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Malaria in Uganda: challenges to control on the long road to elimination. I. Epidemiology and current control efforts

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Abstract

Malaria remains one of the leading health problems of the developing world, and Uganda bears a particularly large burden from the disease. Our understanding is limited by a lack of reliable data, but it is clear that the prevalence of malaria infection, incidence of disease, and mortality from severe malaria all remain very high. Uganda has made progress in implementing key malaria control measures, in particular distribution of insecticide impregnated bednets, indoor residual spraying of insecticides, utilization of artemisinin-based combination therapy to treat uncomplicated malaria, and provision of intermittent preventive therapy for pregnant women. However, despite enthusiasm regarding the potential for the elimination of malaria in other areas, there is no convincing evidence that the burden of malaria has decreased in Uganda in recent years. Major challenges to malaria control in Uganda include very high malaria transmission intensity, inadequate health care resources, a weak health system, inadequate understanding of malaria epidemiology and the impact of control interventions, increasing resistance of parasites to drugs and of mosquitoes to insecticides, inappropriate case management, inadequate utilization of drugs to prevent malaria, and inadequate epidemic preparedness and response. Despite these challenges, prospects for the control of malaria have improved, and with attention to underlying challenges, progress toward the control of malaria in Uganda can be expected.

Keywords

Malaria; *Plasmodium*; Uganda; Insecticide-treated nets; Indoor residual spraying; Artemisinin-based combination therapy; Intermittent preventive therapy

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1. Introduction

Malaria remains one of the most important global health challenges, with an estimated 3 billion people at risk of infection, leading to approximately 500 million cases and 1 million deaths each year (Greenwood et al., 2005; Snow et al., 2005). The bulk of the malaria disease burden is concentrated in sub-Saharan Africa, and in this area nearly all malaria is caused by *Plasmodium falciparum*. Efforts to reduce the burden of malaria have intensified recently through the use of effective tools for malaria control, notably long-lasting insecticide treated nets (ITNs), indoor residual spraying (IRS) of insecticides, treatment with artemisinin-based combination therapies (ACTs), and intermittent preventive therapy (IPT) for high-risk groups (Greenwood et al., 2005). These efforts have been made possible by recent focused policy recommendations and increased support from governments and international organizations. Increased resources for control have come with ambitious targets and expectations of significant reductions in disease burden. Subsequently, calls have been made for the elimination of malaria from endemic areas and eventually the complete eradication of the disease (Feachem et al., 2010). With these developments several success stories have recently been reported from Africa, with marked declines in the burden of malaria following the scale up of control interventions (O'Meara et al., 2010). Successes have included regions near Uganda, such as Zanzibar (Bhattarai et al., 2007) and coastal Kenya (O'Meara et al., 2008). However, marked improvements in malaria disease indicators have been seen principally in areas with relatively low baseline transmission intensity (South Africa, Rwanda, Ethiopia), island communities (Zanzibar, Bioko Island), areas with better public health infrastructure than most of Africa (South Africa), or regions with unusually strong local infrastructure for malaria research and monitoring (parts of Kenya, Gambia, and Zambia). Less information on recent changes in malaria epidemiology are available from most of mainland sub-Saharan Africa.

The greatest burden of malaria, by far, remains in the heartland of Africa, characterized by large contiguous areas of high transmission, low coverage of control interventions, and limited infrastructure to monitor disease trends. In many cases, political and economic factors have greatly hindered even rudimentary control interventions or disease monitoring. Uganda has had quite stable politics and economics for the last few decades, allowing a fairly good appreciation of the malaria situation. The epidemiology of malaria varies widely in Uganda, from highland regions with low prevalence and unstable disease to large regions with dense agricultural settlement and some of the highest recorded malaria transmission intensities in the world (Okello et al., 2006). Thus, Uganda affords a valuable picture of the state of malaria in the part of the world for which elimination will be most challenging-mainland sub-Saharan Africa. In this paper we review the epidemiology of malaria in Uganda and then address the current program for malaria control. We note that, counter to prevailing impressions, the burden of malaria does not appear to be decreasing markedly in Uganda. Further, we note the challenges that help to explain the limited success of malaria control efforts to date in Uganda.

2. Epidemiology of malaria in Uganda

2.1. Overview

Malaria is reported by the Ministry of Health (MOH) as the leading cause of morbidity and mortality in Uganda, accounting for approximately 8–13 million episodes per year, 30–50% of outpatient visits at health facilities, 35% of hospital admissions, 9–14% of hospital deaths (nearly half of those in children less than 5 years of age) and a great many deaths occurring outside of health-care settings (Uganda Ministry of Health, 2005). Available data include a Uganda Demographic and Health Survey (UDHS) in 2006 (Uganda Bureau of Statistics, 2007), a Uganda Malaria Indicator Survey (UMIS) in 2009 (Uganda Bureau of Statistics,

2010), and ongoing health facility-based data routinely collected through the Health Management Information System (HMIS). These data may be limited by incompleteness in data collection, variations in reporting rates between sites and over time, and biases inherent to facility-based data. Nonetheless, they offer a valuable picture of the malaria control situation in Uganda, showing some impressive recent advances in the coverage of control interventions. However, these and other available data argue that the malaria burden in Uganda has not decreased notably in recent years, and it may even be increasing.

2.2. Plasmodial species in Uganda

Although all four species of malaria parasites exist in Uganda, *P. falciparum* is responsible for the vast majority of cases (Uganda Ministry of Health, 2005). Other species appear to each account for <5% of cases, with a few percent of infections due to mixed species. In 2009 determinations based on blood smears, 99% of infected children had *P. falciparum*, 2% *P. vivax*, 2% *P. malariae*, and <1% *P. ovale*; 3% carried mixed species infections (Uganda Bureau of Statistics, 2010). Considering symptomatic infections in a cohort study in Kampala from 2004–2008 in which infecting parasites were speciated by molecular means, 94% of episodes of malaria were caused by *P. falciparum* (including mixed infections), 4.6% solely by *P. malariae*, 0.8% by *P. ovale*, and 0.5% by *P. vivax* (Clark et al., 2010).

2.3. Mosquito vectors

The most common malaria vectors in Uganda are *Anopheles gambiae s.I.* and *A. funestus*, with *A. gambiae s.l.* being the dominant species in most locations (Okello et al., 2006). *A. funestus* appears with frequency in high altitude areas and during the short dry seasons, when permanent water bodies are the most common breeding sites. In some areas of northern Uganda, *A. funestus* is the most common vector. Within the *A. gambiae* complex, the predominantly anthropophilic (prefering humans to other animals) *A.gambiae s.s.* is by far most common. *Anopheles gambiae s.s.* and *A. funestus* are both highly endophagic (feeding indoors) and endophilic (resting indoors), making ITNs and IRS preferable vector control strategies in Uganda.

