Ann. Ist. Super. Sanità
Vol. 21, N. 4 (1985), pp. 439-444

THE ROLE OF THE NATIONAL INSTITUTE FOR MEDICAL RESEARCH IN IMPROVING PUBLIC HEALTH: THE SUPPORT FROM RESEARCH AND TECHNOLOGICAL DEVELOPMENTS

W.L. KILAMA

Director General, National Institute for Medical Research, Dar Es Salaam, Tanzania

Introduction

The United Republic of Tanzania lies on the east coast of Africa, between 1 and 12 °S. With an area of 945,000 km^2, a population estimated at 20 million people, gives a population density of 22 people per km^2. Approximately a third of the country is uninhabited mainly due to inadequate rainfall or tsetse fly infestation. About 90% of the population is rural, and for the most part engaged in agriculture. Tanzania's per capita GNP has been estimated at US$ 230, and is therefore classified by the United Nations as one of the least developed countries. Despite the almost overwhelming poverty, Tanzania has established social service infrastructures that have resulted in universal primary education, adult literacy rate of 85 percent, and in an average life expectancy of 52 years rising from 35 years in 1960, the year preceeding the independence. The per capita public expenditure on health currently runs at about US$ 4. Whereas at independence there were no rural water supplies to speak of, now more than 50 percent of the rural areas have access of clean water. Some of these achievements are unparalleled among the least developed countries.

A closer examination of the Tanzanian health situation however reveals a still gloomy picture: the major causes of morbidity and mortality are avoidable and are mainly due to communicable diseases. These data also indicate that there have not been drastic changes in disease patterns since the introduction of western medicine during the past one hundred years.

History of health research in Tanzania

Modern health research was brought to Tanzania by the Germans starting with the last quarter of the 19th century. Among the distinguished German scientists who worked in Tanzania were such professors as Robert Kock and Gustav Giemsa, of stain fame. After World War I, the British succeeded the Germans, and continued with health research work, although they initially lacked a clear research policy, as there was no co–ordination of the various research projects most of which were for the satisfaction of the individual researchers.

The end of World War II brought profound changes to Tanzania which now became a Trustship Territory of the United Nations. The postwar years then ushered in institutionalized healthy research: the late 1940s saw the launching of the East African Medical Survey at Malya in 1947, the Filariasis Research Unit at Mwanza in 1948 and the Malaria Unit at Muheza in 1949. During the 1950s therefore there were various research projects covering such areas as demography, vital statistics, nutrition, parasitic diseases, especially malaria filariasis and schistosomiasis. These research programmes were undertaken by expatriate staff, the overwhelming majority of whom were British.

The 1960s saw the dawn of independence, which was almost immediately followed by an exodus of British staff, including those in health research. To alleviate the deteriorated situation, the East African Medical Research Council, which was charged with the undertaking of medical research in Tanzania, Kenya and Uganda, had as one of its major objectives, the recruitment and training of future indigenous research personnel. These efforts started bearing fruit in the 1970s, but were terminated in 1977 with the death of the East African Community, under whose wings the East African Medical Research Council operated.

Formation of the NIMR

The National Institute for Medical Research (NIMR) is the natural and legal successor to the EAMRC. This Institute was established by an Act

of Parliament which became operational in 1980 and charges the NIMR with the undertaking, promotion, co–ordination, and monitoring of medical research in Tanzania.

The NIMR has primarily interpreted the enabling Act as charging the Institute with the role of turning research into a tool for socio–economic development. The Institute therefore set out to acquire new information on Tanzania's health problems, to detect faults in our health care and therefore use the acquired data in guiding health planners. The Institute has also taken up the task of filling up gaps in the understanding of health problems, participating in the utilization of new tools in the various phases of the war against diseases.

Faced with the crippling shortage of seasoned research manpower, finances, research equipment and supplies, and realizing that we cannot compete with long established institutions especially those in industrialized countries, the NIMR from the very beginning deliberately chose, at least for the present and the near future, to emphasize public health research, focusing on ecological, parasitological, epidemiological, sociological and health systems research. Rather than to cover many diseases, the Institute has chosen to concentrate research efforts on just a few diseases, the foremost being malaria in which we hope to create such a special research capability that would result in a continuum of laboratory, clinical, epidemiological, ecological, and community based research, utilizing parasitological, immunological, biochemical, statistical, sociological and related approaches.

