUSEA	5. VOMITING	8. DIARRHEA
3. IRRITABLITIY	6. COUGH	9. DIFFICULTY BREATHING

3. HAS ANY MEDICATION ALREADY BEEN GIVEN TO THE CHILD? YES NO

IF YES, WHAT MEDICATION (Circle all that apply)?

1. CHLOROQUINE 2. OTHER _____

4. HAS THE CHILD BEEN OUTSIDE OF YOUR VILLAGE IN THE LAST MONTH? YES NO

WHERE? _____

B. EVALUATION OF THE CHILD:

1. AGE (YEARS,MONTHS): |___|___| Yrs |___|___| Mos

2. SEX: M F

3. WEIGHT (Kg.): |___|___| . |___|

4. AXILLARY TEMPERATURE (°C): |___|___| . |___|

5. RESPIRATORY RATE (In 30 seconds): |_____|_____|

6. IS THERE EVIDENCE OF ANY OTHER MEDICAL PROBLEM? YES NO

IF YES, WHAT? _____

7. IS ADDITIONAL MEDICATION NEEDED? YES NO

IF YES, WHAT MEDICATION? _____

C. LABORATORY EVALUATION:

1. PARASITE DENSITY:_____ 2. HEMOGLOBIN:_____

3. URINE TEST: FOR CQ: _____ FOR SP: _____

STUDY NUMBER: _____ WEIGHT(KG): _____

FOLLOW-UP DAY:	DAY 0	DAY 1	DAY 2	DAY 3					
DATE									
CQ DOSAGE GIVEN									
SP DOSAGE GIVEN									
TEMPERATURE									
RESPIRATORY RATE IN 30 SECONDS									
FEVER SINCE LAST VISIT? (Y/N)									
VOMITING? (Y/N)									
DIARRHEA? (Y/N)									
DIFFICULTY BREATHING? (Y/N)									
BETTER, SAME, OR WORSE? (B/S/W)									
HEMOGLOBIN (g/dl) [HEMATOCRIT (%)]									
PARASITE DENSITY									

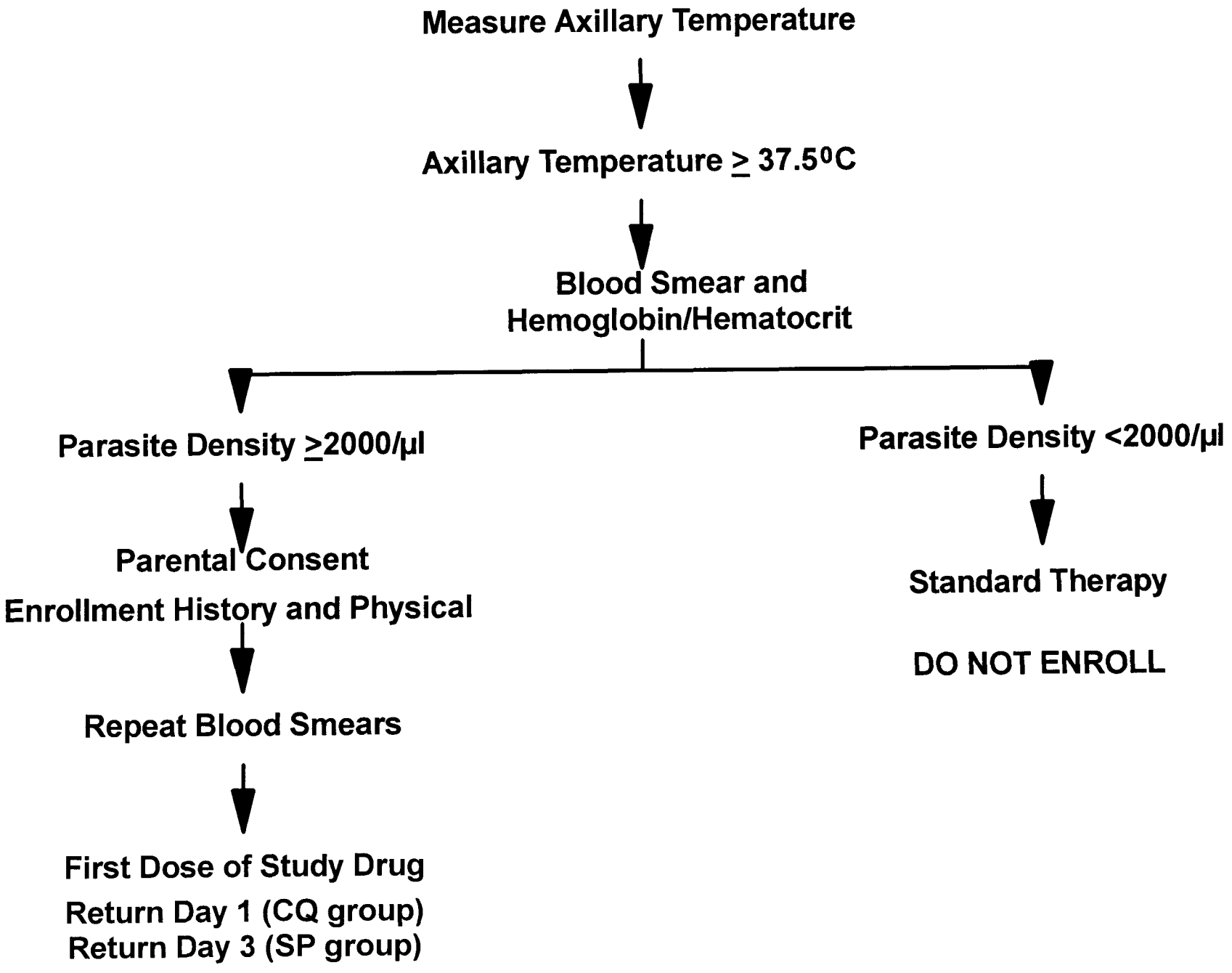
COMMENTS:

ANNEX VII

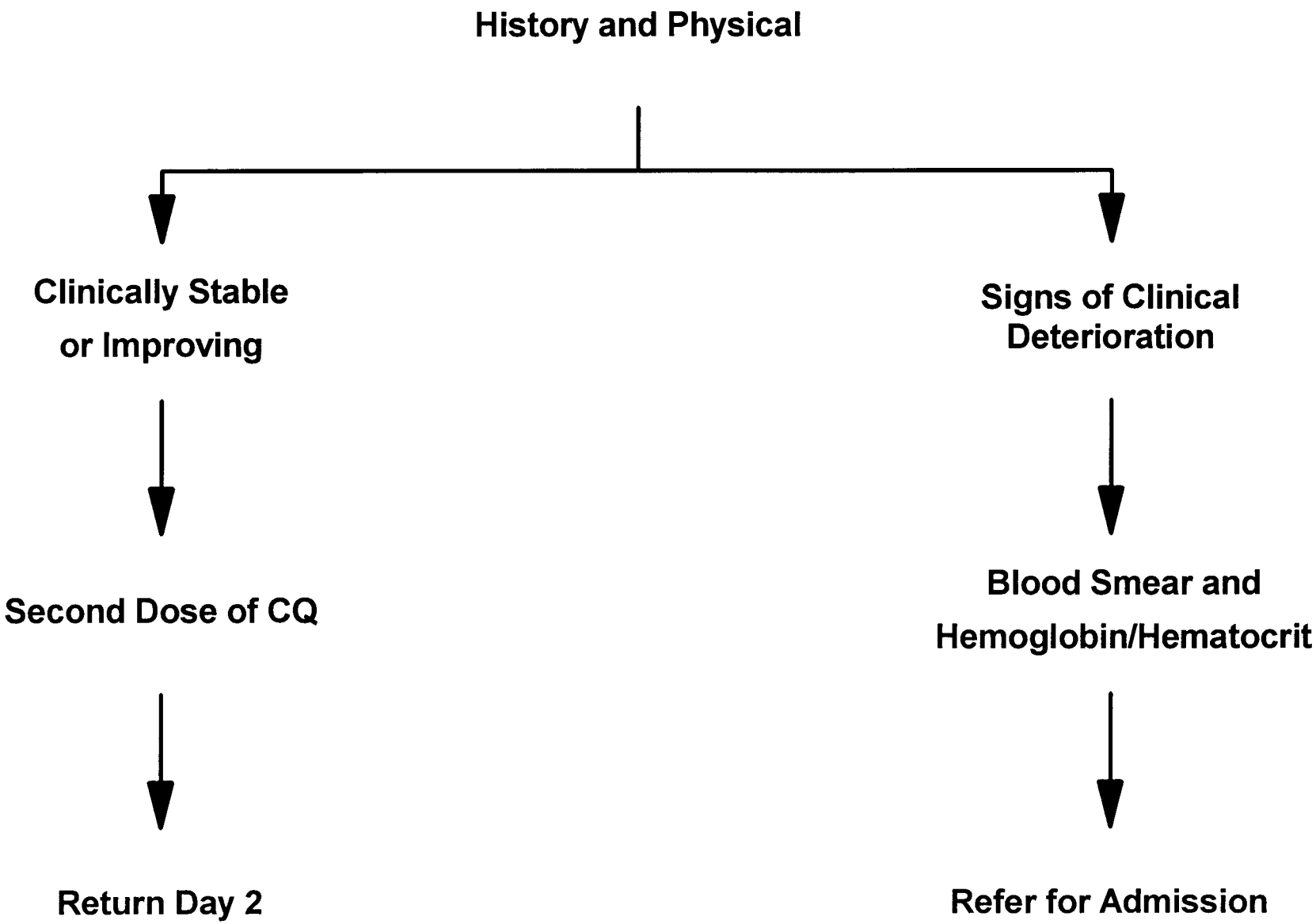
Wall Charts

Note: The following flow diagrams showing the daily activities and decision points for the 14-day test can be copied and placed on the wall of the health facility to assist team members in following each day's procedures.