2.4. Malaria transmission intensity

The climate in Uganda allows stable, year round malaria transmission with relatively little seasonal variability in most areas. Malaria is highly endemic in ~95% of the country, representing ~90% of the population of ~33 million (Figure 1). Indeed, some of the highest recorded entomological inoculation rates (EIR, infective mosquito bites per person year) in the world have been seen in Uganda, including rates of 1586 in Apac District and 562 in Tororo District (Okello et al., 2006) measured in 2001–02. The Uganda MOH estimates that the EIR is >100 in 70%, 10–100 in 20%, and <10 in 10% of the country (Uganda Bureau of Statistics, 2010). However, these estimates are based on little data, as few entomological surveys have been carried out in the country. Transmission is unstable and epidemic-prone in extreme southwestern areas and in the vicinity of the Ruwenzori mountains in the west and Mt. Elgon in the east, all areas extending above 1,800 meters in altitude.

2.5. Malaria prevalence

The 2009 UMIS measured a prevalence of malarial parasitemia, assessed based on microscopy, of ~30–50% in children 6–59 months of age (Table 1, Uganda Bureau of Statistics, 2010). Anemia was also very common, with a hemoglobin <11 g/dl seen in well over half of children (Table 1). Prevalence was high (38–63% by blood smear) in all regions except Kampala (5%), the major city, and in the southwestern region, which includes highland areas (12%) (Figure 2). As expected, prevalence was lower in urban areas, with

increasing educational levels of mothers, and with increasing wealth. These prevalence measures are consistent with very high and stable transmission of malaria in most of Uganda. Because this was the first MIS conducted in Uganda, it is unknown if malaria prevalence has changed in recent years.

2.6. Uncomplicated malaria

As the worldwide focus on malaria is shifting toward planning for eradication, it is remarkable that evidence for a decrease in the malaria burden is lacking in Uganda. One exception may be Kampala, the only major city in Uganda, where decreasing malaria incidence has been noted anecdotally, although definitive data are lacking. A cohort study conducted from 2004 to 2008 noted a remarkable decrease in malarial incidence, although this finding was influenced by other factors, including treatment of all malarial illnesses with highly effective agents, aging of the cohort population, and provision of insecticide-impregnated bednets (Clark et al., 2010).

Regular reports from the Uganda HMIS are likely highly inaccurate, suffering both from underreporting of fevers (as only episodes captured by the national public health system are reported) and overstatement of malaria diagnoses in febrile children without diagnostic confirmation (Rowe et al., 2009). Nonetheless, the HMIS data provide the only available direct measure of disease numbers across the country. In recent years, HMIS reported cases increased since the 1990s, with over 10 million cases reported each year (Figure 3). Notably, 60–80% of fever cases are estimated to be treated in the informal and private sectors (not assessed by HMIS), and it has been estimated that the total number of fever cases in Uganda in 2005 was 60 million (President's Malaria Initiative, 2010). Factors that may have influenced changes in malaria reporting over time include the abolition of user fees for public sector health care in 2001, which led to increased attendance at public facilities and the subsequent roll out of the Home-Based Management of Fever strategy (Uganda Ministry of Health, 2005), which shifted care to community centers without links to HMIS reporting. Another relevant factor is the rapid increase in population of the country, suggesting that, if the overal number of episodes of malaria has been stable, the incidence has decreased somewhat. Overall, it is difficult to ascertain from available data whether the incidence of malaria has decreased or increased over the last decade, but clearly the incidence of the disease in Uganda remains very high.

In lieu of more reliable data, a helpful surrogate for incidence is the slide positivity rate (SPR), which is the percentage of individuals presenting to health facilities with suspected malaria who test positive by either a blood smear or rapid diagnostic test (Jensen et al., 2009). Accurate monthly SPRs have been available since 2007 for children <5 years of age from 6 outpatient sentinel surveillance sites in Uganda with varied levels of transmission intensity (Figure 4). Of note, the SPR has not decreased consistently at any of the sites. At one site with relatively low transmission (Kanungu District), the SPR decreased after indoor residual spraying in early 2007, but this was followed by a slow rebound to prior levels (Bukirwa et al., 2009). In regions of very high transmission, the SPR has remained at ~60–80% in Apac District and 50–70% in Tororo District. Indeed, even in areas with lower rates of transmission the SPR has commonly been measured at 20–60%. The areas with lowest transmission intensity (Kanungu and Kabale Districts) had the most marked swings in SPR, suggesting intermittent epidemic disease. These results belie international enthusiasm regarding successes in malaria control in other regions of Africa. In contrast, Uganda, a country with much more malaria than those with recent publicized successes, does not appear to yet have experienced major decreases in the malaria burden.

2.7. Complicated and severe malaria

Measuring malaria mortality in Uganda remains a challenge due to the lack of good quality data on the determinants of death (Snow et al., 1999) and the propensity for deaths outside the formal health setting (Breman, 2001). It is commonly stated that 70,000–100,000 children under five years die of malaria annually in Uganda (Uganda Bureau of Statistics, 2010; Uganda Ministry of Health, 2005). This estimate was determined in 1998 basing on the the proportionate child malaria mortality rate derived from a burden of disease and verbal autopsy survey in Kabarole district and an estimate of the overall child mortality rate in the same area. However, it was based on inaccurate assumptions, in particular over-estimation of child mortality. A more accurate estimate suggests that about 30,000 children under five years die of malaria each year in Uganda (A. Kilian, personal communication). The 2008 World Malaria Report estimate for total malaria deaths in Uganda was higher, at 43,490, ranking it third in the world behind Nigeria and the Democratic Republic of the Congo (World Health Organization, 2008). Current estimates from data collected through government sources suggest that the number of annual deaths has been quite steady, but that deaths per 1000 population have declined, from about 6.5/1,000 in 2002 to 4.5/1,000 in 2010, although the accuracy of these estimates are uncertain (A. Kilian, personal communication). In any event, although suggestions of a decrease in mortality are encouraging, Uganda continues to suffer a very high and concerning mortality from malaria.

Limited more specific data on malaria mortality are available for some regions, and these do not show obvious improvements in recent years. Considering older data, review of pediatric deaths from two district hospitals located in stable (Hoima District) and unstable (Kabale District) malaria transmission zones showed a linear increase in the number of malaria cases and deaths from 1991 to 2000 (Ndyomugyenyi and Magnussen, 2004). A recent study of pediatric deaths from 1999–2009 in 5 district hospitals across Uganda showed a similar trend (E. Okiro, personal communication). A verbal autopsy study conducted from 2008 to 2009 identified malaria as the cause of 48% of deaths in two hospitals in Tororo District (a holoendemic region), 9% of deaths in Kampala (mesoendemic), but no deaths in the two main hospitals in Kisoro District (hypoendemic; A. Mpimbaza, personal communication).