Similarly we also hope to eventually create such capabilities for schistosomiasis. In the very near future, the Institute plans to strengthen research in microbiology, starting with bacteriology. As with malaria, research in schistosomiasis and microbiology would aim at creating an integrated continuum, around which related problems could eventually be appended and investigated. In the following pages, I shall attempt to present part of this young Institute's present and future research programme in malaria in the hope that the presentation will highlight the role played by NIMR in improving public health in Tanzania. I shall, when possible, attempt to emphasize the support that research and technological developments make to the improvement of public health. Near the end, I shall list the research topics pertaining to the other diseases, and conclude by highlighting the need for research collaboration.

Malaria research

Without doubt malaria is the leading cause of morbidity and mortality in Tanzania, where it occupies the topmost position for hospital attendancies, the second position for hospital admissions, and is among the leading causes of hospital deaths. *Plasmodium falciparum* accounts for 90% of all malaria infections at all altitudes. The other malaria parasite species are therefore rare, and in the Tanzanian context the term malaria is almost synonimous with *P. falciparum*.

Changing pattern of malaria transmission

Up to ten years ago, malaria was a disease of rural areas, and its transmission was usually limited to low altitudes. Recent anecdotal reports by health care deliverers and research undertaken by the Institute have revealed malaria transmission in hitherto malaria free mountainous areas. The Institute's Amani Medical Research Centre is located on the East Usambara Mountains, and for several decades was free of autochthonous malaria, in contrast to the low lying valleys and foot hills which are hyper– to holoendemic. Recent studies at Amani show malaria to be the number one cause of outpatient dispensary attendancies, accounting for an overall infection rate of 60%. Interviews with malaria cases there have revealed that up to 80% of the infections are most probably acquired locally; entomological investigations in the Amani area have uncovered extremely high sporozoite rates in *Anopheles gambiae*. The appearance of malaria at Amani has been blamed on ecological changes due to increased agricultural activities in an area that previously enjoyed abundant forest cover. Unconfirmed reports of malaria transmission in other previously malaria free mountainous areas have been received from Iringa and Hanang, for example.

Besides mountainous areas, changing patterns of malaria transmissions are also expressed in certain rural areas, especially where water impoundments have been erected in semi arid areas. Moreover, malaria transmission is now common in previously malaria free urban areas. I shall return to the latter aspect later.

Malaria control

The control of malaria in Tanzania as elsewhere, is two–pronged, and consists of parasite (chemotherapy and chemoprophylaxis) and vector control. The NIMR has recently been involved in evaluating these programmes. The results from these studies are presented within the following text.

Chemotherapy and chemoprophylaxis. – Efforts at malaria chemotherapy in Tanzania must date back several centuries. Attempts at the treatment of malaria symptoms using traditional remedies were practiced and are still in practice in both urban and rural areas.

Quinine was introduced in Tanzania by the German colonizers during the second half of the 19th century. Before the outbreak of World War I cinch-

ona plantations were already established in several areas of Tanzania. The British introduced chloroquine and later on pyrimethamine during the 1940s. The introduction of chloroquine which proved to be highly effective, safe, and economical both as a chemotherapeutic and chemoprophylactic drug, pushed out the use of any other schizontocidal drugs; even amodiaquine a drug closely related to chloroquine found very little use in Tanzania.

The strategy employed by Tanzania in the chemotherapeutic and chemoprophylactic programme consisted of making chloroquine readily available to the sick through an extensive system of dispensaries and health centres. Village Health Posts were established in some rural areas, and these too were very much involved in chloroquine distribution. The objective in this regard was to treat the acute malaria and therefore prevent death and lessen the suffering.

Chemoprophylaxis on the other hand was mainly targeted at the two major vulnerable groups, *viz*: children under five years of age and pregnant mothers; the drug was to be distributed through MCH Clinics.

