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The Changing Landscape of Malaria Case Management in Uganda: Decades of Struggle with Evolving Malaria Case Management Strategies and Drug Policies

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Abstract

Background: Uganda has some of the highest reported malaria transmission rates in the world.

Methods: We reviewed published and un-published reports to provide a historical perspective and evolution of malaria case management strategies/policies in Uganda.

Review findings: In the 1990s, uncomplicated malaria treatment was hampered by widespread parasite resistance to chloroquine (CQ) and sulphadoxine-pyrimethamine (SP). Paradoxically, faced with this challenge, the country changed the first-line regimen, in 2000, to CQ+SP and adopted home based management of fever (HBMF) for children < 5 years old. HBMF increased the proportion accessing CQ+SP within 24 hours from 7% in 2001 to 39% in 2003. However, after another policy shift, in 2004, to Artemether-Lumefantrine (AL), HBMF is to date implemented in only 34 of 112 districts. The private sector supports first treatment contact for 40-50% of fevers. However, engaging private sector providers remains challenging. Consequently, by 2011, only 30% of febrile children took AL on the same/next day after symptom onset. In 2011 there was a policy shift from presumptive treatment to parasite-based diagnosis. Following the policy change, the proportion of tests by rapid diagnostic tests (RDTs) increased to about 55% compared to 30% by microscopy. However a major challenge remains clinician's adherence to test results. Reassuringly, AL remains efficacious. In 13 studies conducted between 2002 and 2010, the median PCR corrected day 28 efficacy was 98% (range: 71.9%–100%). However, counterfeit medicines remain a threat and the lack of an effective phamacovigilance system is concerning. A recent study demonstrated that 39% of sampled artemisinin combination therapies were counterfeits.

Conclusion: Despite an increase in official development assistance over the last decade, by 2013 there remained gaps in national ambitions for universal access to prompt and effective treatment. A major challenge is the low profile of the national malaria control programme within the ministry of health structure which limits its capacity to coordinate multiple stakeholders. Secondly, there is a need for decentralized planning and implementation with greater involvement of the zonal, district, health facility and community levels. Finally, it will be critical to engage the challenging but very important private sector.

Background

Uganda has the third highest number of deaths from malaria in Africa, as well as some of the highest reported malaria transmission rates in the world [1,2]. The disease accounts for 30%-50% of outpatient visits and 15%-20% of hospital admissions [3]. Malaria infection in pregnant women leads to maternal anaemia, maternal death, miscarriage, pre-mature delivery, and low birth weight babies.

Four of the five plasmodia species that infect humans are present in Uganda. Over the last fifty years *Plasmodium falciparum* has remained the dominant parasite, accounting for over 90% of all infections [4].

Chloroquine (CQ) was the mainstay of therapy for uncomplicated falciparum malaria in most of sub-Saharan Africa until the late 1990s. With increasing parasite resistance to CQ, there were policy shifts to Sulphadoxine-Pyrimethamine (SP), Amodiaquine (AQ), or

combinations of CQ+SP or AQ+SP. However, increasing resistance to these options in the early 2000s led to recommendations for the adoption of Artemisinin Combination Therapy (ACT) [5,6]. Consequently, either Artemether-Lumefanthrine (AL), Artesunate-Amodiaquine (ASAQ) or later Dihydro-artemisinin-Piperaquine (DHA-PQP) were adopted as first-line or alternative first line regimens for treating uncomplicated falciparum malaria in nearly all countries in Africa. In 2004, Uganda adopted AL as the first line regimen and two years later added ASAQ as the alternative first line regimen, with quinine as the second line regimen [7,8].

Quinine was the first established antimalarial medicine, and has been used to treat malaria for centuries [9]. Intravenous quinine was for many decades the standard therapy for severe falciparum malaria in all African countries. Many malaria endemic countries that adopted ACT as first-line therapy recommended quinine as the second line regimen for uncomplicated malaria despite clear guidance from the World Health Organisation (WHO) that antimalarial medicines should be used in combination [10]. Until recently, 29 of the 41 sub-Saharan African countries that used ACT as the first-line treatment for uncomplicated malaria also recommended quinine as second line therapy [11]. Moreover, due to decreased efficacy of older medicines and the limited availability of ACT, quinine became increasingly used as a first-line medicine for treating uncomplicated malaria in Africa, especially in the private sector. For example, a survey conducted in 2007 in four districts in Uganda showed that quinine was prescribed for 4% of all patients with uncomplicated malaria [12]. A similar survey that year, at Mulago hospital, the national referral hospital in Kampala, showed that quinine was prescribed for 26% of diagnosed cases of uncomplicated malaria [13]. Thus, although quinine may not be listed as a first-line regimen for treating uncomplicated malaria in many countries, it continues to be widely used. Recent trials have demonstrated that intravenous Artesunate has superior efficacy in treating severe malaria [14,15], and it is anticipated that this practice will change. However, strong pharmacovilance systems will be required to document the magnitude of isolated episodes of late haemolytic anaemia that has been observed in some settings with intravenous Artesunate [16].

Methods and Literature

We reviewed published and un-published literature about malaria case management, drug policy and antimalarial drug resistance in Uganda for the period 1970 to 2013. Our objectives were to provide a historical overview and evolution of the malaria case management strategies and drug policies in Uganda from the period after the era of the Global Malaria Eradication Programme (GMEP) to the present roll back malaria-RBM era. This review was motivated by a need to: a) capture a historical perspective of the malaria case management strategies and drug policies so as to draw lessons for today's control ambitions; and b) maintain an institutional memory of the last few decades of malaria case management policies in Uganda - who was involved, what was done, what worked and more importantly what did not work. Online electronic literature databases were used as one means for identifying peer-reviewed published papers on malaria case management in Uganda. Due to its wide coverage of the biomedical literature, PubMed [http://www.ncbi.nlm.nih.gov/sites/entrez] was used as the basis for all the initial online searches of published sources. In addition, we used the World Health Organization (WHO) library database [http://www.who.int/library]; and the African journals online (AJOL) [http://www.ajol.info]. In all digital electronic database searches for published work the free text keywords "*malaria*" and "*Uganda*" were used. We avoided using specialised medical subject headings (MeSH) terms in digital archive searches to ensure as wide as possible the search inclusion. Further, we reviewed national malaria control programme documents at the ministry of health headquarters in Kampala, Uganda and requested the worldwide antimalarial resistance network (WWARN) to provide standardized analyses of ACT efficacy data in the WWARN repository (www. wwarn.org).

