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The role of chemotherapy in malaria control through primary health care: constraints and future prospects

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In the context of the malaria situation in tropical Africa, there continues to be an urgent need to make available as widely as possible the treatment of malaria cases and malaria prophylaxis. The current effort to establish community-based primary health care facilities provides an opportunity for application of these measures in wide areas of this region. If successful, the contribution to reducing morbidity and mortality would be substantial. Despite the results of previous studies on the delivery of malaria chemotherapy through primary health care channels, much more information is needed, and careful evaluation of all such programmes is highly important.

There is a continuing need for expert guidance to determine the most appropriate and most effective patterns of drug use under a variety of circumstances. The status of antimalarial drug efficacy is not in any way static, so that constant re-evaluation of drug response, drug acceptance, significant side-effects, and alternative compounds is needed.

The use of chemotherapy in malaria control predated by several centuries the discovery of the etiology and mode of transmission of the disease. During the early years after the discovery that the mosquito was responsible for the transmission of malaria, there was great hope that antimosquito measures could significantly reduce the effects of the disease in endemic areas. Despite some early successes, it soon became evident that there was still heavy reliance on the old stand-by, quinine, to provide, as described by Hackett (*1*), the "irreducible minimum" in malaria control, i.e., the reduction of mortality and morbidity. The advent of new and effective therapeutic drugs—particularly the 4-aminoquinolines—in the 1940s provided, for the first time, reliable and acceptable means for treating acute malaria and for malaria prophylaxis. However, the nearly simultaneous development of the persistent insecticides overshadowed the chemotherapeutic advances by providing a reasonably inexpensive and often effective means for reducing the transmission of malaria. So great was the optimism engendered by the new technology of insecticidal control that worldwide malaria eradication became an accepted concept.

The role of chemotherapy in eradication programmes was initially limited to the treatment of individual cases during later programme phases, but, as insecticide resistance and other technical and administrative problems resulted in failure to meet programme objectives, the introduction of mass drug administration became relatively widespread. This, along with the "presumptive" and "radical" treatment components of eradication programmes, has provided a vast amount of experience in the use of antimalarial drugs during the past 25 years. This widespread use has also resulted in, or perhaps revealed, widespread parasite resistance to the major drugs for prophylaxis or therapy of malaria. During this same period, little has been added to the armamentarium of malaria drugs—only synergistic drug combinations, such as pyrimethamine–sulfadoxine (Fansidar), and one new synthetic schizontocide (mefloquine) have reached or approached usefulness. Both Fansidar and mefloquine have an unpredictable half-life of efficacy before the development of resistance significantly reduces their value. A pessimistic, but undoubtedly realistic, view of the implications of the current status of multi-drug resistance has recently been provided by Wernsdorfer (*2*).

Nevertheless, with malaria showing a resurgence in many areas of the world and with the great pool of hyperendemic malaria in Africa virtually untouched, our reliance on chemotherapy today is greater than at any time in the past. In 1979, the WHO Expert Committee on Malaria (*3*) proposed four "tactical variants", representing antimalaria programme goals and objectives appropriate to a given malaria situation. The objectives vary within a spectrum of control efforts, ranging from the reduction of mortality in limited areas of risk to the implementation

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of a countrywide eradication programme. The two variants appropriate for most of Africa south of the Sahara are (1) the reduction and prevention of mortality due to malaria, and (2) the reduction and prevention of mortality and morbidity, with special attention to reduction of morbidity in high-risk groups. Application of these variants places virtually total reliance on the use of chemotherapeutic agents. In the absence of well organized vertical malaria control programmes in much of Africa, the use of chemotherapeutic methods devolves on the existing health services, some well organized, some more rudimentary in nature. Since the Alma-Ata declaration (*6*), there has been a growing emphasis on utilizing community-based primary health care systems for such control efforts. Incorporating malaria chemotherapy into such systems poses significant problems, and at the same time holds the only immediate prospect for relief from the heavy burden of malaria mortality and morbidity in most of the rural and periurban areas of Africa south of the Sahara.