Both programmes faced many problems in Tanzania, such as:

- difficulties in delivering the drug especially in remote areas;
- difficulties in achieving universal acceptance;
- under or overdosing;
- insufficient labelling;
- using nonstandard measures;
- vomiting of the drug;
- bitter taste;
- pruritis;
- human beliefs;
- enhancing potential for developing drug resistance.

Since delivery constituted a major impediment in the distribution of chloroquine, and therefore in the achievement of the set objectives, programmes were envisaged that would ensure efficient and timely delivery. A programme was, for example, developed for North Mara whereby through Primary Health Care the drugs would be distributed to as many children as possible utilizing community participation including the involvement of political leaders down to the grassroots level. The programme was provided with excellent means of transport, excellent political and community backing, good planning and organization and assured supplies of the life saving drug. Despite all these crucial assurances, the programme, which started with an almost infectious enthusiasm, started running into difficulties: the interest of the community waned, non-compliance became a major drawback and coverage became patchy [1]. Similar observations have been made by Matola *et al.* [2] in Tanga where only about 25% of the women and that of children regularly attending MCH Clinics actually revealed chloroquine metabolities in their urine, although the majority of the mothers claimed to have taken the chloroquine. In a similar study at Kibongoto, Kihamia and Lema [3] revealed similar data in an antenatal clinic.

Since the launching of the country-wide chemoprophylactic programme in the mid-1970s, chloroquine issues from the Central Medical Stores have rocketed threefold, from 102 in 1975/76 to 300 m tablets in 1980/81 [4]. In a recent comparative survey of chloroquine issued by five Anglophone African countries, the World Health Organization [5] put Tanzania's per capita chloroquine consumption at 25 tablets, whereas Zimbabwe had 4.6, Ethiopia 4.4, Kenya 1.9 and Gambia 1.2. The high figure for Tanzania probably reflects the amounts issued in what might conceivably prove to be a dubious MCH malaria chemoprophylactic distribution system.

The non-compliance and high issues of chloroquine constitute the major managerial impediments to Tanzania's ambitious chemotherapeutic and chemoprophylactic programmes. The greatest threat however is technical, and is embodied in the dawn of drug resistance in the indigenous *P. falciparum.*

The development of drug resistance in Tanzanian *P. falciparum* is not new: pyrimethamine resistance was detected, mapped and monitored by Clyde [6], whose studies led to the withdrawal of the drug in the 1960s. Yet studies undertaken more than a decade later unexpectedly revealed the persistance and spread of *P. falciparum* resistance to pyrimethamine in the absence of selection pressure [7]. These field studies strongly suggest that pyrimethamine resistant *P. falciparum* has a biological advantage over the susceptible phenotype.

Although the confirmation of chloroquine resistance in Tanzanian *P. falciparum* has only been reported recently, its possible occurrence has been suspect for many years. Clyde [8, 9] reported that large quantities of chloroquine occasionally failed to clear all trophozoites. Although early experience attested to the extremely high sensitivity of Tanzania parasites to chloroquine, later work by Pringle and Lane [10] revealed a decline in the efficacy of small doses (2.5 mg/kg) in clearing these parasites. A later study by Lelijveld and Mzoo [11] found that 5 mg/kg was needed to produce full parasite clearance. A few years later Goosen [12] revealed that not all asexual parasites would be cleared by 10 mg/kg chloroquine base. A study by Kouznetsov *et al.* [13] revealed that 10 mg/kg chloroquine failed to clear all the parasites in 10% of the carriers; it was therefore in doubt the efficacy of the recommended single dose, and since 15 mg/kg gave full parasite clearance, it was suggested a dose of 20 mg/kg. Studies undertaken soon afterwards reported two chloroquine

resistant cases in Dar es Salaam [14] and many in Zanzibar school age children [15].

Studies, so far unreported have been undertaken in both hospital patients and in ambulatory school children. Two of these will be cited *in extenso* to highlight the problem at hand.

Mutabingwa *et al.* [16] studied 104 indigenous malaria patients at Muheza hospital; the overall rate of resistance to chloroquine 25 mg/kg was 46.2%. An analysis by age group is described in Table 1.