Review Findings

Malaria control 1970-1995: apathy to renewed interest

The malaria eradication experiments conducted in Uganda in the 1950s and 1960s, targeting adult vectors or parasites, provided in some cases impressive findings of the impact on malaria transmission [17-19]. However, following the abandonment of the eradication goal in Africa after the recommendation of WHO in 1969 [20], there was a general sense of disappointment and apathy globally and nationally which was associated with a decline in resource allocation for malaria. Uganda's malaria program collapsed due to lack of human and financial resources. During the period 1970 to 1990, a period of great civil and political turmoil in Uganda, there was little effort to control malaria, resulting in a resurgence of the disease. The years of civil strife left the entire Ugandan health system in disrepair. The malaria control programme lost critical programme staff and the malaria centre at Jinja in eastern Uganda was left in ruins. Efforts to revamp Uganda's health sector in the early 1980s were hampered by rampant insecurity and a de-motivated work force. The only malaria control effort was presumptive treatment with CQ. There was no policy and no strategic plan. From 1986 onwards, Uganda as a country started making some recovery, including a gradual economic growth. However, there was no matched improvement in the health indicators during this period. It was not until the early 1990s, when the global efforts to control malaria were re-started, that malaria gained some greater national prominence. In 1992, a global malaria control strategy aimed at preventing mortality and reducing morbidity was adopted by the health ministerial conference held in Amsterdam. This strategy was adopted by the World Health Assembly (WHA) in 1993 as the global strategy for malaria control [21]. During this period there was hardly any malaria research in Uganda, despite the efforts of the WHO's tropical disease research (WHO-TDR) in other countries. The only significant malaria research leading up to 1995 was undertaken in two western Uganda districts (Kabarole and Bundibugyo), supported by the German development cooperation (GTZ). These studies were important in providing contemporary data on the epidemiology and micro-epidemiology of malaria in Uganda, assessing the knowledge, attitudes and practices towards malaria with an emphasis on how communities understood treatment and prevention as well as estimates of malaria specific mortality rates in different endemicity zones [22].

Uganda's malaria control 1995-2001: defining the challenge

After the endorsement of the global malaria strategy by the WHA in 1993 [21], Uganda's malaria control efforts started gaining some visibility. In the early 1990s, Uganda's ministry of health (MoH) conducted an analysis of the malaria control problems in the country and revealed the following challenges: lack of integration and inter-sectoral collaboration in control; problems with case management due to self-medication and the wide availability of antimalarials on the

open market; failure of vector control and environmental management, partly due to the efficient transmission characteristics of the major vectors and the multiplicity of breeding sites, but also lack of environmental management planning; absence of trained personnel; lack of an information system for monitoring and evaluation; inadequate early detection of malaria epidemics; escalating drug resistance of *Plasmodium falciparum* to CQ; and lack of resources [23].

In 1995, a burden of disease (BOD) study conducted in 13 of the districts supported by the World Bank found that 75% of the life years lost to premature death in Uganda were due to ten preventable diseases, including perinatal and maternal related conditions, malaria, acute respiratory infections, HIV/AIDS, tuberculosis, and diarrhoea [24]. However, the resource allocation for malaria was not commensurate with this disease burden. Faced with these statistics, the MoH, in 1995, established a Malaria Control Unit (MCU).

In 1996, two years prior to the launch of the RBM initiative, the World Bank initiated funding to support malaria control efforts in several African countries. Between 1996 and 1999 the World Bank, WHO and UNICEF led missions to six countries: Kenya, Mozambique, Tanzania, Ethiopia, Malawi and Uganda. In Uganda, the team met with key stakeholders including: government officials, health sector staff, researchers, Non-Governmental Organizations (NGOs) and manufacturers. The mission highlighted the impact of malaria in Uganda and concluded that malaria control activities should be integrated within existing and proposed World Bank operations in the country. However, existing resources were being under-utilized, as the public health sector did not have the capacity to absorb available funding [25]. While these joint missions were a practical step towards creating a national partnership around malaria, it became very clear that partnerships would not establish themselves naturally and cross-sectoral approaches were not well-institutionalized. After the 1996 joint mission, malaria did become more recognized as a national priority and the country developed the first five year malaria strategic plan (MSP) (1996-2001) and a three year malaria policy. The plan was launched under the banner "*the Uganda Intensified Malaria Control Initiative*" [23]. The strategy emphasized the importance of early diagnosis and effective treatment of malaria in all areas, including improving laboratory components. Importantly, it was recognized that implementation had to be through the district health care system in collaboration with other agencies within the communities. It was hoped that there would be significant investment in improving the information platform, through the health management information system (HMIS), to provide evaluation metrics and help define epidemic thresholds for early detection. At the time the intensified malaria control initiative was launched, a complimentary anti-malaria policy was developed and adopted in 1998 [26]. The aims in the policy followed those of the MSP but retained several historic elements of malaria control, including environmental sanitation and the destruction of breeding places where feasible. The policy also covered the treatment of malaria with CQ as the first line regimen, sulphadoxine-pyrimethamine (SP) as the second line regimen and quinine as the medicine for severe malaria and for cases resistant to CQ or SP. The policy further stated that chemoprophylaxis could be useful for first and second time pregnancies, patients with sickle cell disease and visitors from non-endemic countries. The antimalarial policy recommended that legislation should be made on proper mosquito control especially in urban areas and identified priority research, including monitoring treatment efficacy and drug sensitivity,

monitoring the quality of antimalarial drugs present in the country and a broader economic and cost effectiveness analysis [26].

Restructuring Uganda's malaria control unit, the malaria zonal coordination system and staff turn over

After the development of the first MSP (1996-2001), there was restructuring of the MCU and an organogram developed composed of the following sections: Program management, deputy program management/in charge for malaria case management, epidemiology, epidemic preparedness and control, research and data management, vector control and environmental management and information, education, communication (IEC)/behavioural change communication (BCC). Supporting these sections were two technical advisors provided by the German development cooperation and the UK's department for international development (DFID).