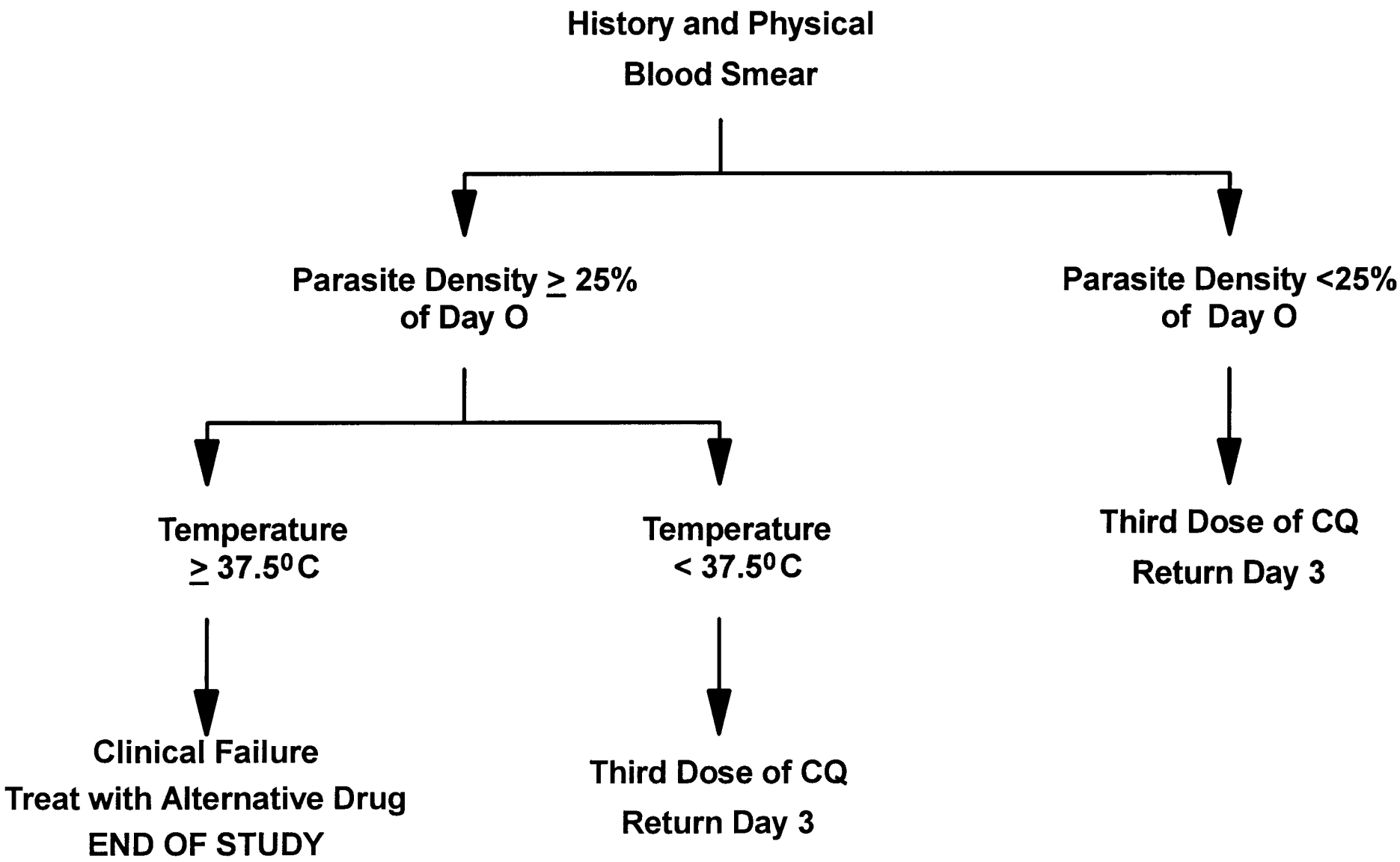
Day 0 Procedures



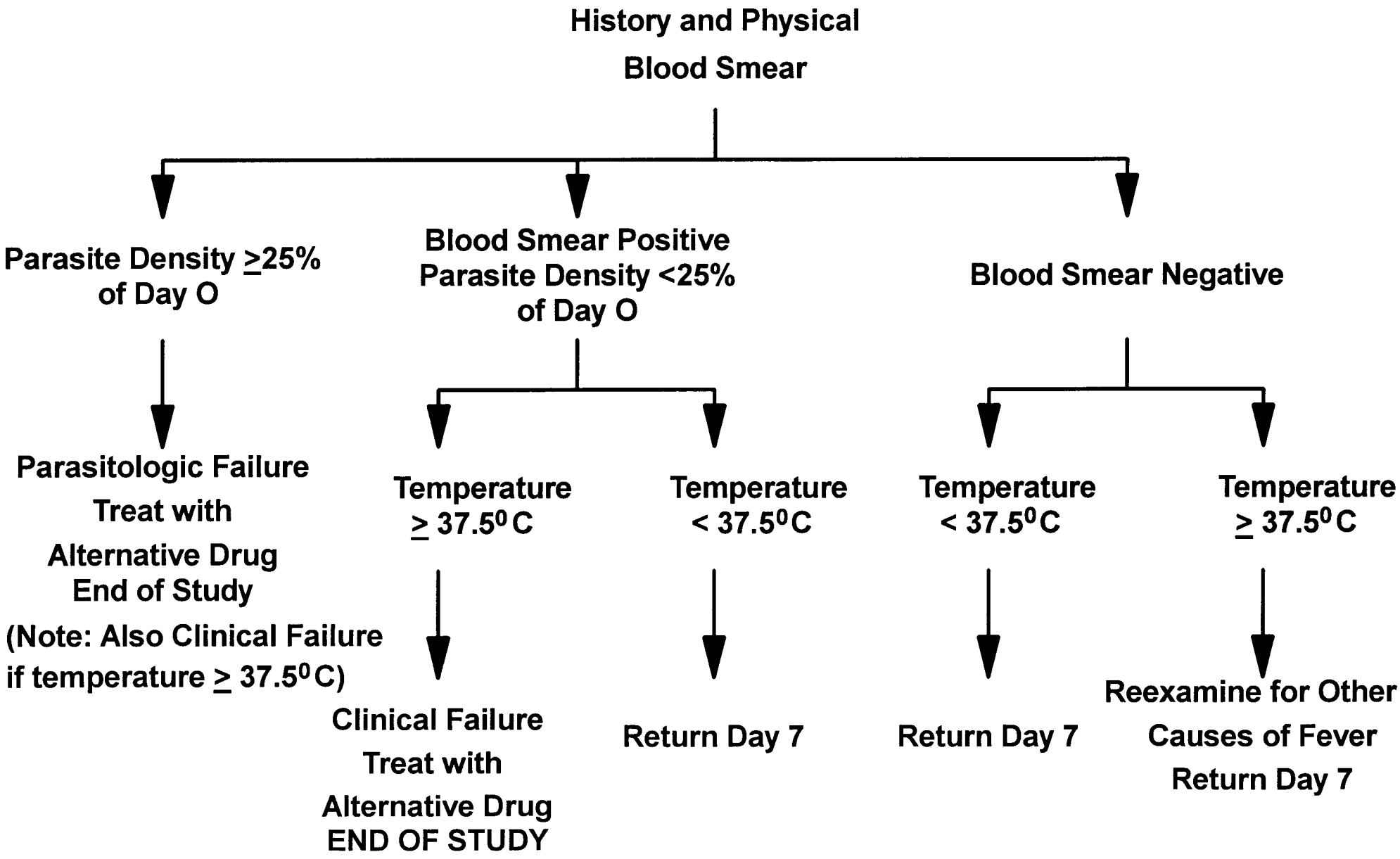
Day 1 Procedures



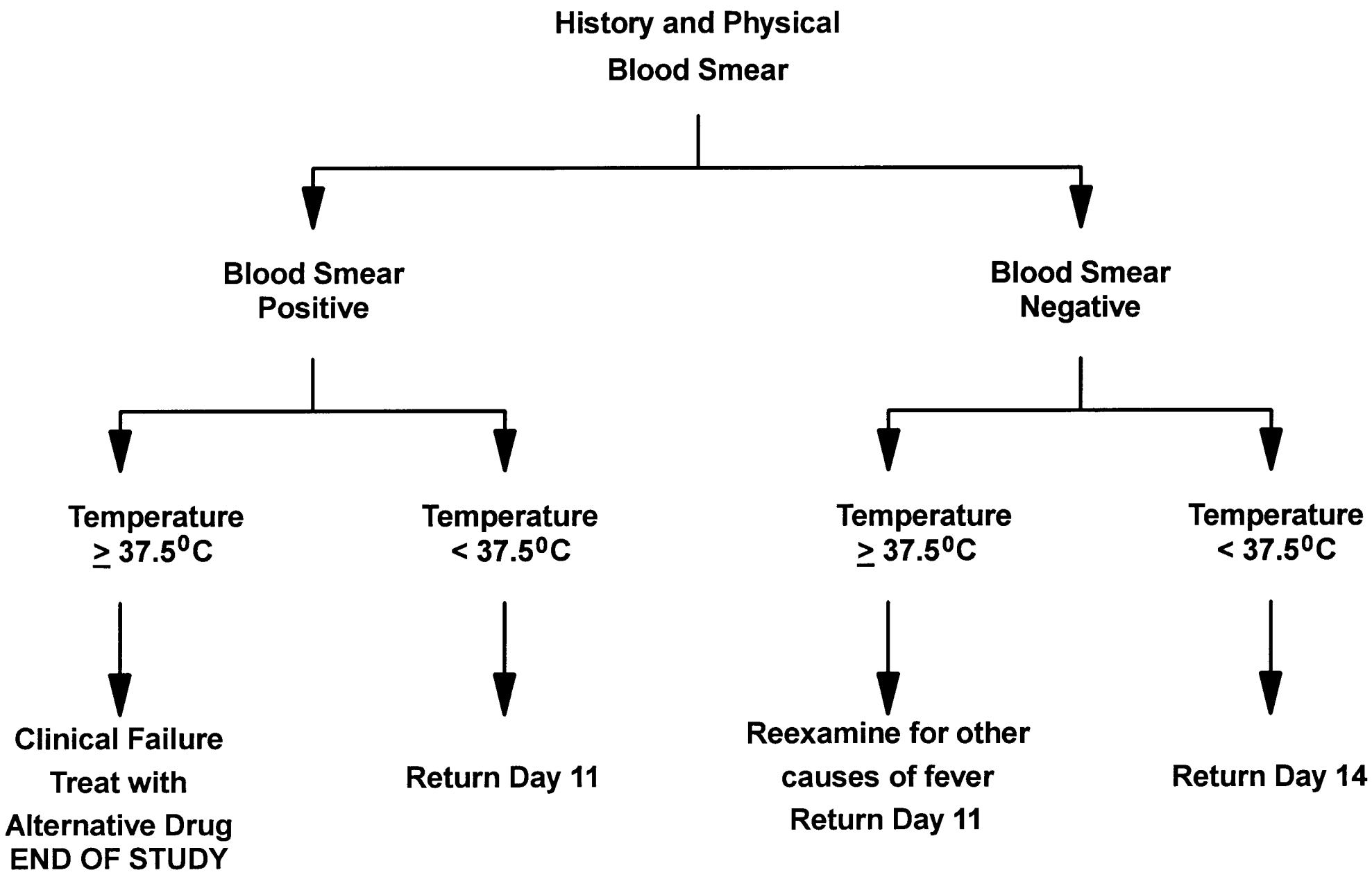
Day 2 Procedures



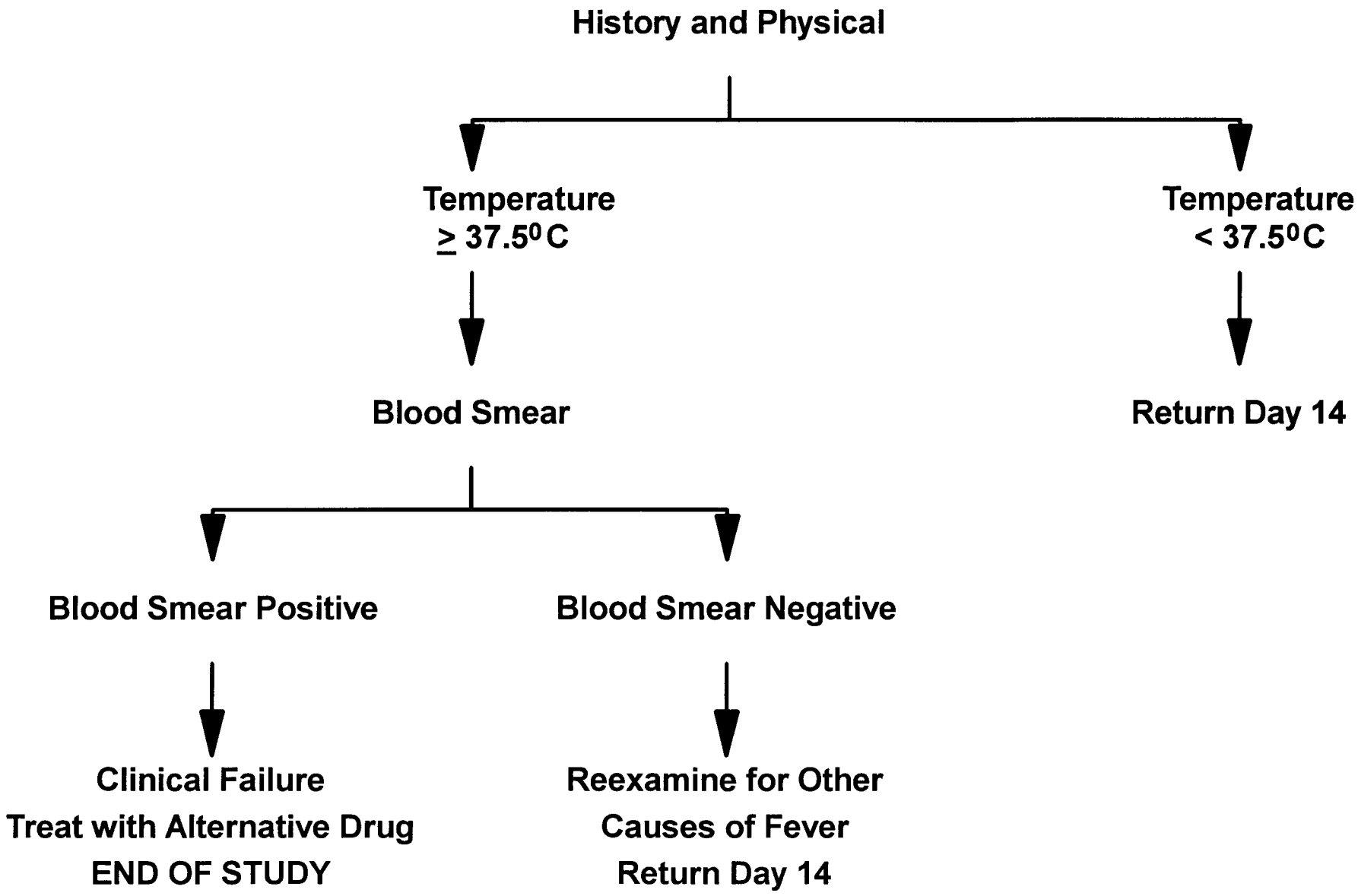
Day 3 Procedures



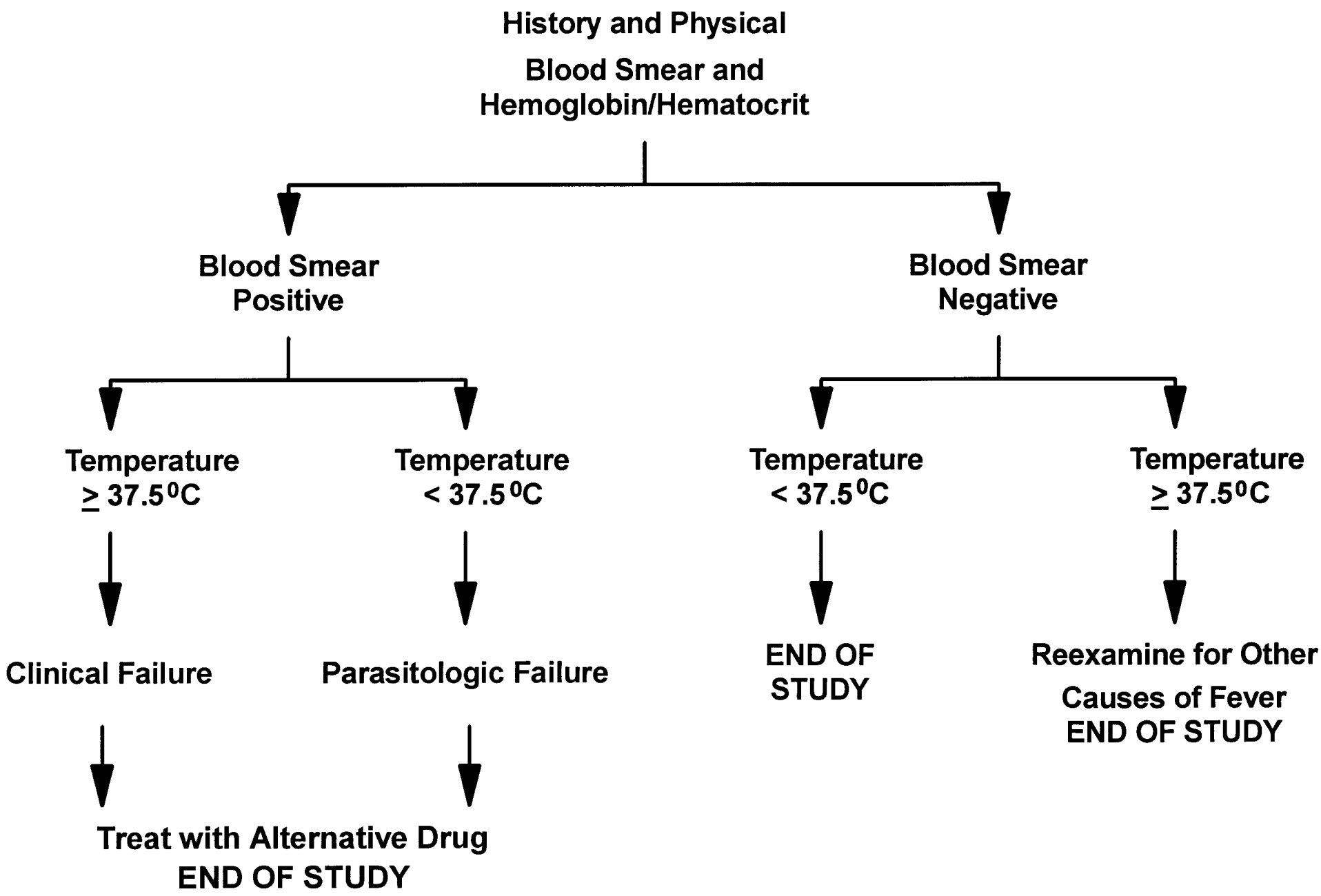
Day 7 Procedures



Day 11 Procedures



Day 14 Procedures



APPENDIX B

EFFICACY OF CHLOROQUINE THERAPY FOR *PLASMODIUM FALCIPARUM* IN ZAMBIA:

Findings from Studies in Chipata District, MayBJune, 1995

Report of a study conducted in Chipata, Eastern Province, Zambia in May and June, 1995.