Table 1. – *Analysis by age group of chloroquine resistance in patients of Muheza hospital*

Age group in years	Number studied	% Parasitaemia not cleared
< 1	20	80
1–5	26	58
6–10	6	50
11–15	7	28.6
> 15	45	26.7
TOTAL	104	46.2

This study very clearly shows chloroquine resistant malaria to be must prevalent in children under five years of age, who also constitute a very vulnerable group. This extremely poor response in infants and young children is a matter deserving grave concern. Mutabingwa and his associates hypothesized that lack of an effective immunity in young children to compliment drug treatment accounted for the observed insensitivity. The authors also suspected that patients attending the hospital experienced failure with home, dispensary or health centre remedies, which probably weed out resistant parasites thus presenting drug tolerant recrudescences to the hospital.

The Institute's Amani Medical Research Centre has studied the sensitivity of *P. falciparum* mostly in school children, in several localities in Tanzania. I shall cite the study at TPC (Tanganyika Planting Company), Moshi, in greater detail. Among 91 *in vivo* tests, 14.3% did not clear on chloroquine 25 mg/kg, and 17 of the 42 *in vitro* tests were resistant. When the *in vitro* results were analyzed, they revealed that the sensitive parasites were homogenous in their response, whereas the resistant isolates exhibited a bimodal curve equally segregating into sensitive and resistant parasites. Twelve and five of the isolates did not clear on 16 and 32 pico–mole respectively, the latter constituting the highest concentration available.

Studies similar to those undertaken at TPC have given the results illustrated in Table 2.

Table 2. – *Rate of resistance to chloroquine in different areas*

Location	% Resistance *In vivo* (25 mg/kg)	% Resistance *In vitro* (5.7 pico–mol)
South Mara	0	3.5
Pangani	6	41.4
Muheza	12.6	20.5
Gonja	19	—
Kibaha	20	50

These and other studies have uncovered resistance, at least *in vitro* in all areas investigated in Tanzania since 1982. Although areas free from chloroquine resistance are yet to be uncovered, the data reveal a rather variagated map in which areas of intense resistance rates fade into areas of faint resistance. The recognition of this fact, spurred the Institute to organize a course for 24 Tanzanian medical laboratory technicians in which the testing of *P. falciparum* sensitivity to antimalarials was taught. As the technicians were drawn from almost all corners of Tanzania, it is our hope that these very important tests will eventually be learned and practiced by technicians in the majority of district hospital laboratories, and that they will not only contribute to better malaria diagnosis and treatment, but also to the mapping and monitoring of drug resistance throughout Tanzania.

The advent of resistance to chloroquine has dictated search for alternative drugs, and the Institute has been spear–heading this activity. The limited *in vivo* tests utilizing pyrimethamine/sulfadoxine have revealed only two local resistant cases, although several purpotedly acquired in Tanzania have already been reported in the literature.

The NIMR is participating in WHO's global *in vitro* testing of *P. falciparum* sensitivity to mefloquine. Base line data from Tanga have revealed several isolates that are resistant to both mefloquine and chloroquine. These results compliment those of Bygjerg *et al.* [17] who encountered a chloroquine–resistant case in Denmark, which was reportedly acquired in Tanzania, and was enhanced by treatment with mefloquine.

Thus although the treatment and prevention of malaria in Tanzania was easy just a few years ago, it is now getting extremely complicated, especially so as we are nearing the exhaustion of potential chemotherapeutic and chemoprophylactic armaments. This has dictated a newer look at quinine, including consideration for its local production.

The results presented above have raised further questions — these relate to the management of chloroquine resistant cases to the few cases that are multi–resistant, the future of chemosupression in children under five years of age and pregnant

women, the administrative problems affecting delivery, compliance, and high issues of the drug.

Vector control. – Full fledged malaria mosquito vector control has only been practiced in urban Tanzania; so far a practical programme for most of rural Africa has not been developed.