In line with Uganda's 1993 policy of decentralization, the first anti malarial policy recommended the creation of a functional level called zonal coordination centres to support the decentralized districts in the implementation of malaria control. These coordination centres were based at the eleven regional referral hospitals. At the district level, an officer was assigned the additional responsibility of serving as a malaria focal person. The operations of the zonal coordinators was initiated in 1998 and their overall objective was to assist the national level in providing support to districts with respect to coordination, planning, implementation, supervision, monitoring and evaluation of malaria control activities. The support to malaria control in the districts was guided by the national MSP. This system of zonal coordination was to be jointly implemented from 1998 with the existing programme for integrated management of childhood illnesses (IMCI) [27,28]. However, insufficient funds for the operational costs of this system of integrated support prevented its smooth functioning.

Uganda's malaria control programme has over the years witnessed an alarming turnover of staff. Between 1997 and 2013 there have been seven different programme managers. A technical advisor who joined the programme in 1998, left in 2004, while another seconded by DFID in 2000 left in 2003, was replaced by yet another who also left in 2005. The MCU organogram was further reviewed and re-defined in 2001 and the programme was transformed into a national malaria control programme (NMCP) with four technical working groups (TWGs) [28]. These TWGs were supposed to report to the inter-agency coordinating committee (ICCM). In 2004, with support from various development partners including the Global Fund (GF) and the Malaria Consortium [*www.malariaconsortium.org*] the zonal system was revitalized and played a significant role in supervision, training and in improving data collection and quality of malaria case management. In 2004, the concept of the zonal coordination system was re-defined, the criteria for selection/ appointment of coordinators set and resource requirements estimated; the terms of reference for the zonal coordinators were clearly stipulated; the 11 coordination zones were demarcated and all vacant positions filled [29].

Grappling with antimalarial drug resistance and the first antimalarial drug policy change

Effective uncomplicated malaria treatment during the mid-late 1990s was complicated by the emergence of resistance to widely used antimalarial medicines such as CQ. There had been no reports (suspected or confirmed) of Plasmodium falciparum resistance to CQ or amodiaquine (AQ) before 1969. In 1969, following a report of

reduced CQ sensitivity from the missionary hospital at Kuluva in West Nile, a field study was conducted. 160 children attending Eruba primary school, 180 children attending Vurra primary school and 90 children attending Kuluva missionary hospital were examined for the presence of malaria parasites daily following standard body weight CQ three day dosing [29]. The trial found that CQ eliminated parasitaemia before the 5th day post-treatment with a large majority clearing parasites on the 3rd day, suggesting normal sensitivity of falciparum malaria to CQ in Kuluva [29]. Between 1970 and the early 1980s there were hardly any drug efficacy studies conducted. However, over the period 1988-2001, several in vivo efficacy studies were conducted with different protocols, different study populations and different outcome measures [30-43], (Table 1). Many of the studies conducted before 1996 used asymptomatic subjects attending schools as recommended by the then WHO protocols [44], while those conducted after 1996 recruited symptomatic patients aged between 6 and 59 months or all age groups [45].

Faced with the lack of standardization of drug efficacy methodology and the limited sharing of data generated in the late 1990s, the East African Network for Monitoring Antimalarial Treatment (EANMAT) was conceived, in 1997, in response to the sub-region's growing need for reliable information on the sensitivity of malaria parasites to antimalarial drugs. The goal of the network was to ensure that rational and evidence based malaria treatment policies were implemented in the East African sub-region. The network began with Kenya, Uganda and Tanzania (mainland), and was joined later by Rwanda, Burundi and Zanzibar [46,47]. Initially the majority of the efficacy test data collection and analysis in Uganda was done by the MCU in collaboration with the staff at eight sentinel health facilities (Figure 1) [48-51]. However, in view of the complexities required to conduct these studies, a model based on collaboration with local research partners was adopted after the formation, in 2000, of the Uganda malaria surveillance programme (UMSP).

Figure 1: MCU in collaboration with the staff at eight sentinel health facilities.

The data generated by the EANMAT/UMSP sentinel surveillance and several other studies conducted in Uganda confirmed that the prevalence of CQ resistance had become a major problem. For the period 1999-2001, CQ treatment failures had reached an average of 33%, based on a 14 day follow up in children less than five years old (Table 1). While SP mono-therapy treatment failure had increased from 5.5% to 12% for the period 1995-1998 (Table 1). Paradoxically, faced with these data, the MOH changed the first-line treatment policy at the end of 2000 to a combination of CQ+SP [52], which had an average failure rate of 7% at the time the policy was launched. This interim solution was adopted because there was a perceived lack of practical alternatives. Treatment guidelines and other training and communication materials were updated, supplies of SP increased to support CQ co-administration and all health staff in the public sector trained on the new treatment guidelines. Following the 2000 decision, the actual launch of the policy took place in April 2002 and by 2003 practically all government health facilities used CQ+SP for malaria treatment. In contrast, uptake was significantly slower in the private sector where in September 2002 only 15% of all shops had both, CQ and SP available [53].