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Annex

Summary of Data from Dropped or Excluded Patients

I. Introduction

The impact of malaria on the health and economic development of human populations is greatest in the tropics and subtropics (Campbell 1991). In Africa alone, the World Health Organization (WHO) has estimated that over one million children under the age of 5 die annually from malaria.

In their efforts to reduce malaria morbidity and mortality, many countries in sub-Saharan Africa have adopted a malaria control policy that relies primarily on prompt and effective treatment. For the past 30 years, chloroquine (CQ) has been the drug of choice for the treatment of malaria throughout Africa, based upon its rapid action, efficacy, safety, and low cost relative to other antimalarials.

Chloroquine-resistant *Plasmodium falciparum* (CRPf) was first described in the late 1970s in East Africa. Since that time, while CRPf was spreading throughout sub-Saharan Africa, resistance was intensifying to intolerable levels in much of eastern Africa. A recent study conducted at a district hospital in western Kenya showed that, among children less than 3 years of age treated with CQ at a dose of 25 mg/kg, 50% had an RII parasitologic response and 25% had an RIII parasitologic response (Bloland et al. 1993). Similar rates of resistance were observed in studies conducted in Malawi during the same period (Bloland et al. 1993 and Bloland unpublished data). There is concern about the declining efficacy of CQ in many areas of sub-Saharan Africa. Currently, countries in southern, central, and western Africa may be experiencing declines in chloroquine (CQ) efficacy that are similar to those that have been occurring in eastern Africa over the last 10 to 15 years. In eastern Africa, recognition of the problem of intensifying resistance and implementation of a response was probably delayed, resulting in otherwise avoidable morbidity and mortality. So that an appropriate response can be made in a timely fashion in other areas of Africa facing declining efficacy, efforts to monitor malaria therapy efficacy must become a priority.

Over the past 10 years, many changes have occurred in the way that drug resistance is thought of and measured. Using both *in vivo* and *in vitro* methods, the first studies of drug resistance in Africa collected data only on the persistence of malaria parasites in the face of known quantities of drug. As resistance intensified and persistence of malaria parasites became an increasingly common occurrence, attention shifted to the clinical response of patients. The observation that even when malaria parasites are not cleared from the blood after treatment with CQ, patients typically respond clinically, with resolution of fever and improvements in activity level and appetite, was used as evidence of continued efficacy.

Many studies have focused on school-aged children, raising concern about the relevance of such data to the age group that carries the greatest burden of malaria related morbidity and mortality, children under 5 years of age. It is unclear whether initial clinical improvement with incomplete parasitological cure can be considered an adequate therapeutic response in all patients, especially those with little or no acquired immunity. Studies conducted on the coast of Kenya have shown that in spite of an initial clinical improvement, about 20% of children treated with CQ returned with a malarial illness within 2 to 3 weeks and required further therapy. In western Kenya it was found that while 83% of febrile (i.e., with fever), parasitemic children under 5 years of age improved clinically within 48 hours of treatment with CQ (as measured by a decrease in axillary temperature to $< 37.5^{\circ}$C), 60% experienced a reappearance of symptoms within 14 days of therapy and 90% failed clinically within 28 days. Similar results have been obtained in studies conducted in Malawi.

Of even greater importance is the fact that hematologic recovery among anemic children treated with CQ may be incomplete. The previously mentioned studies in Malawi and Kenya have demonstrated that the increase in hemoglobin concentration among anemic children treated with an effective antimalarial drug, such as sulfadoxine/pyrimethamine (SP or Fansidar™), was greater and occurred earlier when compared to increases experienced by anemic children treated with CQ. Although a causal relationship has not yet been shown, it is possible that much of the severe anemia associated with *P. falciparum* malaria in Africa and the high mortality associated with that anemia is due to repeated, ineffective therapy with CQ. Unpublished data from a study of malaria and anemia in early childhood in western Kenya indicate that mean hemoglobin concentrations associated with persistent malaria infections, such as might occur with inadequate therapy, were significantly lower than the mean hemoglobin levels associated with either recently cleared infections or new infections (Bloland, unpublished data).

An additional problem is that because of the ready availability of CQ in the community, many children with febrile illnesses believed to have malaria have been treated before going to a dispensary or health center. As a result, many patients seen at health centers have already used CQ and may, therefore, already have experienced therapy failure or are infected with malaria parasites that have been exposed to subtherapeutic concentrations of CQ.

It is now recognized that *in vitro* assessment of malaria parasite resistance and categorization of resistance levels based on *in vivo* evaluations with short duration follow-up (e.g., 7 days) do not adequately assess malaria therapy efficacy. More emphasis needs to be placed on the clinical status of the patient at the time of treatment and on the chronic effects of malaria parasitemia, particularly anemia.

Relevant parameters that have been used to assess malaria therapy efficacy include initial clinical response among febrile patients, parasitologic response, duration of clinical improvement, and hematologic response among anemic children. Initial clinical response is measured as the proportion of initially febrile patients who are afebrile (without fever) within 48 to 72 hours after treatment. Measurement of parasitologic response follows the modification of the traditional RIII/RII/RI/S classification scheme. By extending the follow-up period to 14 or more days post-treatment, the duration of clinical response (i.e., the proportion of patients initially responding who become ill again soon after treatment and the mean number of days between therapy and return of clinical symptoms) can also be assessed as an indicator of how long children will be well after therapy or, conversely, how soon they will need to be treated again. In the context of assessing antimalarial therapy efficacy, hematologic response is best measured using a comparative trial: the change in hematologic status after CQ therapy compared to the change after treatment with an antimalarial known to be effective, such as SP.

Malaria in Zambia is recognized as one of the leading causes of morbidity and mortality, especially among young children and pregnant women, and accounts for more outpatient visits and hospital admissions than any other disease. In 1994, over 3 million cases of malaria were reported in Zambia, a rate of 356/1000 population. The case fatality rate among children < 5 years of age since 1990 has ranged from 21/1,000 to 48/1,000. CQ is currently the drug of choice for the treatment of malaria in Zambia.

Although numerous studies have been conducted in Zambia to document the occurrence and measure the prevalence of CRPf malaria, it is difficult to compare their results because of the lack of a standardized methodology. This may account for the wide ranges of CRPf reported. For example, studies conducted between 1992 and 1994 indicate that between 8% and 39% of *P. falciparum* infections are CQ resistant. Moreover, since these studies were conducted among asymptomatic school-age children, the ability to extrapolate these findings to the population at greatest risk of malaria illness, children < 5 years, is limited.

To address concerns regarding the current therapeutic efficacy of CQ in Zambia, a systematic evaluation has been initiated by the Ministry of Health that will use standardized procedures in multiple sites throughout the country. The findings of these CQ sensitivity trials will allow the Ministry of Health to evaluate and update its current national malaria therapy policy. At the same time, some of the sites selected will be set up to allow ongoing surveillance of CQ efficacy. This will permit the Ministry of Health to recognize rapidly any significant changes in therapy efficacy that occur and to make appropriate adjustments to national therapy policy in a timely fashion. The results of one of the first two studies in this effort are presented here.

II. Methods

The efficacy of CQ and SP or Fansidar™ therapy for *Plasmodium falciparum* infections was measured at two clinics in the town of Chipata in eastern Zambia along the Malawian border. The Kapata Clinic is an urban clinic located within the town limits and next to a large market and bus station. The Prison=s Clinic is located outside of town in a semi-rural setting near a prison, prison staff quarters, croplands, and a large village.

At each site, all children under the age of 5 years attending the day=s clinic were evaluated for fever (axillary temperature $37.5E C). Thick blood smears were obtained from all children under 5 years attending the clinic. Hematocrits (hct) were obtained initially from all children and later only from febrile children. Thick blood smears were evaluated for the presence of a pure *P. falciparum* infection of at least 2000 asexual parasites/mm;. The parent or guardian of children meeting the entry criteria of adequate parasite density and measured fever were informed of the study purposes and asked to participate. The children of those parents giving their informed consent were enrolled into the study.

Upon enrollment, a brief, standardized questionnaire was administered and physical exam performed by a Zambian physician/clinical officer who collected information on the history, signs, and symptoms of the present illness. A second thick blood smear was obtained for definitive calculation of parasite density. Children were treated with either CQ syrup (25 mg/kg over 3 days) or SP (3 tablet for children < 1 year of age; 2 tablet for children 1 to 3 years; 1 tablet for children 4 years old on Day 0 only). All treatments were administered by study personnel, and patients were observed for vomiting for 30 minutes after treatment. Patients who vomited were retreated with the full dose. Patients with persistent vomiting were dropped from the study and referred to the clinic for further attention. The CQ syrup was obtained from the Central Medical Stores, and its potency was confirmed at CDC by high pressure liquid chromatography.

Patients were seen for treatment and brief clinical exams on Days 0, 1, 2 (CQ group) or Day 0 (SP group) and for clinical exams on Day 3 (both groups). CQ patients who, on Day 2, continued to have parasite densities at or above the Day 0 parasite density were treated with SP. Patients with Day 3 parasite densities $25% of the Day 0 density were also treated with SP. SP-treated patients who had Day 3 parasite densities $25% of the Day 0 parasite density were seen again on Day 4; if the parasite density was still high on Day 4, the children were referred to the hospital for quinine (QN) therapy. All patients were evaluated on Days 3, 7, 11, and 14. Evaluation consisted of axillary temperature, respiratory rate, brief history of occurrence of clinical symptoms, and physical exam, including assessment of other potential causes of fever. Blood smears were obtained on Days 0, 2 (CQ only), 3, 4 (SP only, if needed), 7, 14, and any nonscheduled visit at which the patient had measured fever. Hematocrits were obtained on Days 0 and 14 for those children completing 14 days of follow-up. In

addition to evaluating children placed directly on SP (done only at the Prison=s Clinic), a number of children failing CQ from both clinics were treated with SP and followed with the same methods.