In the wake of the Alma-Ata Conference and stimulated by the subsequent adoption by WHO in 1981 of the global strategy for health for all by the year 2000 (*7*), there has been a surge of interest in the development of the community-based primary health care concept in all medically underserved nations of the world. There has been early recognition of the diversity of approaches possible in the various regions and countries. It is apparent that no single model can be offered, but the literature now abounds with reports of pilot schemes and of positive and negative experiences. Indeed, the efforts to define successful methods for organizing and operating community-based primary health care systems have been almost overwhelming. Nearly every volume of the *WHO Chronicle* has an article describing such an effort. The relatively new periodical, *World health forum*, has an entire section devoted to primary health care, usually with as many as 4 or 5 articles per number. Numerous bibliographies on primary health care have appeared and the American Public Health Association has developed a series of monographs on *Primary health care issues*. WHO has prepared reviews of primary health care programmes in several African countries and, in collaboration with UNICEF, has held workshops on the subject in Mozambique and Senegal. In addition to the conceptual and material support given by WHO, UNICEF, and other international organizations, bilateral assistance for the development of pilot systems in developing nations has been extensive. For example, during the years 1977–81, USAID provided assistance for the development of primary health care programmes in a dozen or more African nations in an amount exceeding US$80 million.

A particularly enlightening description of the problems and principles of primary health care organization was provided by Dr R.A. Smith in the *World health forum* (*4*). This did not explore in great detail the particular problems facing the extreme periphery of the community-based primary health care network, but did point out a number of organizational necessities, without which no peripheral unit could succeed. The entire structure of the primary health care system will vary widely in relation to cultural, political, economic, sociological, and many other factors in the various African nations, but it is perhaps at the periphery where the greatest variability in the mechanism and scope of delivery of health services will exist. Nevertheless, there are efforts in every nation to establish and expand primary health care networks to make available a growing spectrum of health services to the entire population. The role of the primary health care system in the chemotherapy of malaria will be a significant one, but will require careful consideration of potential constraints related to areas such as drug efficacy, population coverage, applicability of community participation, and national support.

The constraints at the national/central/provincial levels are well known and need not be repeated in detail. They include a low level of economic development, lack of a clear national health policy and a sound health manpower policy, and lack of suitable planning. Leaving aside these constraints, one can consider those that would principally affect the ability of the most peripheral health unit or worker to provide the chemotherapeutic intervention necessary to implement the first two tactical variants of antimalaria activities given above.

ANTIMALARIA ACTIVITIES APPROPRIATE FOR PRIMARY HEALTH CARE UNITS

Chemotherapy

The successful application of the first tactical variant—the elimination of malaria mortality—would constitute an enormous advance towards the goal of health for all by the year 2000. To progress towards this goal, the initial and overriding priority would be to provide an effective drug to all suspected cases of malaria. There are major limitations in successfully applying this measure, such as:

— limitation of outreach capacity to geographically remote areas and particularly to nomadic populations;
— inability to make efficient use of community resources, both human and material;
— difficulty in achieving full community acceptance of chemotherapy;
— insufficient training of local health workers;

— lack of understanding of health problems and their solutions;
— potential ineffectiveness of the curative drug or drug dosage used, usually through the emergence of parasite resistance to the drug;
— undesirable side-effects of the drug.

Chemoprophylaxis

The second tactical variant includes treating malaria cases and the extending of organized prophylaxis to the groups most vulnerable to malaria — pregnant women and children up to the age of 5 years. Such a programme is considerably more complex than the first variant and, in addition to the constraints associated with treatment of cases, has further limitations, including:

— difficulty in achieving adherence to the reported, periodic administration of prophylactic drugs for extended periods of time;
— excessive burden of work imposed on community health workers.

Health education

It has often been stated that one of the major functions of community health workers should be to provide health education to the population being served. This effort promotes the acceptance and success of all drug distribution programmes and also provides a basic understanding of malaria transmission, enabling populations to begin efforts towards individual and collective self-protection from vector contact. The success of such endeavours depends on the availability of local personnel with proper training and able to devote time to instructional programmes, on the availability of educational materials for training at the community level, and on community will to support health programmes that do not directly involve curative measures.

FUTURE PROSPECTS

Community-based primary health care systems

The prospects for expanding and replicating such primary health care systems seem good for the immediate future, if use is made of models described in the numerous studies of the past few years. The structure of these systems, the involvement of volunteer or paid workers, the spectrum of health services provided, and many other aspects will continue to vary widely, depending on the political, economic, cultural, and ecological characteristics of the areas served. It is likely that malaria treatment will continue to be one of the main concerns of the primary health care units. One of the examples of a thorough study of rural health care in Africa is the Danfa Project in Ghana, and the general conclusions and recommendations developed from this study are undoubtedly widely applicable. The final report on this project (*5*) outlined the essential criteria of a feasible rural health care programme for Ghana as follows:

— it must deal with the major causes of morbidity and mortality to the extent feasible with existing technology;
— it must be accessible to a large proportion of the population and result in high participation rates;
— it must be feasible to implement it with existing national resources;
— its most important objectives must be capable of being evaluated.

