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

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Abstract

In the recent past there have been several reports of successes in malaria control, leading some public health experts to conclude that Africa is witnessing an epidemiological transition, from an era of failed malaria control to progression from successful control to elimination. Successes in control have been attributed to increased international donor support leading to increased intervention coverage. However, these changes are not uniform across Africa. In Uganda, where baseline transmission is very high and intervention coverage not yet to scale, the malaria burden is not declining and has even likely increased in the last decade. In this article we present perspectives for the future for Uganda and other malaria endemic countries with high baseline transmission intensity and significant health system challenges. For these high burden areas, malaria elimination is currently not feasible, and early elimination programs are inappropriate, as they would further fragment already fragmented and inefficient malaria control systems. Rather, health impacts will be maximized by aiming to achieve universal coverage of proven interventions in the context of a strengthened health system.

Keywords

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

1. Introduction

The burden of malaria in Uganda remains enormous, with ~30-50% of children infected in most areas, over 10 million cases reported each year, and tens of thousands of deaths

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believed to be caused annually by the disease (Yeka et al., in press). Despite recent enthusiasm concerning improvements in malaria in some African countries (O'Meara et al., 2010) and the endorsement of malaria elimination as a worldwide goal (Feachem et al., 2010) the burden of malaria in Uganda does not appear to have decreased significantly in recent years, and indeed it may even have increased (Yeka et al., in press). Multiple challenges contribute to the lack of progress in malaria control, as detailed in a paper that accompanies this report (Yeka et al., in press). In this paper we offer suggestions for overcoming these challenges to best address malaria control in Uganda and other settings with similar challenges.

2. The path forward

Despite the availability of cost effective interventions, malaria appears to be on the increase in Uganda (Yeka et al., in press; Okiro et al., 2011). This perverse situation is a result of the low coverage of proven malaria control interventions. Therefore, concerted efforts are urgently needed to radically scale up cost effective interventions. The extent of the malaria problem in Uganda requires a paradigm shift from demand creation to the identification and quantification of needs. The populations at risk of malaria are extremely poor, with many living on less than one US dollar per day. Consequently, strategies based on demand creation, though good, will require several decades for Uganda to achieve targets stated at the African Summit on Roll Back Malaria in Abuja in 2000 and to reach United Nations Millennium Development Goals. However, in malaria prevention and control “one size does not fit all.” Rather, we suggest that the way forward for Uganda be tailored to the local health control situation and epidemiological context. First, the Uganda National Malaria Control Programme (NMCP) and technical partners need to urgently appraise the 5-year National Malaria Strategic Plan (Uganda Ministry of Health, 2005). Second, strong political commitment that translates into adequate financial allocation for malaria is needed. Third, we encourage focused research and inter-country cooperation and exchange to share best malaria control practices. The goal for Uganda should be to quickly scale up malaria prevention and control so as to markedly reduce malaria prevalence and the malaria disease burden.

3. Improving general health systems

In many countries malaria control is effectively delivered through primary health care, and strengthening the health system is crucial. While there has been investment in enhancing diagnostic capacity in Uganda, with varied success, other health system strengthening pillars have been largely neglected. Most development partners have neglected health system strengthening. Consequently, important health system aspects, such as referral mechanisms, health information systems and diagnostic capacities are inadequate for successful malaria control. Health systems improvement is critical, but it is a long-term undertaking. At present, specific focus should be on the infrastructure for improved diagnosis of malaria, the quality of care in primary and referral health facilities, promotion of key family and community practices and joint performance assessment. Support in these areas is needed from both development partners and the Government of Uganda.

3.1 Improving leadership and management capacity

Committed leadership and good governance are critical for malaria prevention and control in Uganda. These will require the availability of strategic policy frameworks, which are combined with effective oversight, coalition-building, regulation, attention to system-design and accountability. The NMCP should maintain strategic directions in policy development and implementation; detect and correct undesirable trends and distortions; articulate the case for malaria prevention and control; regulate the behaviors of participants financing and