2.8. Antimalarial drug efficacy and resistance

Multiple studies over the last decade documented high failure rates with widely used monotherapies, including chloroquine, amodiaquine, and sulfadoxine-pyrimethamine (SP; Dorsey et al., 2000; Staedke et al., 2001). Early studies with combination antimalarial therapies documented unacceptably high failure rates with the combination of chloroquine and SP, which was the recommended first-line treatment for Uganda from 2001–2004 (Staedke et al., 2004; Yeka et al., 2005) and also with the ACT artesunate-SP (Dorsey et al., 2002). Consistent with these findings, in vitro resistance to CQ and AQ was common among parasites collected in Kampala (Nsobya et al., 2010) and the prevalences of molecular markers indicative of resistance to CQ (*pfcrt* 76T), AQ (*pfcrt* 76T, *pfmdr1* 86Y and 1246Y), and SP (5 mutations in *pfdhfr* and *pfdhps*) were all very high (Dorsey et al., 2001; Francis et al., 2006). Other ACTs were much more efficacious. In particular, artemether-lumefantrine, the current national first-line regimen for uncomplicated malaria, was significantly superior to the combinations of amodiaquine-SP and artesunate-amodiaquine (Dorsey et al., 2007), and dihydroartemisinin-piperaquine has also performed very well in recent trials (Arinaitwe et al., 2009; Kamya et al., 2007b; Yeka et al., 2008). However, in areas with very high transmission intensity, although treatment with artemether-lumefantrine (AL) cured nearly 100% of infections, recurrent parasitemia was seen within one month in over half of studied children (Arinaitwe et al., 2009; Bukirwa et al., 2006; Kamya et al., 2007b). These results highlight the extremely high incidence of malaria among children living in high transmission areas and the failure of effective case management to prevent recurrent disease

in high risk populations. However, resistance to leading new artemisinin-based combination therapies does not appear to be a problem in Uganda. Considering preventive therapy, a single dose of SP failed to prevent malarial infection in a high transmission area, questioning the value of SP in IPT regimens (Nankabirwa et al., 2010). However, another antifolate combination, trimethoprim-sulfamethoxazole, which is used daily in HIV-infected individuals, decreased the incidence of malaria in HIV-infected children in Kampala by 80% (Gasasira et al., 2010; Kamya et al., 2007a), and in HIV-exposed children in Tororo, an area of very high transmission, by 40% (G. Dorsey, personal communication). .

2.9. Resistance of anopheline mosquitoes to insecticides

In Uganda resistance to pyrethroids and DDT, the two classes of insecticides most widely used in malaria vector control, has been observed in all three of the major vectors, *A. gambiae s.s.*, *A. funestus*, and *A. arabiensis* (Morgan et al., 2010; Ramphul et al., 2009; Verhaeghen et al., 2010). Based on the limited available data, resistance seems to be most prevalent in the central and southeastern regions of the country, although decreasing susceptibility to pyrethroids has also been observed in wild-caught *A. gambiae s.l.* collected from western Uganda (Rubaihayo et al., 2008). Considering molecular data, mutations in a voltage-gated sodium channel that are strongly associated with resistance to DDT and pyrethroids (Donnelly et al., 2009) have been observed in both *A. gambiae s.s.* and *A. arabiensis* (Ramphul et al., 2009; Verhaeghen et al., 2010; Verhaeghen et al., 2006), and increased esterase activity, which has been implicated in reduced susceptibility to pyrethroids in *A. gambiae s.s.* in neighboring Kenya (Vulule et al., 1999), has been observed in samples of *A. gambiae s.s.* from southeastern Uganda (Verhaeghen et al., 2010). Fortunately, to date there are no reports of resistance to carbamates and organophosphates, the other major classes of public health insecticides.

3. Malaria Control in Uganda

The third Uganda National Malaria Control Program (UNMCP) Strategic Plan is based on the principles and aims of the global Roll Back Malaria partnership, the 2000 Abuja Declaration, and the United Nations Millennium Development Goals (Uganda Ministry of Health, 2005). Through implementation of this plan, the NMCP aims to control malaria such that it is no longer the major cause of illness and death in Uganda, ensure universal access to malaria prevention and treatment, and reduce the mortality rate for children under five years of age. Key intervention strategies and markers of implementation, primarily garnered from the 2006 UDHS and 2009 UMIS, will be discussed below. Principal among these strategies are integrated vector management, effective diagnosis and treatment, prevention of malaria in pregnancy, and attention to malaria epidemics (Uganda Bureau of Statistics, 2010).

3.1. Insecticide Treated Nets (ITNs)

Long-lasting ITNs are the main preventive strategy used in Uganda. Since 2006, over 3 million ITNs have been distributed nationwide. With continued support from the President's Malaria Initiative (PMI) and the Global Fund for AIDS, Tuberculosis, and Malaria, the NMCP aimed to increase the number of households owning one or more ITNs to at least 85%, the number of households owning two or more ITNs to at least 60%, and the percentage of pregnant women and children under five who will have slept under an ITN the previous night to more than 85% by 2010 (Uganda Ministry of Health, 2005). Strategies to achieve these targets have included free distribution to infants and pregnant women through mass campaigns and antenatal clinics, distribution using community based organizations, provision of subsidized ITNs through the private sector, and sale of ITNs at full cost through the commercial sector. In 2009 shops, pharmacies, and open markets remained the main distribution channels for ITNs. However, from 2006 to 2009 the percentage of nets obtained

through these channels dropped from 60% to 33% while the proportion obtained from government health facilities increased from 6% to 23% and from other organizations and churches from 14% to 26% (Uganda Bureau of Statistics, 2010). In the 2006 UDHS, 34% of households owned at least one mosquito net and only 16% at least one ITN, with ITN ownership highest in the north (28%) and lowest in central regions (8%; Uganda Bureau of Statistics, 2007). The 2009 UMIS showed marked increases in ITN usage, with 59% of households owning at least one mosquito net, 47% at least one ITN, and 46% at least one long-lasting ITN (Uganda Bureau of Statistics, 2010). Ownership of at least one long-lasting ITN ranged from 22% of households in the Central region to 76% in the Northeast region. No significant differences in ownership were identified based on rural vs. urban residence or by wealth quintile. Overall, net ownership has increased markedly in Uganda in recent years, although, based on 2009 survey data, it seems very unlikely that 2010 targets have been reached (Table 2).

In addition to ownership, the use of mosquito nets also increased between 2006 and 2009 (Table 2). In children under age 5 years, the percentage sleeping under a net the night before the survey increased from 22% to 41%, and that sleeping under an ITN increased from 10% to 32%. For women, the percentage sleeping under a net increased from 23% to 42% and that sleeping under an ITN increased from 10% to 33%. Net usage was higher among urban than rural women (Uganda Bureau of Statistics, 2010). Importantly, net ownership does not necessarily guarantee usage. Overall, 17% of households had at least one net that was not used during the previous night. Reasons for non-usage of nets included difficulty hanging the net, an uncomfortably hot environment, and ownership of old and damaged nets. Overall, as with measurements of net ownership, there have been remarkable improvements in recent years in Uganda, but it is very unlikely that 2010 targets have been reached.