The second antimalarial treatment policy change and implementation

As had been anticipated, resistance to SP as well as CQ+SP continued to rise and reached an average of 16% and 12% treatment failure at day 28 of follow-up respectively during the period 2002-2004 [43,49,50]. The announcement that CQ+SP would be abandoned in favour of Artemether-Lumefanthrine (AL) was first made on 17th May 2004. Interestingly at this time the data available on AL efficacy from Epicentre at Mbarara were not used by the MoH to arrive at this decision and the new policy seems to have been arrived at as a default position using principally decisions made by the neighbouring countries-Kenya, Tanzania and Rwanda, who were members of the sub-regional network-EANMAT. Further, there was a general reluctance to adopt Amodiaquine (AQ) combinations because of the safety concerns for AQ in the region. The adoption of the new ACT policy was predominantly based on their presumed good efficacy and the likely long useful life-expectancy with low probabilities of resistance. However, the affordability, acceptability, adherence and feasibility remained uncertain. The national malaria programme (NMCP) promoted a vision for ACT of "learning while doing". The Global Fund (GF) round 4 provided approximately US$ 66 million within the US$ 158 million award to accelerate the implementation of the new AL treatment policy, which included funds to purchase AL for the public sector, strengthen distribution systems, train over 5,000 health workers in the new policy during the first year and maintain supervision in the second year. DFID-UK provided funds to the Malaria Consortium to support the NMCP in this difficult drug policy transition and implementation.
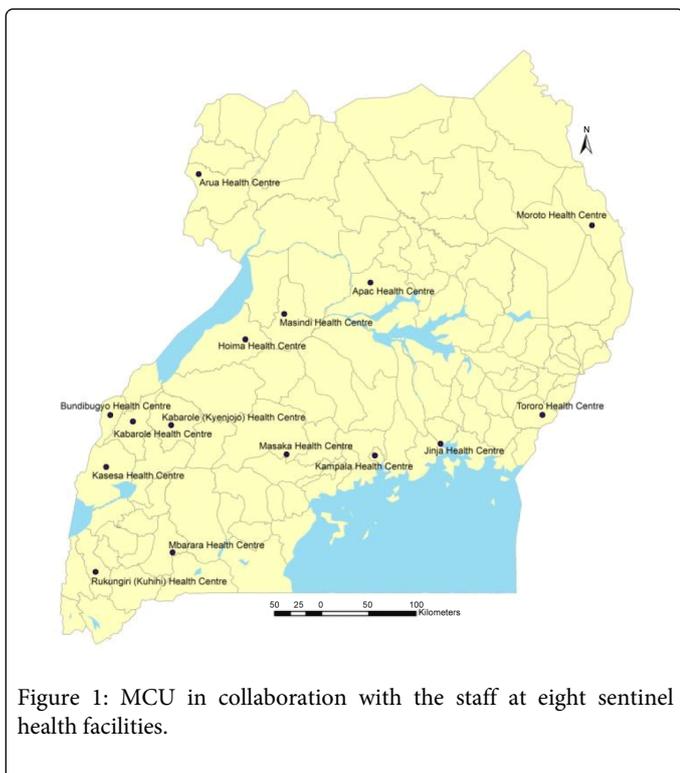
Study districts	Year of study	Subjects recruited, Age group [follow-up duration]	Parasitological failure (%)		Clinical Treatment failure (%)		Reference
			CQ	SP	CQ	SP	
Kampala	1988	Asymptomatic, 5-15 years [7 days]	39	0	-	-	[30]
Jinja	1988	Asymptomatic, 5-15 years [7 days]	23	0	-	-	[30]
Masaka	1988	Asymptomatic, 5-15 years [7 days]	38	0	-	-	[30]
Masindi	1988	Asymptomatic, 5-15 years [7 days]	29	0	-	-	[30]
Kasese	1988	Asymptomatic, 5-15 years [7 days]	21	0	-	-	[30]
Arua	1988	Asymptomatic, 5-15 years [7 days]	3	0	-	-	[30]
Kabarole	1992	Asymptomatic and uncomplicated, 0.5-60 years [7 days]	16	5	-	-	[31]
Kampala	1993	Uncomplicated, 0.5-5 years [14 days]	12	2	-	-	[32]
Apac	1993	Uncomplicated, 0.5-5 years [14 days]	2	0	-	-	[32]
Tororo	1993	Uncomplicated, 0.5-5 years [14 days]	8	0	-	-	[32]
Hoima	1995	Asymptomatic, 7-10 years [7 days]	58	4	-	-	[33]
Jinja	1996	Uncomplicated, 0.5-5 years [14 days]	36	5	12	6	[34]
Bundibugyo	1996	Uncomplicated, 0.5-5 years [14 days]	40	13	33	5	[35]
Kabarole	1996	Uncomplicated, 0.5-5 years [14 days]	77	7	58	4	[36]
Jinja	1996	Uncomplicated, 0.5-5 years [14 days]	36	6	12	6	[37]
Jinja	1998	Uncomplicated, 0.5-5 years [14 days]	33	3	28	2.4	[38]
Tororo	1999	Uncomplicated,	88	72	21	15	[38]

		0.5-5 years [14 days]					
Arua	1999	Uncomplicated, 0.5-5 years [14 days]	43	19	21	10	[38]
Apac	1998/99	Uncomplicated, 0.5-5 years [14 days]	41	14	15	10	[38]
Rukungiri	1998/99	Uncomplicated, 0.5-5 years [14 days]	10	0	10	0	[38]
Kabarole	1998/99	Uncomplicated, 0.5-5 years [14 days]	81	20	44	13	[38]
Moroto	1998	Uncomplicated, 0.5-5 years [14 days]	-	-	48	12	[39
Moroto	1999	Uncomplicated, 0.5-5 years [14 days]	-	-	21	17	[39]
Hoima	1998	Asymptomatic, 4-10 years [7 days]	28	1	-	-	[40]
Mbarara	1998/99	Uncomplicated, 0.5-5 years [14 days]	-	-	81	25	[41]
Kampala	1998/99	Uncomplicated, 0.5-5 years [14 days]	83	-	62	-	[42]
Kampala	1999	Uncomplicated, 0.5-5 years [14 days]	96	33	76	11	[43]
Kampala	1999/2000	Uncomplicated, 0.5-5 years [14 days]	-	-	26	14	[43]

Table 1: CQ and SP resistance studies among children in Uganda (1988-2001).

Problems of effective national consensus following the announcement were similar to those faced by Kenya during this period [54]. These centred around the ability of the Uganda government to finance the long-term supply of AL, single source issues around the Novartis-WHO agreement, the reported global shortages of Artemisinin to produce AL and the possible interruption in manufacture by Novartis Pharma. In July 2005 the policy statement was revised to be more inclusive of other ACT, notably AQ +Artesunate. The policy therefore stated: "The recommended first line medicine is Artemether/Lumefantrine. This medicine (Artemether/ Lumefantrine) is not recommended for children below 4 months of age or 5 kgs body weight and pregnant women in the first trimester. Artesunate + Amodiaquine is the alternative when Artemether/ Lumefantrine is not available" [52]. Oral Quinine was designated the second line treatment for all patients and also for pregnant women with clinical malaria [52]. It was not until 9th September 2005, that the NMCP organized a dissemination workshop to introduce the new policy to a wider set of stakeholders; 80 attendees including members of the iCCM, MoH senior staff members, National Drug Authority (NDA), Ugandan associations of paediatricians, private practitioners, medical associations, the research community, malaria zonal coordinators, integrated management of childhood illness-IMCI and its zonal coordinators and the MoH units responsible for reproductive health and health education and promotion. Various delays occurred in re-developing the national standard treatment guidelines (STG) but the revised policy supporting AL in the public sector was eventually launched in health facilities in May 2006 with the new STG, post-cascade training and emergency funding to procure AL. All implementation activities therefore started 24 months after the policy change was announced; and complete roll out of the new policy for the first line treatment occurred by the end of 2006 [55].