Although it was not one of the project's initial objectives, the programme evolved into a more village-based primary health care programme, and it was concluded that such village-based primary health care, using village health workers, might be the only feasible method at present of bringing health care to rural areas in Ghana that will have a significant impact on health status.

While it is desirable for a primary health care unit to deal with multiple disease control and other health-related tasks, the scope of activities must not exceed that which can be supported by the national health structure, nor that which can be accomplished by the number and quality of health workers involved. It is far better to have a few tasks accomplished well than superficial coverage of a wider range. In areas where the treatment or prophylaxis of malaria is of highest priority, this alone might be an appropriate beginning of a primary health care effort, with the possibility, as human and material resources become available, of adding other health-related measures. Indeed, during the worldwide malaria eradication effort, the community volunteer who distributed antimalarial drugs to suspected cases provided the first evidence of rural primary health care in many areas of the world. It should be noted again that, without community will and community participation, there is little hope of success in such primary health care programmes.

Presumptive treatment

Presumptive treatment is the term often applied to the treatment of cases suspected of being malaria on the basis of symptoms experienced by the patient, but not specifically diagnosed by blood film examination prior to treatment. Its efficacy relies (1) on knowledge of the symptoms suggestive of a malaria attack on the part of the patient who may be seeking treatment or on the part of the health worker who may be seeking malaria cases for treatment, and (2) on the effective-

ness of the antimalarial drug administered. The wide availability and use of presumptive treatment through a primary health care unit is undoubtedly the most effective single measure for reducing malaria mortality. The use of passive treatment posts, i.e., fixed posts where persons with suspected malaria can come for treatment, is reasonably effective, provided the posts are within easy reach of a large proportion of the population and are heavily patronized by the population. Even more effective is the active search for cases where the entire population is contacted on a regular schedule for treatment of symptomatics. Both systems are well within the scope of community-based primary health care units and have been shown to be effective when staffed by community volunteers or by paid community health workers. In some instances, volunteer workers have been successful in reaching a higher proportion of the population.

Selecting the most effective and acceptable drugs and drug dosages for use in presumptive treatment remains a difficult problem. In theory, the drug used should be curative with a single dose, have minimum side-effects, and be acceptable to the population. In the past, chloroquine or other 4-aminoquinolines have best met these criteria, and they remain the drugs of choice in much of Africa. However, in East Africa parasite (*Plasmodium falciparum*) resistance to chloroquine is being seen in a number of areas, and in some, resistance has reached relatively high levels. In these areas, it may soon be necessary to consider the wider use of pyrimethamine–sulfadoxine or other similar drug combinations for therapy.

The most common single-dose treatment for suspected malaria has been 600 mg (base) of chloroquine as the adult dose (approximately 10 mg/kg body weight). This has usually been effective as a curative dose for *P. falciparum* in semi-immune populations, but must be considered to be at the borderline of curative activity. The usual recommendation for fully curative therapy with chloroquine has been the administration of 1.5 g (base) over a 3-day period (approximately 25 mg/kg). Views as to the adjustment of drugs and dosages to deal with the problem of less sensitive strains of *P. falciparum* or with populations with lower immunity are varied, and expert guidance on this question is urgently needed.

Another question that remains unresolved is the desirability of including a sporontocidal drug, e.g., primaquine, as part of the presumptive treatment as a means of securing the immediate elimination of the transmissibility of the infection. The potential impact of this on the transmission of malaria and as a possible protectant against resistance to the accompanying schizontocide requires clarification by field studies; such studies have been urged by WHO scientific groups and expert committees for more than 20 years, but to date no definitive study has been done. It is widely accepted that primaquine toxicity is negligible in the single dosages that have been shown experimentally to be effective as a sporontocide.

As a matter of interest, a few years ago the cost of chloroquine required to administer 100 million adult dosages (600 mg base) for presumptive treatment was about US$6 million, exclusive of all other distribution costs. At today's prices, US$7.5 million is the estimated cost for 100 million doses.

Prophylaxis

It is generally agreed that, in highly endemic areas, significant benefits in reducing morbidity and mortality will accrue to population segments protected by malaria prophylaxis. It is also generally agreed that the two population segments at greatest risk are pregnant women and children up to the age of five years. On other issues, general agreement is difficult to find. There are valid questions as to the desirability of including additional groups (e.g., older children, economically important workers); the selection of drugs, dosages, and treatment intervals; the use of year-round rather than seasonal prophylaxis; the type of personnel or health units used in drug distribution (volunteers as against paid workers, use of maternal and child health clinics and schools, etc.); and many other variables. Here again there is no single model that will satisfy all conditions, but there are many reports of pilot trials, which can suggest the appropriate programme structure for a given situation.