3.2. Indoor Residual Spraying (IRS)

Inclusion of IRS in control programs was reinitiated in Uganda, after a gap of about 40 years, in 2006. The NMCP strategy for IRS, supported by PMI, has emphasized implementation in epidemic-prone areas, high transmission settings, and high-risk situations, such as camps for internally displaced persons or refugees (President's Malaria Initiative, 2010). Thus, IRS has been applied in both highly endemic and epidemic-prone areas, but coverage has been spotty (PMI, personal communication). In the 2009 MIS, only 6% of households had been sprayed in the previous 12 months, coverage similar to that reported in 2006 (Uganda Bureau of Statistics, 2010). Coverage was highest in the Mid-northern region (32% of households). Most recently, attention has moved from epidemic-prone areas to those with very high transmission intensity in central and northern Uganda.

IRS with lambda-cyhalothrin was conducted in 2006 in over 103,000 households in Kabale District, and in 2007 in about 446,000 households, including both relatively low transmission areas in southwestern Uganda (Kabale, Kanungu) and internally displaced persons camps in three districts in the north of the country (Kitgum, Pader, Amuru). In 2008, IRS campaigns with DDT were carried out in the highly endemic districts of Oyam and Apac, covering about 197,000 houses. In 2008, IRS was also conducted in the northern district of Gulu, and a second round of spraying was completed in Kitgum and Pader, in this case with alpha cypermethrin. Two additional cycles with alpha cypermethrin were completed in Kitgum and Pader in early and late 2009. In 2010 IRS was conducted in Apac, Oyam, Gulu, Kitgum, and Amuru with alpha cypermethrin and with carbamate. Overall, 300,000–500,000 houses, housing 1–2 milliion people, have been sprayed yearly from 2007–2010. An environmental assessment for DDT use in Uganda was completed in early 2008, outlining conditions necessary to avoid potential negative impacts of IRS. Strict conditions for IRS were established, including maintenance of strict chain-of-custody of DDT. The impact of IRS with DDT on control personnel was also studied; all studied

control workers had detectable plasma levels of DDT, but no deleterious effects on liver function were observed, suggesting that DDT use was safe (Bimenya et al., 2010). Approximately 10,000 personnel (spray operators, clinicians and environmental officers) have been trained in IRS operation in Uganda. Continued use of IRS is planned.

Studies evaluating the impact of IRS campaigns on malarial morbidity and mortality in Uganda are very limited. At one site with relatively low transmission (Kanungu), the SPR decreased after indoor residual spraying in early 2007, but this was followed by a slow rebound to prior levels (Bukirwa et al., 2009). Resistance to insecticides remains a major concern. Strategies to successfully utilize IRS in the setting of resistance include limiting use to high impact sites, discontinuation of agents with resistance limitations and reintroduction if resistance rates decrease, improved surveillance for resistance determinants, and research to characterize molecular mechanisms of resistance and thereby develop new means of surveillance for resistant mosquitoes.

3.3. Intermittent Preventive Treatment

The original policy for IPTp with SP treatment once during the second and third trimesters for pregnant women was adopted in Uganda in 1998. IPTp is administered as part of an integrated package of care through antenatal clinics, with directly observed treatment. Uganda has a high level of antenatal clinic attendance (95% of pregnant women according to the 2009 UMIS). However, the 2006 UDHS indicated that only 37% of pregnant women received at least one dose and only 16% received two doses of SP, with coverage varying greatly in different parts of the country (Uganda Bureau of Statistics, 2007). These numbers improved to 45% and 32%, respectively, in the 2009 UMIS (Uganda Bureau of Statistics, 2010). Women in urban areas, with more education, and in higher wealth quintiles were more likely than comparators to utilize IPTp.The IPTp policy has recently been revised to provision of SP at every scheduled antenatal clinic visit after quickening (if at least one month apart), to reflect current WHO guidelines. As a result of these efforts, the percentage of pregnant women receiving two doses of SP is expected to increase to 60% in 2011.

In 2010 the WHO recommended IPT for infants (IPTi), utilizing SP, and coinciding with regular immunizations. However, the intervention is not recommended for areas with high (>50%) prevalence of key polymorphisms that mediate diminished parasite response to SP. The prevalence of these polymorphisms has consistently measured well above 50% across Uganda (Francis et al., 2006), and so IPTi is not recommended and is not a goal of the NMCP at this time. These considerations might logically be extended to IPTp. The current efficacy of IPTp with SP in Uganda is uncertain, but no other drugs offer single-dose treatment or have yet been validated for this purpose.

3.4. Treatment of uncomplicated malaria

Effective case management, incorporating prompt and appropriate treatment with affordable, effective, and safe antimalarials, remains a cornerstone of malaria control in Uganda. Resistance to chloroquine and SP in the country was common by the late 1990s (Kamya et al., 2001), limiting the efficacy of these monotherapies. The combination of CQ and SP became the first-line regimen for uncomplicated malaria in 2001, but not surprinsingly the efficacy of this combination of sub-optimal therapies was unacceptable (Staedke et al., 2004; Yeka et al., 2005). In 2004 the first-line therapy was changed to ACTs, with artemether-lumefantrine (AL; Coartem) routinely available and artesunate plus amodiaquine as an alternative (Uganda Ministry of Health, 2005). Quinine was recommended as the second-line treatment.

During 2005 and 2006, the NMCP implemented the new treatment policy by revising national malaria case-management guidelines, in-service training for health workers, and provision of AL to government, and private-not-for-profit health facilities (Uganda Ministry of Health, 2005). AL is delivered to the facilities in 4 standard weight-specific blister packages, each containing a different number of the same strength tablets and is provided free of charge. However, ensuring availability and proper use of the recommended drugs at all facilities countrywide has proven to be a large challenge. A survey done in four districts two years after the beginning of the new policy implementation revealed that there are often stock-outs of the recommended drugs (13% of the facilities reported complete lack of AL in the past 2 weeks), and even when drugs were present, clinicians prescribed non-approved therapies, including CQ, SP and CQ+SP in 18% of patients (Zurovac et al., 2008). The 2009 UMIS reported that among children under five years with fever, 60% took an anti-malarial drug, and of these, 23% took an ACT (Uganda Bureau of Statistics, 2010).

In 2002, the Uganda MOH initiated a national program to improve home based management of fever (HBMF) through distribution of pre-packaged drugs (Uganda Ministry of Health, 2005). The program initially promoted the use of CQ and SP, but more recently has begun implementation of AL. HBMF was incorporated in 2010 under an integrated community case management program that includes using AL to treat malaria, oral trimethoprim-sulfamethoxazole to treat pneumonia, and oral rehydration solution for diarrhea at the community level. Case management is also being strengthened at the health facility level. Treatment guidelines and training curricula have been produced, and more than 2,500 health workers have been trained on case management. Clinical audits have been used to improve operational efficiency and quality in the management of severe malaria in 23 pilot districts, and there are plans to scale up this approach.

A pilot project to deliver subsidized medicines in the private sector commenced in 2008. This pilot, supported be the Medicines for Malaria Venture, has demonstrated that providing subsidized ACTs through the private sector can lead to a dramatic improvement in the availability (~70% market share) of effective treatment and the level of uptake (Talisuna, A., personal communication). Given the importance and reach of the private sector in Uganda, its continued inclusion in healthcare provision, complementing public sector and community-based treatment channels, will be crucial to ensuring that children have prompt access to effective treatment. Improving access to effective treatment in remote areas, however, will require further actions to ensure enhancements in the supply chain.