Urban malaria vector control in Tanzania dates back to the turn of the century when the German colonizers introduced source reduction, source treatment and a mosquito control ordinance. The British continued these activities and by the early 1960s all urban areas had mosquito control programmes. Indeed two decades ago malaria transmission in urban areas was rare.

Deteriorations in urban mosquito control activities date back to 1963 when they were integrated into general urban health services. A major consequence was the gradual loss of mosquito control expertise since the training of Malaria Assistants and the lower cadres was terminated at about the same period. By 1982, Tanzania's urban mosquito control programmes were left with only 16 former Malaria Assistants the youngest of them being 50 years of age and therefore eligible for voluntary retirement. There is therefore pressing need to immediately resurrect the local training of vector control personnel. Of equal importance is the training of medical entomologists, sanitary engineers to man national and other large vector control programmes.

Another major drawback in urban mosquito control has been very heavy reliance on source treatment. The present mosquito control technicians were trained in the 1950s when insecticidal chemicals were still regarded as the universal panacea in vector control. The present control programmes are therefore faced with the twin problem of relying on very costly larviciding with its attendant threat of insecticide resistance, environmental pollution, toxicity, transient success, and reliance on an almost non–existant foreign exchange.

Funding has proven to be a most formidable foe to all urban mosquito control programmes in Tanzania. An examination of the funding pattern for Dar es Salaam for example shows only slight increases in overall funding, which were most probably swallowed by virulent inflation and an escalating cost of living. An analysis of the allocation is presented in Table 3.

The decreased manpower competence, coupled with dwindling real financial allocations have combined to lead to a boom in the number of anophelines. Dar es Salaam for example witnessed a steady fall in anophelines throughout the 1950s, 1960s and into the early 1970s, but with decentralization in the 1970s anopheline numbers resumed their population boom. The average numbers caught per house were for example 11.68 in 1961, 2.9 in 1971, 81.18 in 1981 and more than 133 in 1982. A parallel study in Dar es Salaam has revealed escalating human malaria infections in the last five years.

Table 3. – *Allocations for urban mosquito control programmes*

	1961	1971	1981
Allocation (Shs)	1,155,880	1,836,970	1,992,160
Per capita expenditure (Shs)	8.14	4.51	1.90
Per km² (Shs)	?	24,493	16,601
Personnel emoluments (%)	79.3	80	97.8
Sprayers in good working order	?	212	134

Current joint efforts led by the Ministry of Health are aimed at reviving training of various cadres of vector control personnel and boosting community participation in vector control, which should ideally emphasize source reduction.

Future research programmes in malaria

As with current work, future research programmes in malaria will attempt to utilize available and new tools in the various phases of malaria control. For the most part, we shall emphasize the type of research that can only be undertaken in malarious area. The envisaged research programmes are:

1) delivery of antimalarial drugs to vulnerable groups in rural areas utilizing community participation;

2) the effect of primaquine on the spread of chloroquine–resistance;

3) optimum treatment schedules for *Plasmodium falciparum* with alternative drugs in area of drug resistance;

4) immunological methods for the detection of sporozoites in mosquitoes and antisporozoite antibodies in man;

5) experimental evaluation of methods of personal protection against mosquitoes;

6) assessment of *Nothobranchius* spp. against *Anopheles* spp.;

7) behavioural and vectorial variation within and between *An. gambiae* sibling species populations.

Other research undertaken by NIMR

Besides malaria, the Institute undertakes research on schistosomiasis, onchocerciasis, Bancroftian filariasis, plague and tuberculosis.

Most of this research is still collecting epidemiological data, although in some cases, especially in tuberculosis, the Institute's personnel are fully involved in manning the national war against this scourge. The Institute's laboratory receives sputa from several dozen hospitals throughout the country,

evaluates cures obtained on varying treatment schedules and regimens and runs sensitivity studies. Results from such a study will assist in identifying the best treatment for tuberculosis.

Teething problems and need for linkages

The NIMR was founded on 1st October 1980, right in the middle of an economic crisis, that has continued haunting the growth and development of the Institute. The funds allocated by the Tanzania government have mostly gone into meeting recurrent costs, and the little increases voted have gone into dampening the fulminating inflation.