Blood smears were stained with 3% Giemsa and evaluated by experienced microscopists. The number of asexual parasites per 300 white blood cells (WBC) was obtained and the parasite density/mm; was calculated by assuming a standard total WBC count of 8000 WBC/mm;. Blood smears were examined or reviewed by more than one trained and experienced microscopist.

Therapy efficacy was evaluated on the basis of four parameters: parasitologic response, initial clinical response, proportion of clinical failure, and duration of clinical response. Parasitologic response was defined using a modification of the traditional categorization into RI/S, RII, and RIII resistance levels (Bruce-Chwatt 1986). Because blood smears were scheduled only for Days 0, 2, 3, 7, and 14, these categories were slightly modified. Briefly, the RI/S category was defined as a parasitologic response where peripheral blood smears were negative for asexual parasites on or before Day 7. Because of the 14 day follow-up schedule and the lack of ability to prevent reinfection, late RI responses could not be distinguished from truly sensitive responses and, therefore, these responses were combined. An early RI response was defined as a positive Day 3 blood smear with a parasite density that was < 25% of Day 0, a negative blood smear on or before Day 7, and a positive blood smear on any day between the first negative blood smear and Day 14. An RII response was defined as an asexual parasitemia that was, on Day 3, < 25% of Day 0 but did not clear on or before Day 7. An RIII response was defined as a Day 2 parasitemia $100% of Day 0, a Day 3 parasitemia $ 25% of Day 0, or a positive Day 3 blood smear and persistent fever (clinical RIII).

Initial clinical response was defined as the proportion of initially febrile patients who were afebrile by Day 3. Clinical failure was defined as the presence of both measured fever (axillary temperature $37.5EC) and an asexual parasitemia (of any density) on or after Day 3. Duration of clinical response was defined as the number of days between Day 3 and clinical failure among patients with a favorable initial clinical response. Patients who either required alternative therapy on Day 2 or were febrile and parasitemic on or after Day 3 were considered to have clinically failed therapy and were treated with SP or QN.

III. Results

Initial screening: At both clinics, the majority of patients came from the nearby community; Kapata Clinic had a small number of patients who came from outside the immediate area, presumably their families came to use the market. In spite of the proximity of Malawi and the belief that a large number of patients being seen along the border were patients from Malawi, no patients appeared to come from outside of Zambia.

All children under 5 years were screened for fever and parasitemia using axillary temperatures and thick blood smears. A total of 312 children under the age of 5 years were screened at the Prison=s Clinic and 246 were screened at the Kapata Clinic. The overall slide positivity rate was much greater at the Prison=s Clinic than at the Kapata Clinic (83% [254/307] and 26% [64/246], respectively). At the Prison=s Clinic, where more complete screening data are available, the mean age of screened children was 20.6 months (SD = 14.0, n = 312) and 56.4% were female. The prevalence of measured axillary temperature $37.5°C was 50.3%. Of 95 consecutively collected hematocrits, none were below 15% (severe anemia), 8 (8.4%) were between 15% and 23% (moderate anemia), 22 (23.2%) were between 24% and 32% (mild anemia), 54 (56.8%) were 33% or above (not anemic), and 11 (11.6%) were clotted and could not be analyzed. Enrolled children at the Prison=s Clinic were slightly older than children who were not enrolled (mean age 24.2 months, SD = 14.1, n = 96 and 19.5 months, SD = 14.3, n = 211, respectively, p = 0.01, ANOVA), but the sex distribution was the same (p = 0.8, $?^2$ test).

Characteristics of enrolled patients: The characteristics of children at enrollment are presented in Table 1. Briefly, 81 children were enrolled into the study and treated with CQ, 27 at the Kapata Clinic and 54 at the Prison=s Clinic. Forty-four (54.3%) of the children enrolled were females and the mean (standard deviation

[SD]) age was 24.2 (13.7) months. The mean enrollment hematocrit was 33.8% (SD = 7.245). The geometric mean parasite density (GMPD) at enrollment was 39,498 asexual parasites/mm^3 (range 1,992-244,507). There were no significant differences in these characteristics between the two sites except for GMPD. Children enrolled at the Kapata Clinic had a higher GMPD than those enrolled at the Prison=s Clinic (61,945 and 31,508 asexual parasites/mm^3, respectively, p = .005).

Table 1
Day 0 Characteristics of Enrolled Children[1]

	Chloroquine		Sulfadoxine/Pyrimethamine	
Clinic	Kapata	Prison	Kapata	Prison
Number	27	54	4[2]	44[2]
Mean Age (months)	21.2	25.7	24.5	22.8
Sex (% female)	51.9	55.6	25	54.6
GMPD[3] on Day 0	61,945	31,508	19,732	35,668
Mean Hematocrit, Day 0	35%	33%	na	34%
History of prior CQ treatment	33%		18.2%	

1. All differences are nonsignificant (p > 0.05) except for the difference between the Day 0 GMPD among CQ-treated children at Kapata and Prison=s (p = 0.005).
2. All 4 children from Kapata and 3 children from Prison=s were treated with SP after failing CQ therapy in this study. All of these children met the original entry criteria.
3. GMPD = geometric mean parasite density.

Of the initial 81 patients enrolled, 9 (11%) were dropped during the study. Reasons for removal included moving out of study area (n = 3); meningitis (1); refusal to participate (1); missed CQ dose (1); child received extra CQ from parent (1); persistent vomiting (1); and removal and referral to hospital at request of mother (1). All of these patients were removed before Day 7 and the three children moving out of study area did so after receiving the full course of CQ. Two more patients (2.5%) were removed from analysis because of a Day 0 temperature < 37.5E C (see Annex 1 for summary of known data from patients dropped or excluded from analysis).

A total of 65 patients were treated with SP and monitored over time; 23 (35.4%) were treated with SP after failing CQ therapy and 42 (64.6%) were treated with SP as first-line therapy. Of these 65, 48 children (4 at Kapata Clinic, 44 at the Prison=s Clinic) met the original entry criteria (Day 0 parasite density $ 2,000 parasites/mm^3 and axillary temperature $37.5EC). Of these 48 children, 7 (14.6%) were treated with SP after being enrolled into the CQ treatment group and failing; 41 (85.4%) were enrolled and treated with SP as first-line therapy. There were 25/48 (52.1%) females and the mean age was 23 months (S.D. = 13.7). The mean Day 0 hematocrit was 34.3% (S.D. = 7.353, n = 30) and the Day 0 GMPD was 33,928 asexual parasites/mm^3 (minimum 3,421; maximum 448,650). Day 0 characteristics did not differ statistically between enrollment sites or between children receiving SP as first- or second-line therapy (Day 0 hematocrits were available from children receiving SP as first-line therapy only at the Prison=s Clinic). Day 0 characteristics of children treated with SP (as either first- or second-line therapy) did not differ statistically from Day 0 characteristics of children treated with CQ.

	1st line	2nd line	Total
SP treatment:	42	23	65
Not meeting entry criteria	1	16	17
Available for analysis	41	7	48
Lost to follow-up			3
Used in analysis			45

Of the 48 children treated with SP, three (6.3%) were lost to follow-up (one moved away, one received extra treatment from mother, and one was taken to a traditional healer against clinical recommendation).

Information about history of prior treatment for the current illness was available for a total of 115 enrolled children (27 from Kapata, 88 from the Prison=s Clinic). Although children were more likely to have been treated with CQ prior to attending the Kapata Clinic than the Prison=s Clinic, the difference was not statistically different (33% and 18.2%, respectively, p = 0.1).

Parasitologic response (Figure 1 and Table 2): Of the 70 CQ-treated patients who completed follow-up, 15 (21.4%) were classified as RIII parasitologic failures and were treated with SP. A further 33 patients (47.1%) were classified as having an RII parasitologic response; 22 patients (31.4%) were classifiable as having an RI/S response. Of the 33 children with RII parasitologic responses, 17 (51.5%) had parasite densities less than 1,000 parasites/mm^3, and none cleared their parasitemia

without further treatment. Of the RI/S responses, 18 patients (25.7% overall) were aparasitemic on Day 7, and an additional 4 patients (5.7% overall) had a negative blood smear prior to Day 7 but were parasitemic on Day 7. Of these 22 patients, however, 12 (17.1%, overall) became parasitemic again on or before Day 14 (early RI). Only 10 (14.3%, overall) were negative on or before Day 7 and remained negative through Day 14 (late RI/S).**

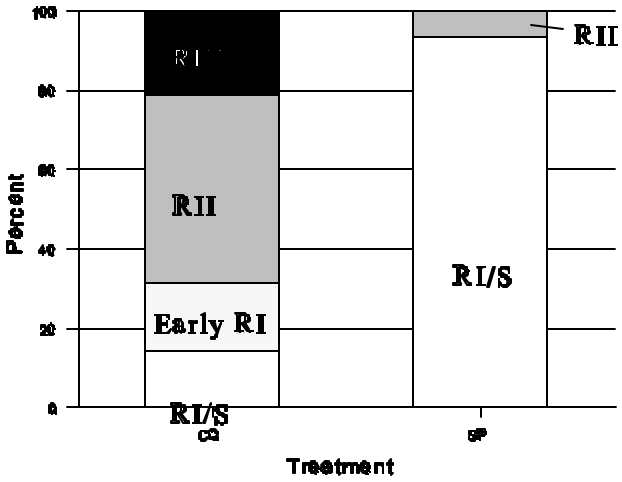

Figure 2: Comparison of the parasitologic response to CQ and SP.