A challenge is balancing the competing goals of maximizing coverage for patients with malaria and minimizing unnecessary treatment. WHO guidelines now recommend routine parasitological diagnosis of malaria before treatment if possible (World Health Organization, 2010). However, the majority of fever treatments in Uganda take place at the community level, outside of the formal health care system (Kengeya-Kayondo et al., 1994; Nshakira et al., 2002), and even when patients with suspected malaria present to a health facility, the majority do not undergo diagnostic testing due to a lack adequate laboratory facilities and trained staff . Plans in Uganda include strengthening of the availability and quality of malaria microscopy at higher (Health Center III-IV and hospitals) level health facilities and improving availability of RDTs at lower level facilities.

3.5. Treatment of severe malaria

A priority is early recognition of the signs and symptoms of severe disease that should lead to emergency care, including parenteral therapy, in an in-patient setting. Intravenous quinine remains the recommended treatment for severe malaria in Uganda. In a recent survey conducted in 11 districts, quinine was prescribed for 94% of patients hospitalized with a diagnosis of malaria (Achan, J., personal communication). Despite this widespread use, data

on quinine efficacy are limited. Two previous studies conducted in pediatric populations provide evidence of good efficacy in the management of cerebral malaria (Aceng et al., 2005; Achan et al., 2007). However, in another recent Ugandan study, 23% of children with uncomplicated malaria experienced genotype-corrected recrudescence within 28 days after quinine treatment, compared to no failures after AL treatment (Achan et al., 2009). These results are limited because treatment was not directly observed, but they offer concern regarding quinine efficacy. In addition, in vitro sensitivities to quinine in parasites collected in Kampala varied widely, suggesting that some limitations in quinine efficacy may be due to decreased parasite sensitivity to the drug (Nsobya et al., 2010).

Challenges to the use of quinine for the treatment of severe malaria include its poor tolerability and the need for a prolonged (one week) treatment course. In addition, intravenous administration may not be feasible in some settings. Intramuscular administration may also be utilized, but is associated with complications including sterile abscess formation and sciatic nerve paralysis. Another option is rectal administration, which has shown good efficacy (Achan et al., 2007). Due to limitations in administration, length of treatment, tolerability, and efficacy, replacements for quinine for the treatment of severe malaria are of interest. Importantly, a new international gold-standard for the treatment of severe malaria has arisen.

A recent multi-center trial in Asia showed superiority of intravenous artesunate over quinine for the treatment of severe malaria, with a 35% reduction in mortality in a population that was mostly adults (Dondorp et al., 2005). Very recently a similar study was completed in Africa (Dondorp et al., 2010). In 5425 children from 9 African countries, artesunate, administered intravenously or intramuscularly, was significantly superior to quinine, with a 23% decrease in mortality. These results will likely lead to firm recommendations for parenteral artesunate as the first-line therapy for severe malaria in Africa in the near future. However, current availability of intravenous or other parenteral formulations of artesunate is poor, and it is unclear how long it will take for artesunate to replace quinine for the routine treatment of severe malaria.

In addition to limitations in the availability and utilization of optimal drugs, other factors limit satisfactory management of severe malaria in Uganda. Referral systems are often weak, patient evaluation is usually sub-optimal, laboratory based diagnosis is often limited, and supportive therapy may be very limited. By far, the biggest challenge has been frequent stock-outs of essential dugs and supplies. In a recent survey in Uganda, intravenous quinine was found to be available on the day of the survey in only 75% of health facilities, and intravenous artesunate in less than 2% (Achan, J., personal communication). Remarkably, none of the studied health facilities had constant availability of 7 basic medicines and supplies needed for severe malaria management in the 3 months prior to the survey.

4. Monitoring and Evaluation of Malaria in Uganda

4.1. Malaria case reporting

The main source of malaria data in Uganda is routine morbidity case reports. All health facilities are required to provide monthly reports on malaria diagnoses. However, these reports are subject to gross over- or under-estimations of malaria cases, as they are generally based on diagnoses without laboratory confirmation and represent only cases presenting to public sector health facilities. Monitoring and evaluation capacity remains a significant gap; the NMCP has only one staff member assigned to monitoring and evaluation and no statistician.

4.2. Uganda Demographic and Health Surveys (UDHS) and Malaria Indicator Survey (UMIS)

The UDHS provides comprehensive surveys every 5 years as part of a worldwide project. They are based on representative household samples, providing estimates of a range of demographic and health indicators. In Uganda, 4 surveys have been conducted, in 1988–89, 1995, 2000–01 and 2006. Malaria indicators from these surveys include ownership and use of ITNs, use of IRS, coverage of IPTp, and nature of treatment of childhood fevers. The next DHS is scheduled to be conducted in 2011. In November 2009 the first UMIS was conducted, sponsored by PMI. The MIS collected comprehensive data relevant for assessing core malaria indicators, including population-level coverage of ITNs, IRS, IPTp, and ACTs as well as markers for anemia, parasite prevalence, and infecting parasite species. Although not fully comparable, comparison of results from the 2006 DHS and 2009 MIS provides a longitudinal measure of progress in malaria control interventions in Uganda, as described throughout this paper.

4.3. Uganda Malaria surveillance project

Malaria drug efficacy monitoring has been ongoing in Uganda since 1997–98 under the East African Network for Monitoring Antimalarial Treatment and since 2001 through a collaborative project between the NMCP, Makerere University, and the University of California, San Francisco. Six malaria sentinel sites, with wide variation in malaria transmission intensity, are currently operational. With recent funding from PMI and the United States National Institutes of Health, the system is expanding to incorporate routine surveillance of prevalence of asymptomatic malaria infections, uncomplicated malaria, and severe malaria; mathematical modeling of malaria prevalence and incidence; surveillance of markers of antimalarial immunity; surveillance of markers of parasite drug resistance; evaluations of transmission intensity based on studies of mosquitoes; and evaluation of insecticide resistance in mosquitoes.

5. Coordination and support for malaria control in Uganda

The Uganda MOH established the Malaria Control Unit in 1995 and the UNMCP in 1997, with the mandate to control and prevent malaria morbidity and mortality and to minimize the negative social and economic impact of malaria in the country. The objectives of the UNMCP are to implement a package of effective and appropriate interventions to promote positive behavior change and improve the prevention and treatment of malaria and to achieve high coverage levels for this intervention package. The UNMCP spearheads malaria control through policy formulation, quality assurance, coordination of health research, and monitoring and evaluation of performance. Policies and strategies for malaria control are detailed in the Uganda Malaria Control Strategic Plan (Uganda Ministry of Health, 2005). Activities at the grassroots are implemented through the formal health system, which is stratified into hospitals and health centers. District Health Officers are responsible for overseeing malaria control activities. Coordination of malaria control interventions with other organizations is achieved through the Interagency Coordination Committee for Malaria (ICCM), with technical working groups for each strategic intervention. The ICCM was established with broad participation from government departments, development partners, civil society and the private sector. However, it has not met regularly, and has at times been by-passed during crucial decision making processes.