Monitoring ACT resistance

Between 2002 and 2012, 13 ACT efficacy studies with 28 days of follow up were undertaken at six sites (Table 2) [56-73]. Overall the median PCR adjusted day 28 efficacy for AL was 98% (range: 71.9%–100%) showing that this drug remains effective (Table 3). However, slow clinical and parasitological response with ACT for treating uncomplicated *P. falciparum* malaria has emerged in Western

Cambodia and may have independently emerged or spread to other sites in the Mekong region [74,75]. Tracking the evolution of artemisinin resistance is of paramount importance in Africa [76,77]. The WHO recommends that the proportion of patients remaining parasite positive at day 3 exceeding 10% should serve as a definition for suspected resistance [78], while others suggest a resistance rule out threshold of 3% [79].

Study site and year started	N	Malaria transmission intensity	Days of follow up	PubMed ID	Reference
Kampala, 2002	400	Moderate	28	15567011	[56]
Mbarara, 2006	304	Moderate	42	20932805	[57]
Mbarara, 2002	957	Moderate	28	15850630	[58]
Tororo, 2004	408	High	28	16871329	[59]
Mbarara, 2005	577	High	42	19936217	[60]
Apac, 2002	542	High	28	16033307	[61]
Arua, 2002	534	High	28	16033307	[61]
Jinja, 2002	543	Moderate	28	16033307	[61]
Tororo, 2002	541	High	28	16033307	[61]
Kampala, 2001	448	Low-Moderate	14	12641399	[62]
Apac, 2006	421	High	42	17525792	[63]
Kanungu, 2006	414	Moderate	42	18545692	[64]
Kampala, 2007	175	Moderate	28	19622553	[65]
Tororo, 2008	232	High	28	19877969	[66]
Kampala, 2004	1409	Moderate	28	20689585	[67]
Tororo, 2007	584	High	28	22087077	[68]
Jinja, 2007	496	Low	28	22087077	[68]
Mbarara, 2007	404	Moderate	28	22087077	[68]
Bundibugyo, 2002	178	High	28	15078262	[69]
Tororo, 2007	218	High	28	23349741	70
Amudat, 2003	212	Moderate	28	Unpublished	Epicentre
Kampala, 2008	416	Moderate	42	Unpublished	Sanofi

Table 2: Summary of antimalarial drug efficacy studies in Uganda, 2001-2013, Source: WorldwideAntimalarial Drug Reisistance Network-WWARN.

Study ID	N	D28Efficacy adjusted	95% CI	D28Efficacy unadjusted	95% CI
Mbarara_2002	957	99.9	99.2 – 100	96.5	95.1 – 97.5
Kampala_2004	579	99.8	98.8 – 100	95.4	93.3 – 96.9
Tororo_2004	204	96	91.1 – 98.2	34.2	27.7 – 40.7
Mbarara_2005	191	96.4	89.1 – 98.8	79.7	69.7 – 86.7
Kanungu_2006	199	97.4	93.9 – 98.9	83.1	77.0 – 87.7
Mbarara_2006	152	99.3	95.4 – 99.9	99.3	95.4 – 99.9

Apac_2006	210	100	98.3 – 100	69.8	63.0 – 75.5
Tororo_2007b	35	92.3	71.9 – 98.1	41.8	25.3 – 57.5
Jinja_2007	227	98	95.7 – 99.2	94.1	89.9 – 96.6
Tororo_2007a	221	95.8	91.8 – 97.9	57.5	50.6 – 63.8
Kampala_2007	89	100		95.9	87.8 – 97.7
Tororo_2008	113	100	96.8 – 100	80	71.2 – 86.4
Kampala_2008	205	97.9	93.9 – 99.1	52.5	45.4 – 59.2

Table 3: D28 adjusted and un adjusted treatment efficacy AL.

The Worldwide Antimalarial Resistance Network (WWARN) [www.wwarn.org] has conducted a systematic review to search for the individual patient level data from clinical efficacy studies (available online). As of June 2013, there were 25 studies in the WWARN data repository from Uganda undertaken between 2000 and 2010, comprising 12,098 patients. Based on these data there seems to be no evidence suggesting artemisinin resistance (delayed parasite clearance) at any of the Ugandan sites. No site and no treatment regimen (AL, Amodiaquine –Artesunate-ASAQ or Dihydro Artemisinin-Piperaquine-DHAPQP) had a point estimate of the proportion with persistent parasitemia at day 3 exceeding 3% (Figures 2-4). However, the coverage of drug resistance surveillance sites needs to be further improved to reduce nationwide data gaps, especially in the North Eastern part of the country (Figure 5). Further, none of the existing studies employ rich parasite density sampling which might be required to detect emerging Artemisinin resistance. The latter is now planned under the East Africa Public Health Laboratory Network project (EAPHLNP) which is supported by the World Bank [http://www.eac.int/health/index.php].

Figure 3: (AL, Amodiaquine –Artesunate-ASAQ or Dihydro Artemisinin-Piperaquine-DHAPQP) had a point estimate of the proportion with persistent parasitemia at day 3 exceeding 3%.

Figure 2: (AL, Amodiaquine –Artesunate-ASAQ or Dihydro Artemisinin-Piperaquine-DHAPQP) had a point estimate of the proportion with persistent parasitemia at day 3 exceeding 3%.

Figure 4: (AL, Amodiaquine –Artesunate-ASAQ or Dihydro Artemisinin-Piperaquine-DHAPQP) had a point estimate of the proportion with persistent parasitemia at day 3 exceeding 3%.

Figure 5: North Eastern part of the country.

Grappling with sub-standard and counterfeit medicines

A major concern during the early years of the malaria case management policy in Uganda was the quality of medicines available in the private sector. In 1997, the drug regulatory body, the National Drug Authority (NDA), sampled 12 quinine mixtures/syrups from nine local manufacturers and found that none of them produced quinine in standard strengths (i.e. 100-mg quinine base/5 mls) [80]. In 1998, a study of the quality of CQ reported that up to 30% of the tablet samples and 33% of the injectable CQ samples contained less than the normal amount of the active ingredient; only 45% of tablet samples and 38% of injectable samples of CQ contained the normal amount of active ingredient [81]. A major challenge for Uganda remains the weak system for post marketing surveillance and pharmacovigilance [82]. To date, the use of counterfeit artemisinin combination therapy (ACT) medicines remains a very real threat to emerging resistance and the lack of effective pharmacovigilance is a major weakness. In a recent study between 2010 and 2011, at 93 drug stores in five Ugandan districts, 558 ACT products were tested using Raman spectroscopy and 39% were shown to be fakes [83].