Table 2
Parasitologic Resistance to Chloroquine in Chipata

Resistance Level	Kapata	Prison	Overall % *# (%) Clinical failures*
Number of Patients	22	48	70
RIII	27.3%	18.8%	21.4% *3/15 (20%)*
RII	45.5%	47.9%	47.1% *5/33 (15.2%)*
RI/S	27.3%	33.3%	31.4%

**WHO has proposed a different classification scheme to be used in interpreting *in vivo* studies (WHO 1994). The proposed system categorizes responses into three groups labelled A, B, and C. A AC@ response is any response with a Day 3 parasite density $25% of the Day 0 density or alternative medicine required on or before Day 3. A AB@ response is a positive Day 3 density that is < than 25% of the Day 0 density and a positive Day 7 blood smear or alternative therapy required on any day between Day 3 and 7, inclusive. All other responses are classified as AA@. In practice, this does not differ from the R categories as defined in this study with RIII responses = AC@, RII = AB@, and RI/S = AA@.

RI/S	27.3%	33.3%	31.4% *9/12 (75%)*
early RI	18.2%	16.6%	17.1%
late RI/S	9.1%	16.7%	14.3%
Overall % Clinical Failures	31.8%	20.1%	17/70 (24.3%)

Editorial note: Table 2 became fragmented when prepared for pdf format for the web site. The cells on this page should be read as a continuation of the table on the previous page.

Comparing the parasitologic responses to CQ therapy between the Kapata Clinics and the Prison=s Clinic, there was a suggestion of differing responses. Children attending the Kapata Clinic (n = 22), in an urban setting, tended to exhibit higher levels of resistance than children attending the semi-rural Prison=s Clinic (n = 48). The proportion of RII responses was similar at both sites (45.5% at Kapata, 47.9% at the Prison); however, there were more RIII responses and fewer RI/S responses at Kapata than at the Prison=s Clinic (27.3% vs. 18.8% RIII and 27.3% vs. 33.3% RI/S, respectively). Additionally, there were fewer late RI/S responses at the Kapata Clinic (9.1% vs. 16.7%). Finally, there were more clinical failures at the Kapata Clinic than at the Prison=s Clinic (31.8% vs. 20.1%). None of these differences are statistically significant ($p > 0.3$ for all comparisons).

In comparison to the parasitologic experience of children treated with CQ, of the 45 children treated with SP and completing follow-up, all but 15 (33.3%) were negative by Day 3 (none met the criteria of an RIII parasitologic response and none required examination on Day 4), and all but three (6.7%) were negative on or before Day 7. All three of the children meeting the definition of an RII parasitologic response had very low Day 7 parasite densities (106, 25, and 25 parasites/mm^3). None of the 45 children treated with SP were positive for malaria parasites on Day 14; all three children meeting the definition of an RII response were negative on Day 14 without further treatment.

Initial clinical response: Of the CQ-treated children who were febrile on Day 0, 83.1% were afebrile by Day 2 and 93% were afebrile on Day 3. Of the CQ-treated children who were febrile on either Day 2 or Day 3, only one child on each day was both febrile and parasite negative. Only one (2.2%) of the 45 initially febrile children treated with SP was febrile on Day 3; this child was parasite negative.

Proportion of clinical failure: There were a total of 17/70 (24.3%) CQ-treated children who experienced a clinical failure on or before Day 14. Clinical failures occurred on Days 3 (n = 3), 6 (1), 7 (4), 8 (1), 11 (2), 12 (1), and 14 (5). Twenty percent (3/15) of RIII parasitologic responses, 15.2% (5/33) of the RII responses, and 75% (9/12) of the early RI responses were classifiable as clinical failures (Table 2). One of the SP-treated children exhibiting an RII parasitologic response also had fever and met the definition of a clinical failure. This child had 25 parasites/mm^3 on Day 7, but was negative on Day 14 without further treatment (although this child met the definition of a clinical failure and qualified for alternative therapy with QN, the child had a very low parasite density, and the risk associated with not treating this child and observing for another week was felt to be less than the risk of side effects of treatment with QN).

Duration of clinical response: Among the 17 CQ-treated children experiencing clinical failure, the mean time between initiation of therapy and clinical failure was 9.1 days. If the additional 12 afebrile Day 2 and Day 3 parasitologic failures (nonclinical RIIIs) are included, the mean time between initiation of therapy and clinical failure was 6.6 days. Among the 14 children experiencing a favorable initial response (i.e., afebrile by Day 3) and eventually failing clinically, the mean duration of clinical response was 7.4 days.

Only one SP-treated child met the definition of clinical failure on Day 7; all other children treated with SP had a favorable clinical response and remained well for the 14 days of follow-up.

Hematologic response: Because the prevalence of anemia was too low to include anemic children preferentially and conduct a comparative study between CQ and SP, the hematologic response could not be adequately assessed. However, of the 75 CQ-treated children with Day 0 hematocrits, 8 (10.7%) were moderately anemic

(Hct < 24%) and 21 (28%) were mildly anemic (Hct 24% to 32%); the remaining 46 children (61.3%) were not anemic. Day 4 hematocrits were obtained from a total of 38 CQ-treated children. Of these, 27 (71.7%) were not anemic, 10 (26.3%) were mildly anemic, and 1 (2.6%) was moderately anemic.

Thirty SP-treated children had Day 0 hematocrits; 2 (6.7%) were moderately anemic, 9 (30%) were mildly anemic, and 19 (63.3%) were not anemic. Forty-three of the 45 SP-treated children had Day 14 hematocrits obtained; none were moderately anemic, 34.9% (15/43) were mildly anemic, and 65.1% (28/43) were not anemic.

The overall mean change in hematocrit between Day 0 and Day 14 among 36 CQ-treated children with both values available was +2% (SD = 9.902; range -18% to +24%). Among children initially not anemic (n=19), the mean change in hematocrit was -3.8% (SD = 6.946; range -18% to +7%). Among children with mild anemia initially (n=12), the mean change in hematocrit was +5.583% (SD = 7.128; range -3% to +21%). Among children who were initially moderately anemic (n=5), the mean change in hematocrit was +15.6 (SD = 8.325; range +3% to +24%). The differences in mean hematocrit change over 14 days between these three groups were statistically significant ($p < .001$, ANOVA).

The mean change in hematocrit between Day 0 and Day 14 among 27 SP-treated children with both values available was +1.2% (SD = 7.3). Hematologic responses among SP-treated children who were initially not anemic, mildly anemic, or moderately anemic were similar to the responses seen among CQ-treated children (-3.3%, +6.4%, and +14% respectively). The overall mean hematocrit change between Day 0 and Day 14 was statistically similar between children treated with SP and those treated with CQ ($p = .73$, ANOVA).

IV. Discussion

This study measured a high incidence of CQ resistance in the Eastern Province of Zambia. Overall, 68.5% (48/70) of malaria infections studied demonstrated moderate (RII) to high (RIII) levels of parasitologic resistance to chloroquine. There were an additional 17% (12/70) who experienced a recrudescence between becoming parasite negative and Day 14 (early RI). Only 10 children (14.3%) experienced a parasitologic cure and remained aparasitemic for the duration of the 14 day follow-up period. The parasitologic resistance found in this study was accompanied by a measurable decrease in clinical response to therapy. Of the 70 patients treated with CQ, 41.4% (29/70) experienced either a clinical failure or needed to be switched to an alternate antimalarial drug due to unacceptable parasite response; the mean number of days between initiation of therapy and this failure was 6.6. Therefore, on average, almost half of the children receiving CQ treatment got sick again and needed retreatment in less than one week. In comparison, only 1 (2.2%) of the 45 children treated with SP experienced a clinical failure during the 14 day follow-up period.

An interesting observation was the potential difference between parasitologic and clinical response to CQ between the two clinics. Although the number of children tested at each site was too small to prove or disprove statistically that the difference was real, the tendency for the more urban of the two clinics to have more evidence of declining efficacy, as measured by parasitologic and clinical responses, suggests that future comparisons between urban, peri-urban, and rural populations might be useful. Variations in drug pressure, health facility usage, recognition and response to febrile illness in the home, and other related factors may become important issues not only for therapy efficacy monitoring but also in planning faciltiy-based malaria control activities.

An important parameter for assessing the efficacy of antimalarial drugs is the hematologic response to therapy. This is best accomplished by preferentially enrolling moderately anemic children, randomizing them into groups receiving either CQ or SP treatment, and comparing the change in hemoglobin or hematocrit over the course of follow-up. This obviously makes most sense in epidemiologic settings where anemia is highly prevalent; in areas where anemia is less prevalent, preferential enrollment of anemic children might produce an unrepresentative sample and biased results. Initial screening of children in Chipata District demonstrated that at this time of year in this location, anemia was not of sufficient prevalence to allow an adequate evaluation of hematologic response to therapy without running the risk of biasing the results of the parasitologic and clinical evaluation components. Nonetheless, between 36.7% and 38.7% of enrolled children and 31.6% of screened children were mildly or moderately anemic, suggesting that even during the relatively low malaria transmission season during which this study was conducted, the ability of malaria therapy to resolve malaria-associated anemia should remain a primary concern.

The mean change in hematocrit among anemic CQ-treated children was 8.5% (95% confidence interval [95%CI] = 4.4% to 12.6%), which is comparable to the hematologic response to SP in other areas of Africa where this type of study has been conducted (Bloland et al. 1993). Additionally, the hematologic response among CQ-treated children was not statistically different from the hematologic response among SP-treated children, although the number of anemic children enrolled was insufficient to adequately evaluate the current efficacy of CQ with regard to resolution of anemia with any reasonable statistical power.