In order to supervise and technically support health districts in the provision of health services and implementation of programs, a system of zonal coordinators was introduced in 1998 jointly with the Integrated Management of Childhood Illness program. The zonal coordinators facilitate supervision, training, and improvements in data collection and quality. A non-governmental organization secretariat was formed to bring together groups

engaged in malaria and child health activities, enhance coordination, increase the level of technical skills and enhance quality of implementation. The UNMCP further participates in the East Africa Roll Back Malaria Network.

The main contributors to malaria control in Uganda are PMI and the Global Fund. Other contributors include the United Kingdom Department for International Development, the World Bank, the Danish International Development Agency, the Swedish International Development Coordination Agency, Irish Aid, the United Nations Children's Fund, WHO, the Norwegian Agency for Development Cooperation, the Italian Development Cooperation, the Japanese International Cooperation Agency, and the African Development Bank (President's Malaria Initiative, 2010). Ideally, the government and partners jointly agree on priorities, performance targets and the budget framework. However, the malaria community remains quite fragmented and there is poor coordination of malaria partners.

6. Challenges to malaria control in Uganda

6.1. Very high malaria transmission intensity

Uganda has some of the highest recorded measures of malaria transmission intensity in the world. In this setting malaria elimination is not a realistic short- or medium-term goal, and even advances in control are challenging. Lessons from regions in which elimination efforts have already been successful may be of little relevance for Uganda. In highly endemic areas, profound decreases in transmission will likely be required to impact significantly upon the incidence of disease. If such advances are achieved, they may be accompanied, as in areas of Uganda with lower transmission intensity, by epidemic disease, as populations with diminished antimalarial immunity are periodically beset by transmission of infections that are increasingly likely to cause severe disease. Key features of the Uganda vector control strategy are distribution of ITNs and utilization of IRS. The roll out of ITNs has been fairly successful in recent years, but only about a third of children and pregnant women reported sleeping under a net on the night prior to the UMIS (Uganda Bureau of Statistics, 2010). Some targeted IRS has been carried out, but implementation has been irregular, with interruptions in spraying activities and limited geographic coverage. Poor communication on the IRS strategy and the safe use of DDT has caused misperceptions about this strategy within communities and other interest groups. In addition, resistance to insecticides may compromise the overall vector control program. Importantly, there remains uncertainty about the advisability of IRS in high transmission areas and so, while the strategy is validated for some areas, and successes have been seen in Southwestern Uganda, the appropriate role of IRS for most of the country is uncertain. More broadly, a full integrated vector management system, including evidence-based decision-making; integrated approaches; collaboration within the health sector and with other sectors; advocacy, social mobilization, and legislation; and capacity-building is not yet in place (Beier et al., 2008).

6.2. Inadequate health care resources

All public health is seriously compromised in Uganda, and throughout sub-Saharan Africa, by limited resources. Considering malaria, this situation has improved somewhat in recent years, with significant increases in international investment in malaria control and elimination. However, resources remain very inadequate, and there is fear that they will decrease. This decrease may be driven by global economic circumstances, donor fatigue, and also misplaced appreciation of the new malaria elimination agenda. This agenda may drive increased investment in malaria, but it may falsely impress donors that control is of decreasing importance. It is very important that, as enthusiasm for elimination in other areas increasingly gains attention, interest in strategies for control in areas with persistent high transmission intensity and malarial incidence, such as Uganda, is not lost.

6.3. Weaknesses in the health system

The Ugandan healthcare system is seriously compromised by limitations in resources, governance, and accountability. While there are many different partners, working groups, and committees, the malaria community remains quite fragmented. There remains poor coordination of malaria partners and interventions, and engagement among groups is irregular. Weaknesses and gaps in this system include poor coverage of lower-level health centers and village health teams, lack of effective supervision, high attrition of staff at health centers, irregular availability of drugs and other supplies, and poor coordination and leadership.

6.4. Inadequate understanding of malaria epidemiology and of the impact and optimal use of interventions

A major challenge to malaria control is our lack of a detailed understanding of the epidemiology of malaria in Uganda and of the impact of available control interventions. The epidemiologic data described throughout this paper are, for the most part, estimates based on inadequate information. More detailed surveillance is needed to better characterize the malaria situation. Of perhaps even greater importance is the determination of the impact of control interventions. Indeed, although the potential value of various interventions is clear, it is difficult to determine whether utilization of ITNs, IRS, treatment with ACTs, or targeted use of IPT has yet importantly impacted on malarial morbidity and mortality in Uganda. Further, with identification of optimal control interventions, operations research addressing how to scale up interventions to maximize effectiveness and cost-effectiveness, and how to prioritize combinations of interventions and effectively target high-risk groups, is essential. Critical for assessing the effectiveness of malaria control activities is the ability to measure and monitor the quantitative impact of interventions on malaria-associated morbidity and mortality. Ideally, accurate data on malaria-associated morbidity should be linked to implementation projects in order to evaluate their impact. Practical and sustainable programs are needed in order to provide baseline surveillance statistics and to measure impact following implementation of control activities. Monitoring and evaluation to measure progress against project goals and targets, to inform policy-making processes, and to facilitate adjustments in implementation is a critical requirement of effective health care management and delivery. Considering the knowledge gaps described above, the institution of an integrated and in depth research program on malaria epidemiology and vector dynamics in Uganda would be an important advance.

6.5. Increasing resistance of parasites to drugs and of mosquitoes to insecticides

As described above, malaria control is challenged both by resistance of *P. falciparum* to available drugs and of anopheline mosquitoes to available insecticides. Regarding drugs, we are fortunate that resistance to artemisinin-based drugs does not yet appear to be a problem in Uganda (Nsobya et al., 2010). However, resistance to long-acting partner drugs utilized in ACTs is concerning, both in regard to drugs that already suffer from resistance (amodiaquine) and those for which resistance may be selected (lumefantrine, dihydroartemisinin). Resistance also jeaopardizes continued efficacy of antifolates to prevent malaria in IPT regimens, as will be discussed below. Regarding insecticides, resistance to the two main classes of insecticides utilized in Uganda, DDT and pyrethroids, is of great concern, in particular because only pyrethroids are available for ITNs. However, the extent of resistance, especially to insecticides, is not well described for much of the country.