Bridging the access to treatment gap-Home based management of fever (HBMF)

After several studies trying to improve malaria case management at home [84-86], in 1998, WHO-TDR spearheaded pilot studies to assess the feasibility of using pre-packaged medicines for home based management of malaria fevers (HBMF). The first pilot countries were Ghana, Nigeria and Uganda. In Uganda the pilot studies were conducted between 1998 and 2000, in three districts. The studies demonstrated that HBMF was feasible and could improve access to malaria treatment [87]. Consequently, HBMF was adopted as a policy in 2001 [88]. In order to complement the availability of free malaria treatment through public health facilities and bring it closer to the home, the programme of HBMF for children less than 5 years of age was introduced initially in 10 districts in 2002 [89]. The blister packed combination treatment of CQ+SP was developed in two age-dependent and colour-coded packages; one for children 6 months to 2 years and another for the 2-5 year olds. The treatment was branded "HOMAPAK" and was produced by a local pharmaceutical company. The medicines were initially distributed directly to the districts by the NMCP but delivery was later integrated into the existing essential medicines supply system. Caregivers of children with fever accessed the treatment through volunteers called Community Drug Distributors (CDD) or Community Medicine Distributors (CMD), two of whom were selected and trained per village (approximately 500 people). These CDDs/CMDs reported to and received supplies from the nearest health facility which was also responsible for supervision.

Rolling out of the HBMF strategy continued between 2003 and 2006 and was assisted by the GF Round 2 and Round 4 funding. A 2003 evaluation of the HBMF program found an increase from 7% in 2001 to 39% of febrile children receiving malaria treatment within 24 hours in nine districts receiving the HBMF intervention. By 2005, HBMF had been scaled-up across communities in 47 districts, including the internally displaced persons (IDP) camps in the North of the country [90-92]. The approach was widely researched and it was generally felt to be an effective vehicle to ensure malaria medicines were close to the household when needed for prompt treatment [93-95]. However, HBMF faced many challenges, including: an inability to sustain the initial motivation of the volunteers due to lack of remuneration or other incentives; inability to ensure adequate supervision, data flows and drug supply management challenges; problems associated with being a vertical programme with inadequate integration with other community-based health activities such as IMCI; and finally an inability to transition to the new treatment policy in 2004-2007 using ACT. The latter had regulatory challenges beyond the NMCP, for example whether community volunteers were allowed to handle the new drug whose safety remained uncertain and there was no pharmacovigilance linked to HBMF. Moreover, an alternative strategy became more popular, with a focus on integrated community case management (iCCM) and several assessment studies were conducted in the country that demonstrated that iCCM was feasible [96,97]. ICCM using ACT is presently implemented in only 34 of 112 districts.

Challenges during the ACT era and improving access to treatment in the private sector

The private sector supports first treatment contact for an estimated 40-50% of fevers [98,99]. As HBMF is yet to be scaled up nationwide for AL, engaging private sector providers was seen as a key element of improving AL access. In 2008, the consortium for ACT private sector subsidy (CAPSS) pilot project introduced a subsidized, first-line AL product in the private sector in Uganda. Four intervention districts were purposefully selected to receive branded subsidized medicines, while the fifth district acted as a control. Products in the intervention districts were branded "*ACT with a leaf*" to distinguish them from all other ACTs and antimalarials. A maximum recommended retail price (MRRP) for each age-pack was printed on the product. The final price per age-pack ranged from US$ 0.10 to US$ 0.40 [100,101]. At baseline, ACT accounted for less than 1% of anti-malarials purchased from licensed drug shops for children less than five years old but at the end of the pilot "*ACT with a leaf*" accounted for 69% of anti-malarial purchased in the interventions districts [101].

A broader initiative to increase nation-wide AL availability through the private sector was launched in 2010 by the GF's Affordable Medicines Facility for malaria (AMFm) initiative [102-104]. Uganda was part of the pilot 10-country study. AMFm negotiated with manufacturers to reduce the price of their ACT, offered a co-payment of approximately 95%, reducing the factory price of ACT to US$ 0.05 per adult dose. In-country national importers/wholesalers and retailers worked out an affordable profit margin to ensure affordable quality assured AL to consumers at the periphery through drug shops and

general shops. Based on the CAPSS experience in Uganda, the AMFm products were branded *"ACT with a leaf"*. However, AMFm elected not to print the maximum recommended retail price for each age-pack. The AMFm independent evaluation for Uganda indicated a high achievement on the indicator for availability of quality assured ACTs (QAACTs) which rose from 21% to 67% and medium achievement on the indicator for market share of QAACTs, which rose from 40% to 57%. However, there was poor achievement on the indicator for price of QAACTs US$ 1.96 vs. US$ 0.59 [102,103].

The Uganda AMFm was not as successful as the CAPSS pilot project largely because the grant amendment was signed late because of an initial objection from the Uganda government that AMFm would "kill" local pharmaceuticals companies. Further, the scope, scale and intensity of the demand generation under the Uganda AMFm were sub-optimal compared to that of the CAPSS pilot project. After the AMFm phase 1 independent evaluation report was presented to the Global Fund [102,103], the Global Fund Board decided to integrate the AMFm into core Global Fund grant management and financial processes. AMFm phase 1 countries such as Uganda were encouraged to incorporate AMFm-like strategies within their broader funding requests and national strategies. How this might evolve as true private sector integration continues to pose a challenge in Uganda and raises major concerns [105].

Improving Malaria Diagnosis

Repeated attempts were made to improve the availability and the quality of laboratory diagnosis for malaria through training and provision of microscopes. The proportion of health facilities with functional microscopy services modestly increased over the second MSP period (2001-2005); only 8% of all cases reported in the HMIS in 2004 were laboratory confirmed. In 2009 this had increased to 17% [106] and to 24% by 2010 [107-109]. Based on the confirmed RDTs quantities available in the country and the shift to voluntary pooled procurement - VPP delivery schedules, the country seems to be on track to achieve the 2015 diagnostics targets. However, regular supervision and quality control of laboratory services in the public sector has been insufficient or absent. Rapid diagnostic tests (RDTs) for *Plasmodium falciparum* have been repeatedly investigated to assess their accuracy and feasibility at peripheral health facilities in the public, private and community level [110-123]. Most of the studies found RDTs to be useful in settings where no laboratories were available. While RDTs have been routinely used for the investigation of suspected malaria outbreaks and by some NGOs in the context of clinical services in the IDP camps in Northern Uganda, they need to be quickly scaled up in the public sector and at community level. In 2007, the WHO and MoH with support from DFID to the Malaria Consortium provided an in-country forum to debate and provide a road map for scaling up the use of diagnostics for malaria [124]. Late in 2009, a further consensus meeting proposed the scale-up of RDTs at lower level health facilities and the community level starting as operational research [125]. Numerous local and international NGO and agencies provided technical support in the development of implementation tools, including a trainer's manual, user's guides, job aids and quality control frameworks. A central coordination and steering committee was established and was responsible for planning, quantifying and providing leadership to the role-out of universal parasite diagnosis. The roll-out of diagnostics and the large scale use of RDTs by village health teams-VHTs was launched in 2010 under the iCCM strategy in mid western and central Uganda; this initiative led to

a sharp rise in the use of malaria diagnostics for febrile patients from 8% to 30% during 2010 [126].