A non–monetary but major weakness of the NIMR is its lack of a core of experienced research scientists. The NIMR has therefore embarked on a vigorous programme of staff recruitment and training both locally and abroad. It is also our hope that the Institute will be able to establish linkages, and even undertake joint research projects with more experienced institutions, which might desire to gain field experience, or test their new found diagnostic or control tools. The Institute extends a welcoming hand to such institutions.

REFERENCES

1. MacCORMACK, C.P. & LWIHULA, G. 1983. Failure to participate in a malaria chemosuppression programme: North Mara, Tanzania. *J. Trop. Med. Hyg.* 86 (3): 99–107.

2. MATOLA, Y.G. & MALLE, L.N. 1984. *Malaria prevalence in selected MCH clinics in Tanga region and chloroquine chemosuppression usage: non compliance.* 3rd annual joint scientific conference. National Institute for Medical Research, Dar es Salaam.

3. KIHAMIA, C.M. & LEMA, K.N. 1984. *Utilization of chloroquine for malaria chemoprophylaxis by pregnant women attending an antenatal clinic in northern Tanzania.* 3rda annual joint scientific conference. National Institute for Medical Research, Dar es Salaam.

4. CHIDUO, A.D. 1982. *Hotuba ya Waziri wa Afya katika Bunge, Julai, 1982: Siasa na Makadirio ya Matumizi ya Fedha ya Wizara kwa Mwaka 1982/83.* Ministry of Health (Mimeo), Dar es Salaam

5. WORLD HEALTH ORGANIZATION. 1983. *Primary health care and malaria in Africa.* (Report of a workshop WHO/MAP/SHS/83.1).

6. CLYDE, D.F. 1967. *Malaria in Tanzania.* Oxford University Press.

7. KOUZNETSOV, R. *et al.* 1980a. *Spread of pyrimethamine resistant strains of* Plasmodium falciparum *into new areas in the absence of drug pressure.* (WHO/MAL/80.926).

8. CLYDE, D.F. 1961. Chloroquine treatment of semi-immune patients. *Am. J. Trop. Med. Hyg.* **10**:14.

9. CLYDE, D.F. 1966. Drug resistance of malaria parasites in Tanzania. *East Afr. Med. J.* **43** (10): 405–408.

10. PRINGLE, G. & LANE, F.C. 1966. An apparent decline in the efficacy of small doses of chloroquine in suppressing malaria parasitaemia in semi–immune African schoolchildren. *East Afr. Med. J.* **43** (12): 575–578.

11. LELIJVELD, J. & MZOO, F. 1970. The effect of small single doses of chloroquine on *Plasmodium falciparum* infections in north–eastern Tanzania. *Bull. WHO* **42** (3): 471–477.

12. GOOSEN, TH. J. 1975. *Studies on sensitivity of* P. falciparum *to antimalaria drugs: studies at Kicheba and Tororo.* Annual Report of the East Afr. Inst. Malaria and Vector-borne Diseases. Jan. 1974-Dec. 1975, pp. 9-14.

13. KOUZNETSOV, R. *et al.* 1980b. In vivo *and* in vitro *methods for the assessment of* Plasmodium falciparum *response to chloroquine in highly endemic malarious areas of Bagamoyo, Tanzania.* (WHO/MAL/80.928).

14. KIHAMIA, C.M. & GILL, H.S. 1982. Chloroquine–resistant falciparum malaria in semi–immune African Tanzaniana [letter]. *Lancet* **2** (8288): 45.

15. SCHWARTZ, I.Y. *et al.* 1983. *In vivo* and *in vitro* assessment of chloroquine–resistant *Plasmodium falciparum* malaria in Zanzibar. *Lancet* **1** (8332): 1003–1005.

16. MUTABINGWA, *et al.* 1984. *Response of* Plasmodium falciparum *to chloroquine in hospital patients in Muheza, Tanzania* (in press WHO/MAL).

17. BYGBJERG, I.C. *et al.* 1983. Mefloquine resistance of falciparum malaria from Tanzania enhanced by treatment [letter]. *Lancet* **1** (8327): 774–775.