6.6. Inappropriate case management

The new national case management strategy is to confirm all suspected cases of malaria and treat confirmed cases with ACTs, while referring or managing those without malaria for other possible causes of fever. Major weaknesses currently hindering effective malaria case management are delays in seeking treatment, lack of diagnostic tests, and lack of access to ACTs. A major challenge has been the slow transition of health worker practices from presumptive to confirmed malaria case management. This problem has been exacerbated by a lack of laboratory diagnostic capacity in many health facilities. Even in those facilities with malaria microscopy, many clinicians lack confidence in the results and may disregard them when making a diagnosis. Laboratory diagnostic capacity for malaria (by microscopy and, to a much smaller extent, rapid diagnostic tests) exists in only 26% of all health facilities (Uganda Ministry of Health, 2008). The 2009 UMIS indicated that only 17% of children treated for malaria had a diagnostic test done (Uganda Bureau of Statistics, 2010). With these limitations, presumptive treatment of all suspected malaria cases without a diagnostic test remains common in Uganda. The 2009 UMIS also showed that there remain significant delays in seeking treatment for malaria and in accessing ACTs. Only 36% of febrile children received an antimalarial within 24 hours. Furthermore, although 23% of febrile children received ACTs, only 14% did so within 24 hours of the onset of fever .

6.7. Inadequate utilization of drugs in malaria prevention

The only established program to use drugs in control is IPTp, but utilization remains inadequate. Although the IPTp policy has been in place for more than ten years, and despite good antenatal clinic attendance, according to the 2009 UMIS only 33% of pregnant women received the minimum recommended two doses of SP. Further, the efficacy of IPTp in Uganda is likely seriously jeopardized by resistance of *P. falciparum* to SP. In contrast to pregnant women, WHO recommendations do not support use of IPT in Ugandan infants due to the prevalence of resistant parasites in the country. Replacements for SP for IPT are of great interest, but no other regimen is validated for this purpose, and use of long-acting ACTs, which will likely offer the best clearance of parasites, is discouraged by many authorities due to potential selection of drug resistance. The effectiveness of IPT for older children, including programs directed at schoolchildren, has not been evaluated in detail in Uganda, but it is noteworthy that a single dose of SP offered no benefit over placebo in preventing infections in schoolchildren in eastern Uganda (Nankabirwa et al., 2010).

6.8. Inadequate epidemic preparedness and response

Epidemic malaria transmission occurs in approximately 15 districts in the southwest and eastern highland regions of Uganda. National recommendations and guidelines for epidemic preparedness are in place for early detection and rapid containment of malaria epidemics. Epidemic thresholds are established for each district based on past data. The Epidemic Surveillance Department of the MOH provides weekly updates on cases of epidemic-prone diseases, including malaria. However, case reporting is inadequate, and districts are often unable to implement epidemic control recommendations due to limitations in resources and availability of supplies, including diagnostics and drugs.

7. Summary: prospects for malaria control and elimination in Uganda

Malaria remains an enormous burden for Uganda, with extremely high transmission intensity in much of the country, very high prevalence of infection and incidence of disease in most areas, and substantial mortality. Important advances in malaria control efforts have been made in recent years, facilitated by new international priorities and funding mechanisms, but the impact of these efforts remain uncertain. Indeed, it seems that, despite clear advances in other regions of Africa, malarial incidence has not yet diminished

significantly in most of Uganda. This problem is fostered by inadequacies in malaria control, as detailed above, but likely in addition is a result of the unusually high transmission intensity in much of the country. More comprehensive and sustained control measures will likely be required to begin to decrease the massive malaria burden in Uganda. Looking beyond efforts to decrease malaria morbidity, the goal of elimination is appealing. However, available data and models suggest that, even with improvements in control efforts, considerations of malaria elimination in Uganda within the next few decades are unrealistic (Tatem et al., 2010). Rather, the appropriate strategy should be the strategic implementation of available tools, which have improved remarkably in recent years, to aggressively control malaria, and thereby markedly decrease the burden of this disease in Uganda.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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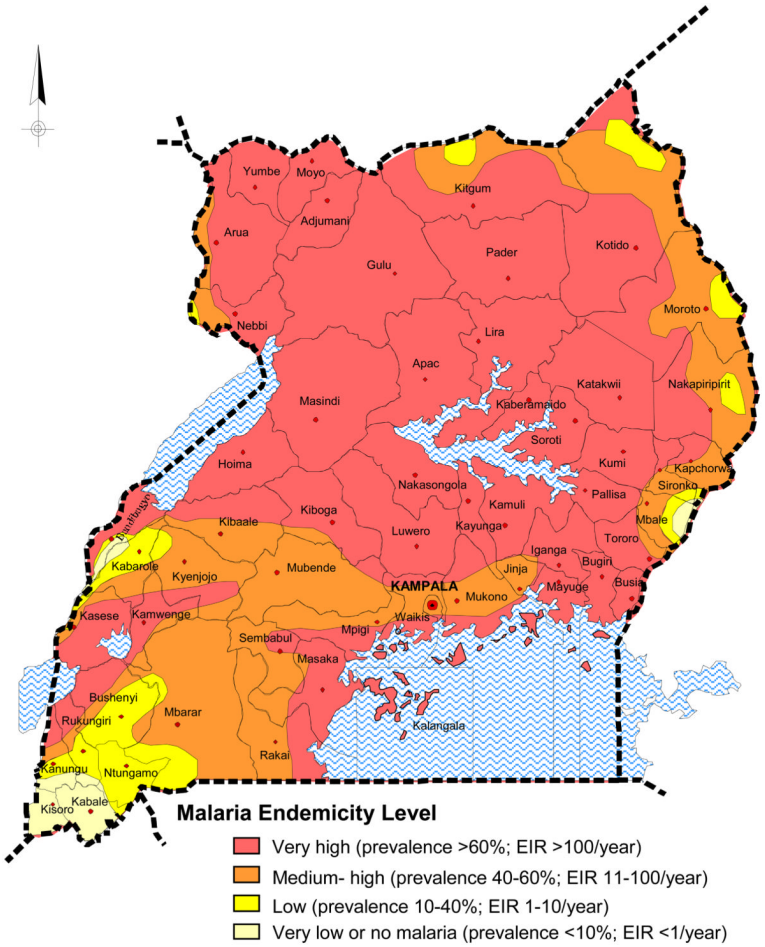

Figure 1. Malaria endemicity in Uganda

Values are estimated based on available data, which are limited for many regions of the country. Parasite prevalence estimates are for children under 10 years of age. EIR, entomological inoculation rate.