While there is no doubt as to the benefits of regular prophylaxis in pregnant women (reduced fetal wastage, higher birth weights, etc.) and in young children (reduced mortality and morbidity), there are still several important unanswered questions as to the possible undesirable effects of such programmes. One is the presumed reduction in acquired immunity in children maintained on prophylaxis during the first five years of life, making them more susceptible to severe malaria attacks when prophylaxis is withdrawn. While this is a theoretical hazard, there is little evidence that there have been severe consequences in such populations. In a normally imperfect programme of prophylaxis there are likely to be frequent inoculations, which would result in at least occasional brief parasite experiences; further, the older child should be better able to withstand a severe malaria attack than the child of 1–5 years, and might be more apt to receive timely therapy. One would expect that, in any area where programmes of prophylaxis are under way, treatment of suspected cases would also be readily available.

The second problem associated with prophylaxis is the increased potential for the development of drug resistance in the parasite. This has been well demonstrated where either pyrimethamine or proguanil have

been used as the prophylactic drug, but not where the 4-aminoquinolines have been used. Nevertheless, on theoretical grounds, there is concern that the use of the latter drugs in prophylaxis will, especially in areas where less sensitive strains have emerged, contribute to the accelerated development of chloroquine resistance.

In any area where there is wide usage of drugs for malaria prophylaxis or therapy, it is essential that there should be an organized effort to monitor the sensitivity of the parasite to the drugs in use. While this organized effort is more appropriate as a function of the national health structures, there is a role for the peripheral primary health workers in noting and reporting to higher levels of health care any unusual drug response. This mechanism would be of great value in providing an early warning of impending drug resistance problems.

It should be noted that programmes of prophylaxis are relatively costly — much more so than programmes of presumptive treatment. One study has estimated the cost of application throughout tropical Africa to the two groups — pregnant women and children up to the age of five — to exceed US$36 million annually, just for the drugs alone, excluding costs of distribution and administration.

RÉSUMÉ

RÔLE DE LA CHIMIOTHÉRAPIE DANS LA LUTTE ANTIPALUDIQUE PAR LE CANAL DES SOINS DE SANTÉ PRIMAIRES : CONTRAINTES ET PROMESSES

En ce qui concerne le paludisme, la situation actuelle en Afrique tropicale rend toujours aussi impératif et urgent d'assurer aux populations une couverture thérapeutique et prophylactique aussi large que possible. Les efforts qui sont déployés en vue de créer à l'échelon communautaire des services de soins de santé primaires vont permettre d'appliquer ces mesures dans de vastes zones de cette région. En cas de succès, la réduction de la morbidité et de la mortalité serait importante. L'accès de la population à la chimiothérapie antipaludéenne par le canal des soins de santé primaires avait déjà fait l'objet d'études, mais il y a encore beaucoup à faire sur ce plan, outre d'ailleurs la nécessité d'évaluer soigneusement tous ces programmes.

Parmi les activités antipaludiques qui sont adaptées aux unités de soins de santé primaires figurent la chimiothérapie, qui vise à éliminer la mortalité due au paludisme, et la chimiopropylaxie, qui vise à protéger les groupes à haut risque. La mesure la plus efficace pour réduire la mortalité palustre consiste à faire bénéficier largement d'un traitement présomptif, par le canal du système de soins de santé primaires, les sujets ayant des symptômes évoquant le paludisme et chez lesquels le diagnostic n'a pas été confirmé par un frottis de sang. Dans la mesure du possible, la population entière sera contactée à intervalles réguliers en vue d'un dépistage actif. Il a été démontré que des bénévoles peuvent ainsi souvent atteindre une proportion élevée de la population.

Une prophylaxie systématique chez les femmes enceintes et les jeunes enfants est, certes, incontestablement bénéfique, mais elle est beaucoup plus coûteuse que le traitement présomptif. En outre, il existe la possibilité qu'elle réduise l'immunité acquise chez les enfants et augmente le risque d'acquisition d'une pharmacorésistance par le parasite. Il convient que les agents de soins de santé primaires soient attentifs à toute réaction inhabituelle aux médicaments pouvant être l'indice précoce de problèmes imminents de résistance à la chimiothérapie.

L'avis des experts est toujours aussi nécessaire pour déterminer les schémas d'utilisation chimiothérapeutique les plus appropriés et les plus efficaces dans les diverses circonstances. L'efficacité chimiothérapique des antipaludéens n'étant en aucun cas acquise une fois pour toutes, il importe de réévaluer constamment la réponse aux médicaments, leur acceptation, leurs effets secondaires, quand ils ne sont pas négligeables, et de songer aux produits de substitution possibles.

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