Another possible explanation for a lack of difference between the hematologic response to CQ and SP might be the relative proportion of anemia that is due to malaria infection; malaria-specific therapy would not be expected to have a significant impact on non-malarial anemia. If, in this area and at this time of year, the majority of anemia is related to nutritional deficiency, for example, then a measurable difference between treatment groups might not be seen. While these issues need to be addressed in future studies, the results of this study suggest that the hematologic response to CQ therapy may still be relatively good.

These results more strongly illustrate that at least in this area of the Eastern Province of Zambia, CQ resistance has intensified to levels only slightly lower than those found in Kenya (between 75% and 82% RII + RIII), and Malawi (between 81% and 82% RII + RIII), and well beyond the level in Rwanda (24% RII + RIII) prior to those countries' decision to change their national malaria treatment policies replacing CQ with SP as the first-line therapy for uncomplicated malaria.

V. Policy/Program Implications

It is difficult to set firm guidelines on when to change first-line malaria therapy, and any decision to change first-line malaria therapy must be based upon the specific needs and situation of the country considering such a change. Nonetheless, a number of suggestions have been made as to what a reasonable decision point might be. WHO has suggested that clinical failures of 25% is an upper limit that should not be allowed to be reached (WHO 1994, Shapira et al. 1993). Based on a 28-day *in vivo* test in areas with a high prevalence of malaria-associated anemia, Bloland et al. (1993) have suggested that first-line antimalarial therapy be changed when the mean duration of clinical response decreases below 14 days and optimal hematologic response does not occur. In Chipata, at least, clinical failures accounted for between 24.3% (excluding parasitologic RIII responses requiring second-line therapy during the first two to three days of therapy) and 41.4% (including parasitologic RIII

responses) of CQ treatments. The study conducted in Chipata had only 14 days of follow-up, making it difficult to estimate the duration of clinical response that is comparable to previous studies. Nonetheless, 41.4% of CQ-treated children required alternate therapy in a mean of only 6.6 days after initiation of therapy. In comparison, 97.8% of children treated with an effective antimalarial improved clinically and remained well for the full 14 days of follow-up. Clearly, CQ therapy in Chipata offers only limited chances of producing a cure in sick children and, by the standards proposed, should be abandoned in preference to an effective antimalarial therapy.

There are measurable benefits to changing the first-line malaria therapy when high degrees of resistance occur. In a study conducted in Kenya shortly before its decision to change to SP as the drug of choice for uncomplicated malaria, children with a primary diagnosis of malaria were monitored during hospitalization and for 8 weeks afterward. The malaria-specific case fatality rates (CFR) were compared between children receiving CQ therapy (then the recommended first-line therapy) and children receiving an alternate, effective antimalarial therapy (either SP, cotrimoxazole for five days, or QN). The CFR for children receiving CQ was an astounding 33% whereas the CFR for children receiving effective therapy was 11% (Zucker et al., in press). The proportion of deaths that were statistically attributable to receiving ineffective malaria therapy was 67%.

Surveillance of malarial illness in pediatric populations being conducted in Malawi since the change in malaria therapy policy has demonstrated decreases in hospitalizations and deaths in hospital attributed to malaria (Ziba et al, personal communication).

In addition to reducing hospitalizations and mortality due to malaria, it has been suggested (although not yet quantitatively proven) that effective antimalarial therapy will decrease the need and frequency of pediatric blood transfusions. Finally, by improving the cure rate and extending the period between initial malaria therapy and reappearance of malaria illness (associated with either a clinical recrudescence or reinfection), the number of clinic visits and malaria treatments devoted to retreatment of therapy failures will be reduced, yielding cost savings and improvements in the ability of clinical staff to administer quality care.

One concern often raised when a change in the first-line malaria therapy policy is considered is the cost of making such a change. Based upon a number of educated assumptions and a cost-effectiveness analysis, Sudre et al. (1992) have shown that when the prevalence of RIII-level CRPf is greater than 14% to 31% (depending upon anticipated compliance with the CQ treatment regimen), SP becomes the most cost-effective therapy. Indeed, based on the retail cost of 1,000 tablets of SP bought in Lusaka and current exchange rates (Kw 850/US$), the cost of treating a child under 5 years of age with SP would be between less than US$0.03 and US$0.10, depending on the child=s age. For patients in this study, the average cost per child treated with CQ syrup was US$0.14 or 119 Kwacha (average dose based upon 25 mg/kg was 26.3 mls of CQ syrup), whereas the average cost per child treated with SP was only US$0.05 or 43 Kwacha (average dose was **2** tablet of SP). Further cost reductions could be expected if SP is bought in bulk by the government.

In this study the efficacy of CQ treatment was compared to that of SP. SP was chosen because it is probably the most viable alternative to CQ in terms of efficacy and cost. Other available alternatives, such as mefloquine, although highly effective, are much more expensive. There are some concerns with the use of SP, however. The pharmacokinetics of the components of SP, sulfadoxine and pyrimethamine, are not well matched (serum half-lives are 180 days and 90 days, respectively). This raises the possibility of facilitating the

development of resistance by leaving one component Aunprotected@ by the second. Other sulfa-dihydrofolate reductase inhibitor combinations, such as metakelfin (pyrimethamine and sulfalene), are better matched and may avoid this theoretical concern. The use of long half-life sulfa drugs has also been associated with severe and occasionally fatal allergic cutaneous reactions. These reactions have been seen predominantly with prophylactic rather than therapeutic use of SP. Finally, there are concerns about a higher incidence of severe reactions to SP among populations with a high prevalence of HIV. All of these concerns need to be weighed against the known risks of inadequate malaria therapy, as is seen with CQ.

A rational approach needs to be used in conducting a complete evaluation of national malaria treatment guidelines. A conceptual model for such an approach is being developed for use by sub-Saharan African countries that are or soon may be facing the need for revision of malaria treatment policy. The model begins with a recognition at the national level that a problem with the current guidelines exists, frequently exhibited by a growing impression by medical practitioners and patients that treatment failures are increasing in frequency. Countries with well-developed health information systems may recognize increases in admission or deaths attributed to malaria or increases in pediatric blood transfusions. This is followed by the collection of baseline information using established, standardized methods with which to verify this impression.

Very early in this process, a meeting should take place involving national policymakers, practicing physicians or clinical officers, university or research center staff who are working on malaria within the country, representatives of governmental and nongovernmental agencies involved with the health sector, and appropriate members of the private sector (such as representatives of pharmaceutical concerns). The primary purpose of this meeting would be to review the existing data and define as specifically as possible the goals of malaria therapy (i.e., what, on a national, regional, or individual level, is expected of malaria therapy with regard to resolution of the acute illness, duration of clinical response, ability to resolve malaria-associated anemia, ability to interrupt the progression of illness towards severe disease or death). The usefulness of these goals of therapy would lie in their ability to provide an objective measure by which to judge existing therapy guidelines; without such a measure, the decision of whether a particular therapy option does or does not Awork@ becomes problematic and prone to either belated or premature changes. Once these goals of therapy are articulated and agreed upon, the assembled experts can identify what additional information is needed for decision making, decide on standardized methodologies to be used to collect that information, allocate responsibility for the collection of the information, define the time-line for data collection, and coordinate resources.

A period of collection of data needed for decision making would follow the meeting. Using the new data and information collected, the current malaria treatment guidelines would be re-evaluated against the previously defined goals of therapy (i.e., does the currently recommended first-line malaria therapy meet or exceed the stated standards and goals of therapy or not?). Rational, informed decisions can then be made about the appropriate response and actions to be taken.

Experience in other countries suggests that even when a less formal approach is taken, several years are needed to decide upon and implement a change in malaria treatment policy. Conducting additional research (if needed), training medical staff and developing the necessary training materials,
organizing the logistics of purchase and distribution the new drug, and patient education, for example, all take a considerable amount of time. If a change in therapy policy is expected, a minimum of two to three years before complete implementation must be anticipated.

A number of options exist for addressing increasing CQ resistance that stop short of total nationwide abandonment of CQ. If research indicates that CQ resistance is approaching but has not yet reached intolerable levels (such as the proposed 25% clinical failure figure), operational improvements in early identification of CQ failures can be made. Although most countries have written policies concerning the proper use of second-line malaria therapy, patients with believable histories of repeated CQ treatment failure are frequently placed yet again on CQ. This is often due to lack of available therapeutic alternatives or lack of understanding or initiative on the part of the health care provider. In areas of subcritical CQ resistance, improved availability and use of second-line therapy might decrease the burden of illness due to CRPf while still having CQ available as the

first-line therapy. This latter approach, however, must be implemented in a way that assures the proper training of staff and the ready availability of and access to the the second-line drug at all levels of health care; realistically, anything less than this would be equivalent to no change at all.

If research suggests that intolerable levels of CRPf can be associated with geographically definable areas, a targeted approach can be applied where the first-line therapy is changed only in those areas that are in need. Continued surveillance of CRPf could then be used to monitor the needs in other areas, and changes in first-line therapy could be phased in to other areas of the country when and if needed. This might be an appropriate response to the situation in Chipata, if further research suggests that the district is more the exception than the rule with regard to CRPf.

Finally, whether a total change in first-line malaria therapy is required or not, continued monitoring of malaria therapy efficacy, using standardized methodology and rigorous quality control, is essential. Whatever the first-line therapy, whether it is continued use of CQ, targeted use of SP, or a total switch to SP, there will be a continued need to assess the efficacy of CQ periodically and judge it against defined goals of therapy. The reality of the malaria situation in most of the world today is that it is highly unlikely that any antimalarial drug will have an unlimited useful lifespan. If CQ is replaced by SP as first-line therapy for malaria, there will be an ongoing need to monitor the efficacy of SP in order to recognize and address in a timely fashion the advent and intensification of SP-resistant malaria. Although many are concerned with what seems to be a future of constantly switching from one drug to another in the face of developing resistance, the only alternative at present is to continue using a drug of known inefficacy and face a future of increasing incidence of illness and death associated with treatment failures due to CRPf.