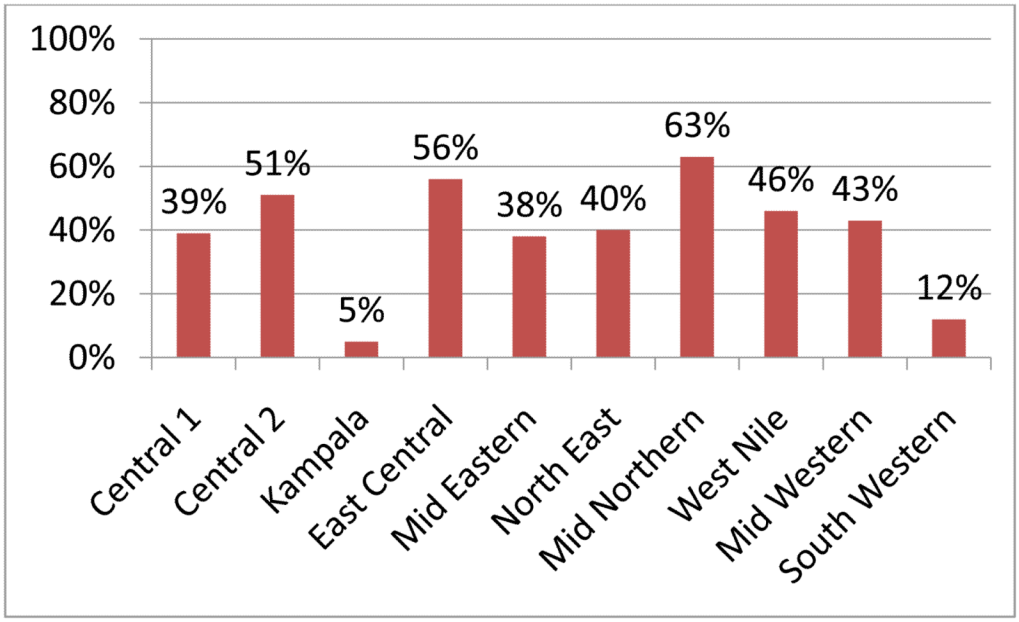

Figure 2. Malaria parasite prevalence in Ugandan children under 5 years of age in 2009
Data are from the 2009 Uganda Malaria Indicator Survey (Uganda Bureau of Statistics, 2010).

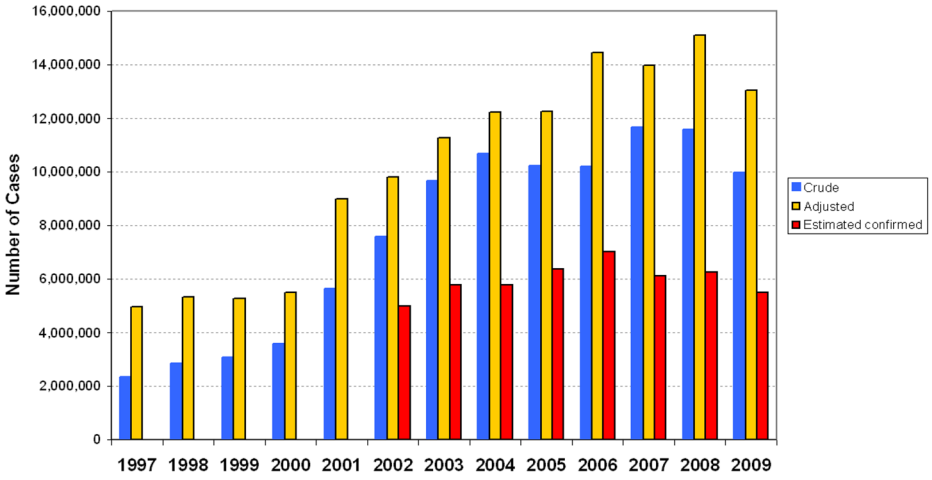

Figure 3. Reported malaria cases in Uganda: 1997–2009

Total cases reported to the Uganda Health Management Information System are shown, including crude numbers (blue), those adjusted based on an estimate of episodes missed due to absent reports from health facilities (yellow), and estimates of cases confirmed by diagnostic tests, based on smear positivity rates determined from the 2009 Uganda Malaria Indicator Survey (Uganda Bureau of Statistics, 2010; red). Cases for 2009 are projected for the full year based on data from January-June.

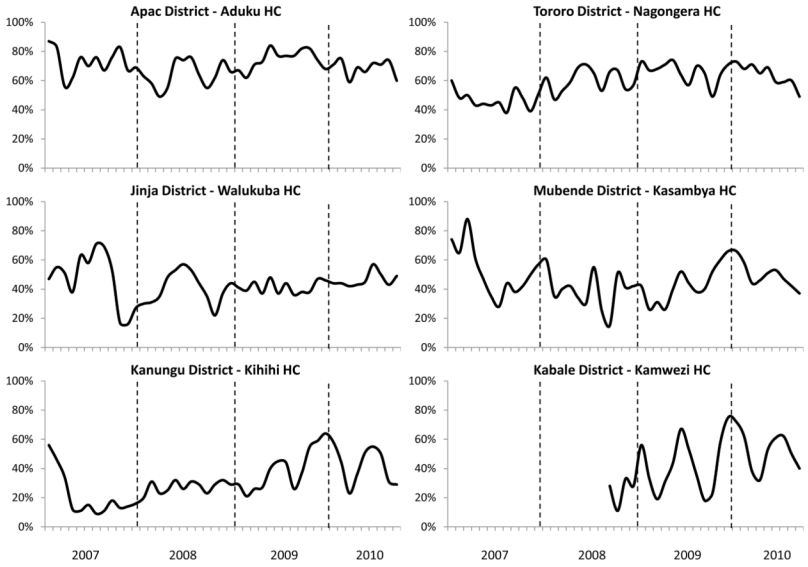

Figure 4. Smear positivity rates for children under 5 years of age at 6 health centers representing regions of very high (Apac, Tororo), moderate (Jinja, Mubende), and relatively low (Kanungu, Kabale) malaria transmission intensity

Graphs show the proportion of diagnostic tests that were positive for children suspected of having malaria at each site. The diagnostic test was usually microscopy, but an HRP2-based rapid diagnostic test was used in some cases.

Table 1

Prevalence of anemia and malarial parasitemia in Ugandan children, 2009[1]

Age (months)	Anemia (g/dl, %)[2]				Malarial parasitemia (%)[3]
	Mild (10.0–10.9)	Moderate (8.0–9.9)	Severe (<8.0)	Total (<11.0)	
0–5	17.6	25.1	9.7	52.5	16.3
6–11	22.1	38.0	20.6	80.7	31.5
12–17	20.8	38.3	20.8	79.9	38.5
18–23	22.2	36.6	9.8	68.7	35.8
24–35	23.0	31.8	10.1	64.9	45.2
36–47	19.9	26.6	6.3	52.8	49.5
48–59	22.3	24.6	2.0	48.9	53.2

[1] Source: Uganda Malaria Indicator Survey (Uganda Bureau of Statistics, 2010). At least 300 children were tested for each age range.

[2] Hemoglobin levels (g/dl) are shown.

[3] Assessed by microscopy.

Table 2

Baseline and targeted levels of key malaria control interventions[1]

Indicator	2006 UDHS	2009 UMIS	2010 Target
Households that own at least one ITN	16%	47%	85%
Children <5 yrs sleeping under an ITN the previous night	10%	33%	85%
Pregnant women sleeping under an ITN the previous night	10%	44%	85%
Households receiving IRS in previous 12 months	6%	6%	6 districts
Pregnant women who received at least 2 doses of IPTp	16%	33%	85%
Febrile children <5 yrs treated with an ACT within 24 hours	1%	14%	85%

[1]Results shown are from the 2006 Uganda Demographic and Health Survey (Uganda Bureau of Statistics, 2007) and the 2009 Uganda Malaria Indicator Survey (Uganda Bureau of Statistics, 2010). Targets are from the Uganda Malaria Control Strategic Plan 2005/6–2009/10 (Uganda Ministry of Health, 2005).