A major strategic shift in 2011 was the expansion of parasite diagnosis in the management of malaria in line with WHO recommendations for Test, Treat and Track-T3 [127]. The policy and STGs on malaria case-management were subsequently changed from presumptive treatment to parasite based diagnosis and treatment [128]. With this new policy it is likely that RDT scale up will be rapid and the aim is to ensure that there are microscopy services at all health facilities from level III and above and RDTs at health centres II-HC II and community levels and to fill the gaps at higher level health facilities whenever microscopy services are not possible.

Improving malaria case management commodity tracking

An initiative to improve malaria drug management, malaria diagnosis and treatment in the public sector, mTRAC, was piloted in 2010 in two districts [129]. mTRAC uses internet or mobile phone SMS based interfaces to enhance real time reporting on various malaria indicators including the availability of ACTs, Quinine and RDTs stocks, malaria cases confirmed by microscopy or RDTs, malaria cases treated and other health service delivery monitoring indicators. MTrac has now been adopted beyond the pilot districts.

Quality of malaria case management (uncomplicated and severe)

Uncomplicated malaria

Treatment guidelines and training curricula have been developed and health workers trained on malaria case management by the MOH and partners. However, the availability and the proper use of the recommended medicines at peripheral health facilities has been challenging. A survey done in four districts in 2008 revealed that there were often stock-outs of the recommended drugs. 13% of the facilities reported complete lack of AL in the two weeks preceding the survey, and even when drugs were present, clinicians prescribed non-approved therapies, including CQ, SP and CQ+SP in 18% of patients [12]. Further, the 2009 malaria indicator survey reported that among children under five years with fever, 60% took an anti-malarial medicine, and of these, only 23% took an ACT.

Severe malaria

In the previous couple of years, several activities have been undertaken to enhance the effective management of severe malaria, including: the use of Artesunate suppositories administered close-to-home under ICCM; revision of the training manuals for severe malaria; as well as efforts to make relevant supplies available at referral health facilities. Clinical audits have also been used in an attempt to improve the operational efficiency and quality in the management of severe malaria in 34 pilot districts. However the management of severe malaria remains sub-optimal. A cross sectional survey, conducted in 2009, in 11 districts in the eastern and mid-western parts of Uganda documented the following: none of the inpatient facilities had all seven components of the basic care package for the management of severe malaria consistently available in the 3 months prior to the survey. Referral practices were appropriate for less than 10% of the patients [130]. Prompt care at any health facility was reported by only 29% of patients. Severe malaria was correctly diagnosed in 27% of patients. Though the quinine dose and regimen was correct in the majority

(70.4%) of patients, it was administered in the correct volumes of 5% dextrose in only 18% of the patients. Most patients (80.1%) had several doses of quinine administered in one single 500 ml bottle of 5% dextrose. Further, medications were purchased by 44% of the patients and medical supplies by 70.6% of the patients. The authors of the survey concluded that the management of severe malaria in Ugandan health facilities was sub-optimal. Priority areas for improvement were identified as: triage and emergency care, referral practices, quality of diagnosis and treatment, availability of medicines and supplies, training and support supervision [130] (Table 4).

Study ID	N	D28Efficacy adjusted	95% CI	D28Efficacy unadjusted	95% CI
Mbarara_2005	386	98.9	95.7 – 99.7	91.7	86.6 – 94.9
Kanungu_2006	215	99.1	93.6 – 99.8	96.2	92.6 – 98.1
Apac_2006	211	100	98.3 – 100	89	83.9 – 92.5
Tororo_2007b	72	93.6	90.2 – 99.8	77.5	65.9 – 85.6
Jinja_2007	227	98.6	95.6 – 99.5	96.6	93.0 – 98.4
Mbarara_2007	159	99.3	95.3 – 99.9	93.9	88.5 – 96.8
Tororo_2007a	220	95.7	91.9 – 97.7	75.5	69.2 – 80.7
Tororo_2008	119	100	96.9 – 100	96.6	91.1 – 98.7

Table 4: D28 adjusted and un adjusted treatment efficacy for DHA-PQP.

An malaria programme review-MPR conducted in 2011 identified the following issues with respect to malaria case management in Uganda [131]: frequent stock-outs of antimalarial medicines and supplies at health facilities and community level; although the NMCP had conducted training of health workers in 21 districts on the use of RDTs, implementation was hampered by non-availability of RDTs; integrating private sector providers into national case management programme was a major challenge; there were weak services for management of severe malaria below HCIV level; poor laboratory personnel staffing at all levels; inadequate technical supervision to service delivery points; obsolete equipment (microscopes); inadequate linkages with the regional and district laboratory focal persons; lack of a malaria reference laboratory; inadequate staffing, inadequate knowledge, skills and attitudes; piecemeal and fragmented implementation of activities in the era of universal coverage (e.g. HBMF, amidst weak facility systems); inadequate collaboration mechanisms with private facilities and inadequate job aids and guidelines in the health facilities (Table 5).

Study-Site	N	D28Efficacy adjusted	95% CI	D28Efficacy unadjusted	95% CI
Apac_2002	174	89.6	83.2 – 93.6	46.5	38.9 – 53.8
Arua_2002	174	92.2	86.6 – 95.5	49.3	41.7 – 56.6
Kampala_2002	134	96.7	91.3 – 98.7	82.2	74.4 – 87.8
Jinja_2002	189	95.8	91.4 – 98.0	80.1	73.5 – 85.2
Tororo_2002	194	87.6	79.3 – 92.7	25.5	19.4 – 32.0
Amudat_2003	106	95.7	88.8 – 98.4	27.3	19.1 – 36.1
Kampala_2004	434	98.7	97.0 – 99.5	93	89.9 – 95.1
Tororo_2004	204	93.1	87.9 – 96.4	49.8	42.7 – 56.4
Mbarara_2007*	160	98.6	94.6 – 99.7	85.6	78.7 – 90.4
Kampala_2008*	208	99	95.9 –99.7	52.3	45.1 – 59.0

Table 5: D28 adjusted and un adjusted treatment efficacy for ASAQ.