In summary, this first of a number of investigations into the efficacy of malaria therapy in Zambia has identified a serious problem at one site in Eastern Province. While more data are clearly needed to ascertain the national distribution of CRPf and the intensity of resistance in other regions of the country, the information derived from this study supports the need to begin the process of formally addressing CQ resistance and to move toward replacing CQ as the drug of choice for nonsevere malaria, at least locally if not nationally.

ANNEX

Summary of Data from Dropped or Excluded Patients

Nine patients were dropped from the CQ arm of the study and two were excluded from analysis. The following is a brief description of what is known about these patients.

K048 Moved away. Day 2 last day seen. Parasite density on Day 2 was 400/mm^3 (1.2% of Day 0).

P077 Moved away. Day 3 last day seen. Parasite density on Day 3 was 3,809/mm^3 (3.9% of Day 0).

P118 Moved away. Day 3 last day seen. Parasite density on Day 3 was 180/mm^3 (1.0% of Day 0).

K114 Hospitalized and diagnosed with meningitis. Day 1 last day seen.

K218 Refused. Day 2 last day seen. Parasite density on Day 2 was 13,333/mm^3 (64% of Day 0). Father was given SP to give to child at home.

P088 Mother felt child was not getting better. Day 2 last day seen. Parasite density on Day 2 was 27,033/mm^3 (67% of Day 0). Child was treated with SP by study team on Day 2 and mother told to take child to hospital.

P106 Missed CQ dose on Day 2. Incorrect directions given to home; patient could not be found.

P163 Persistent vomiting. Day 2 last day seen. Parasite density on Day 2 was 727/mm^3 (4.9% of Day 0). Mother was given SP to give to child at home.

P167 Mother gave extra CQ. Day 1 last day seen. Mother was given SP to give to child at home.

K108 Afebrile on Day 0. Excluded from analysis. Child experienced an RII parasitologic response and a clinical failure on Day 14.

K124 Afebrile on Day 0. Excluded from analysis. Child experienced an RII parasitologic response and an asymptomatic recrudescence on Day 14.

Appendix C
Training Provided and Studies Conducted
January 31-March 30, 1996

1. Places and Dates of Travel

Barat:	Lusaka, Zambia	31 January-5 February, 1996
	Chipata	6 February
	Lundazi	7-19 February
	Lusaka	20-29 February
	Lundazi	1-3 March
	Lusaka	4-8 March
	Choma	9-10 March
	Lusaka	11 March
	Mansa	12-23 March
	Lusaka	23-28 March
Ruebush:	Lusaka	31 January-6 February, 1996
	Lundazi	7-17 February
	Lusaka	18 February
	Choma	19-24 February
	Lusaka	25 February-3 March
Ettling:	Lusaka	17-21 March
	Mansa	22 March
	Lusaka	23-30 March

2. Principal Contacts

Lusaka:
- Dr. K. Kamanga, Permanent Secretary, Ministry of Health (MOH)
- Dr. D. L. Kasanda, Director, Basic Health Programs, MOH
- Dr. D. Phiri, Director, MCH/Family Planning, MOH
- Dr. B. Himonga, Director, National Malaria Control Centre (NMCC)
- Dr. S.L. Nyaywa, Team Leader, Health Reform Implementation Team
- Prof. G.J. Bhat, Director, Department of Pediatrics and Child Health, University Teaching Hospital
- Dr. C. Mukuka, Staff Pediatrician, University Teaching Hospital
- Dr. Remi Sogunro, Chief of Party, Zambia Child Health Project, BASICS

Lundazi:
- Mr. Peter Mphande, Director, District Health Management Team (DHMT)
- Dr. Fasola, Director, Lundazi District Hospital

Chongwe:
- Mr. A. Musole, Director, DHMT and Director, Chongwe Health Center

Choma: Dr. M. M. Silomba, Director, Choma General Hospital
Dr. C. Sichone, Deputy Director, Choma General Hospital
Mr. Mwa-anga, Director, DHMT

Chipata Compound (Lusaka):
Dr. C. S. Wamulume, Acting Director of Public Health, Lusaka City Council
Dr. S. Malumo, Director, Chipata Clinic

Mansa: Dr. Kaoma, Medical Director, Mansa General Hospital
Mr. A. Mungole, Senior Principal Clinical Officer, Luapula Province Health Management Team

3. Findings from Studies at Five Sites
January 31-March 30, 1996

A. Screening:

As shown in Table 1, there were differences in both age and sex distributions of febrile children presenting at the five hospital or clinic outpatient departments. Children screened in Lundazi were significantly younger (mean age, 15.2 months) compared with the other four sites (mean age, 19.9-22.9 months). There was a female predominance in Chongwe and a male predominance in Mansa. The other three sites had relatively equal sex distributions. These differences are not thought to have appreciably influenced the results of testing.

Table 1. Characteristics of Febrile Children Presenting to Outpatient Departments at Five Sites Who Underwent Screening for Antimalarial Drug Efficacy Studies

Site	Lundazi	Choma	Chongwe	Mansa	Isoka
Number Screened	350	207	119	100	116
Number Enrolled (%)	98 (28)	51 (25)	54 (45)	52 (52)	57 (49)
Mean Age (months)	15.2	22.9	21.6	19.9	21.3
Female (%)	182 (52)	97 (47)	68 (57)	42 (42)	61 (53)
Smear Positive (%)	280 (80)	169 (82)	83 (70)	82 (82)	105 (91)

Slide positivity rates were similar in the five sites, ranging from 70% in Chongwe to 91% in Isoka. Of note, screening of 100 febrile children at Chipata Clinic, Chipata Compound, Lusaka District demonstrated malaria parasites in only 15% (results not shown in table) and most of those who were smear positive had traveled to other areas of Zambia in the last month. (That site was dropped from the study.) There was a large difference in

the percentage of febrile children with high-level parasitemia (> 2000 parasites/µl) ranging from 39% in Lundazi to 68% in Mansa.

B. Patient Characteristics on Enrollment:

Differences in mean age and sex distribution among study participants at the five study sites appear to reflect the demographics of the screening population, although a higher percentage of females was enrolled in Chongwe (Table 2). From 11% to 26% of enrolled children had received at least one dose of CQ for treatment of their current illness prior to enrollment. Differences were also apparent in the geometric mean parasite densities on enrollment, ranging from 26,485 parasites/µl of blood in Mansa to 63,095 in Isoka.

Table 2. Characteristics of Children with *Plasmodium falciparum* Infection Enrolled in Studies to Assess Antimalarial Drug Efficacy

	Lundazi	Choma	Chongwe	Mansa	Isoka
Number Enrolled	98	51	54	52	57
Mean age (months)	15.0	24.9	24.9	21.2	22.0
Female (%)	51 (52)	24 (47)	36 (51)	25 (48)	28 (49)
Prior Treatment with CQ (%)	20 (20)	11 (22)	6 (11)	10 (19)	15 (26)
Geometric Mean Parasite Density (/µl)	41,400	52,723	31,623	26,485	63.095

C. Parasitologic Outcomes:

The percentage of children treated with CQ who were classified as either RIII (high) or RII (moderate) parasitologic failures were similar in Lundazi (55%), Choma (55%), Chongwe (47%), and Isoka (50%); 33% in Mansa were classified as RII/RIII parasitologic failures (Table 3). Seventeen percent of children treated with SP in Lundazi were RIII/RII parasitologic failures. Five of the six children with RII resistance had parasite densities of < 200 parasites/ul on Day 7 and had negative blood smears on Day 14 without additional treatment.

Table 3. Parasitologic Outcomes of Children with Malaria Treated with Chloroquine (CQ) or Sulfadoxine-Pyrimethamine (SP)

Site	Lundazi	Choma	Chongwe	Mansa	Isoka	Lundazi
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Treatment	**CQ**	**CQ**	**CQ**	**CQ**	**CQ**	**SP**
Evaluable	40	49	47	39	54	41
RIII	10 (25)	9 (18)	11 (23)	3 (8)	11 (20)	1 (2)
RII	12 (30)	18 (37)	11 (23)	10 (26)	15 (28)	6 (15)
Total RIII/RII	**22 (55)**	**27 (55)**	**22 (47)**	**13 (34)**	**26 (48)**	**7 (17)**
RI/S	18 (45)	22 (45)	25 (53)	26 (66)	28 (52)	34 (83)

D. Clinical Outcomes:

From 79% (Chongwe) to 90% (Mansa) of children treated with CQ had a favorable Initial Clinical Response by Day 3 (Table 4). However, 28% (Mansa) to 53% (Chongwe) were classified as Clinical Failures. Only one child treated with SP was still febrile on Day 3, and this child was the only SP-treated child classified as a Clinical Failure.

Table 4. Clinical Outcomes of Children with Malaria Treated with Chloroquine (CQ) or Sulfadoxine-Pyrimethamine (SP) at Five Study Sites

Site	Lundazi	Choma	Chongwe	Mansa	Isoka	Lundazi
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Treatment	**CQ**	**CQ**	**CQ**	**CQ**	**CQ**	**SP**
Evaluable	40	49	47	39	54	41
Initial Clinical Response	33 (83)	41 (84)	37 (79)	35 (90)	45 (82)	40 (98)
Clinical Failure	13 (33)	21 (43)	19 (40)	11 (28)	25 (46)	1 (3)