Changing funding landscape for malaria case management strategies

In submitted a successful malaria proposal to the Round 2 call for proposals and another successful application to the Round 4 call in 2004. The round 4 GF funding, over US$ 150 million, was targeted at procuring ACT and RDTs and supporting HBMF. In August 2005 the GF suspended all funding (Rounds 2 and 4) to Uganda following a Pricewaterhouse Coopers financial audit highlighting gross mismanagement of funds [132]. The government of Uganda appointed Ernst & Young as GF managers including responsibilities for procurement of commodities. Following several months of lobbying and reorganizing the national GF management system, the GF ban was lifted in November 2005. The Malaria Consortium and the WHO were active participants in ensuring that the suspension would not interrupt activities deemed to be life-saving such as procurement of AL and the operational costs to support health worker training. In 2005, the United States Government announced a new five-year, US$ 1.2 billion initiative to rapidly scale-up malaria prevention and treatment interventions in high-burden countries in sub-Saharan Africa, known as the President's Malaria Initiative (PMI) [http://www.fightingmalaria.gov/]. Fortunately, when GF funding had been suspended, the country became one of the first of three countries to benefit from this new PMI funding and began with "jump start" funding of circa US$ 500,000 in 2005. In 2006, PMI awarded US$ 9.5 million to Uganda, which increased to between US$ 19 million and US$ 35 million per annum between 2007 and 2013 [133]. In 2010, the GF awarded additional funds under Round 10, US$ 156 million, for the procurement of ACT and RDTs [134]. Therefore, between 2005 and 2010, Uganda had an unprecedented access to malaria development assistance, able to transform how successful the malaria case management strategies would be relative to previous periods. However, there was also a rapid turnover of staff within the malaria programme and universal access to malaria case management was never achieved (Table 6).

No	Description of Indicator	Target	Achieved
1	Proportion of malaria cases with confirmed diagnosis by microscopy or RDTs	85% by 2015	24%
2	Proportion of the districts with at least 80% of targeted HWs trained on RDT	100%	22.8%
3	Proportion of districts with at least 80% of targeted laboratory technicians trained on malaria microscopy	100%	38.3%
4	Number of health facilities participating in malaria slide rechecking (EQA)	200 by 2015	60
4	Proportion of the population accessing effective treatment with 24 hours of symptom onset	85% by 2015	30%

Table 6: Status of achievement on the indicators for malaria diagnosis and treatment.

Malaria control 2010-2015: sustaining the gains

In 2010, Uganda defined its fourth MSP (2010-2015) [135], tied to Uganda's broader development context as detailed in its Vision 2040 [136] and the national development plan [137]. The government of Uganda, with the stewardship of the MoH, developed the third National Health Policy (NHP III) that covers a five year period 2010/11-2014/2015 and includes malaria as part of the minimum essential package. The MSP has as its vision *"Malaria will no longer be the major cause of illness and death in Uganda and families will have universal access to malaria prevention as well as treatment by 2015"*. The overall goals of the 2010-2015 MSP are two-fold: 1) to control and prevent malaria morbidity and mortality, and thereby minimize the social effects and economic losses attributable to malaria in the country; and 2) to contribute to the reduction of under-five all-cause mortality rate, as a result of reduced malaria mortality. The case management related objectives are to: provide a definitive diagnosis to at least 85% of suspected malaria cases in the public sector; provide effective ACT treatment to at least 85% of people with uncomplicated malaria within 24 hours of onset of symptoms in the public or private sectors; provide preventive treatment to pregnant women with at least two doses of IPT with a safe antimalarial; create an enabling environment for the implementation of key malaria interventions through behavioural change initiatives, obtain adequate financing and appropriate human resources, conduct relevant operational research, strengthen M&E and overall health systems [138]. Despite these broad ambitions, access to effective and prompt malaria case management remains sub-optimal in Uganda. During the national household survey of 2011, 43% of febrile children took an antimalarial on the same/next day of symptom onset, with still only 30% of fevers treated with AL [139].

Conclusion and Perspectives for the Future

The evolution of Uganda's malaria case management strategies and drug policies has been a journey mirrored by its social and political struggles. The significance of malaria as a barrier to the country's development was evidenced by pre-independence urban control approaches and was resurrected as a development priority by the World Bank in the 1990s. There has been no shortage of timely research evidence that replacing failing mono-therapies can reduce malaria risk and reverse trends in disease burden. However, malaria case management interventions of proven efficacy have all struggled to achieve ubiquitous and equitable coverage despite their promotion in national strategic plans since the late 1990s. Arguably, the slow progress was a direct consequence of poor funding and a rapid turn-over of staff leading to a constant loss of institutional memory within the national programme-seven NMCP heads since 1996. Significant official development assistance only became available from 2006 onwards, yet by 2013, there remained important gaps in national ambitions for universal coverage of malaria case management services.

Since 1996, when Uganda developed the first malaria strategic plan (MSP), post the malaria pre-eradication era, the country has developed three other MSPs- all in line with broad WHO recommendations to scale up effective diagnosis and treatment coverage universally. However, Uganda has struggled to scale up implementation nation-wide. A major challenge noted by all previous reviews is the low profile

of the NMCP within the MoH structure which limits its capacity and capability to coordinate multiple stakeholders in the country. Secondly there is limited involvement of the decentralised structures and the community in planning and implementation. In order for the country to rapidly achieve universal coverage of malaria diagnosis and treatment, there is a need for reforms in the profile and structure of the NMCP to facilitate better coordination of all malaria case management stakeholders. Further, there is a need for decentralized planning and implementation with greater involvement of the zonal, district, health facility and community levels. Moreover, it will critical to engage the challenging but very important private sector.

Finally, we believe such historical overviews should be periodically conducted to provide a form of institutional memory to current and future players in malaria case management in Uganda, highlighting some of the historical and current challenges for universal access to prompt and effective malaria case management.

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Author Contributions

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