delivering malaria interventions; establish effective accountability mechanisms; and promote public policy and timely legislation. In addition, resources should be managed to contribute to the achievement of policy goals. Malaria technical leadership needs to be empowered through capacity building and secure tenure of managers. Uganda has had high turnover of management (6 different NMCP managers in the last decade), a lack of technical empowerment, and occasional political interference with malaria control. Better technical empowerment has been observed in Rwanda, where program decisions have been based on evidence and supported by political leaders. In contrast, in Uganda and other neighboring countries, strategies without an evidence base (e.g. larviciding, mass drug administration, and use of medicines not recommended by the WHO) are, unfortunately, routinely proposed. Success in scaling up interventions in Uganda will depend on the adoption of bold, sustained approaches, including emphasis on the development of leading individuals and institutions in malaria prevention and control, as well as building networks that connect them. It will also require real human and financial investment, not only to prepare individuals and institutions for leadership roles in malaria education, research and service delivery, but also to create an enabling environment in which malaria leaders can thrive. Expansion of malaria leadership training opportunities should cover health care professionals and political leaders, ensuring strong mentorship and career development. Capacity should be strengthened at the Ministry of Health, regional referral hospitals and districts to facilitate carrying out core functions at multiple levels. In addition, there is a need to invest in leadership programs at relevant institutions and universities. A leadership program, jointly developed by the NMCP and academia, should be based on five guiding principles: focus on outcomes, leadership at all levels, leadership can be learned, leadership is learned over time, and progress is maintained through management systems.

3.2. Strengthening community initiatives

Access to formal health care is still low in Uganda. Persons living within a 5 km radius of a formal health care facility increased from 49% in 2000 to 72% in 2010 (Uganda Health Facility Inventory, 2010, unpublished). However, public facilities are characterized by grossly inadequate and poorly motivated staff (only 56% of the available staffing positions filled), inadequate and poorly maintained equipment and perennial drug stock outs, and service quality remains poor. Consequently, most malaria cases are managed at home or in the informal private sector, and many malaria deaths are not reported (Foster, 1995; Marsh et al., 2004; Mwenesi et al., 1995). In these settings, malaria control and prevention without a strong community component is likely to be inadequate. A key malaria program component should, therefore, be the strengthening of community-based initiatives Uganda's community drug distributors, under the home based management of malaria strategy, should serve as the core of the village health team, which offers a range of services that are free of charge. These services should include increased access to effective case management mainly for children under five years old, identification of vulnerable groups that require specific interventions, and maintaining a basic community health information system. An appropriate incentive/motivation scheme, to curtail high attrition rates as seen in prior schemes, might include provision of uniforms or T-shirts, transport (e.g. bicycles), bednets for health workers, quick access to health services and activity related allowances. In addition, extension of partnerships with community based organisations, non-governmental organisations, community resource persons, the private sector and other existing community structures should be fostered. Of particular interest is the development of strategies for increasing access to effective case management in the informal private sector using a subsidy scheme.

4. Improving the coverage of malaria control interventions: case management

4.1. Improving diagnostics and rational drug use

World Health Organization guidelines were recently revised to recommend parasitological confirmation of the diagnosis of malaria before treatment whenever feasible (World Health Organization, 2010). Widespread misdiagnosis of malaria leads to wasted resources and contributes to drug resistance. Poor quality diagnostic services are increasingly but belatedly recognized as a major barrier to providing effective treatment and accurate public health information. Increased access to clientfriendly diagnostic strategies are urgently required. The well established diagnostic technique of microscopy needs improvements in infrastructure (laboratories, equipment and consumables), training and quality control for malaria diagnosis. Newer rapid diagnostic tests (RDTs) are increasingly used, but are poorly standardized. Widespread implementation of RDTs, including at the community level, should be accompanied by systematic training of health workers, quality control of specific tests and of test performance, and attention to maintenance of test supplies. Multiple other diagnostic modalities are now under study. New technologies may offer important advances in malaria diagnosis and control, but only if the tests can be reliable and cost effective.

4.2. Improving access to life saving medicines for malaria

The populations most vulnerable to malaria have difficulties in accessing health services. Such difficulties include poverty; lack of client-focus; poor quality services and lack of empowerment of women, as both patients and caregivers, to mobilize resources. In light of increasing resistance to inexpensive older drugs, Uganda changed its first-line recommend therapy for uncomplicated malaria to artemether-lumefantrine (AL) in 2004. However, this change has been hampered by commodity shortages. There is an urgent need to support commodity procurement, supply and delivery as well as to eliminate corruption in drug procurement and tendering. In addition, there is a need to monitor the implementation of the drug policy including uptake, drug quality, and pharmacovigilance. Uganda also needs to perform accurate quantification of commodity needs to avoid rampant stock outs. In 2008 in Uganda, AL stock outs were present on one-third of clinic days and for a median duration of 60 days (IQR 23-117) over the prior 6 months (Zurovac et al., 2008). Stock outs are an enormous challenge; improving clinical performance without ensuring availability of medicines will have limited impact on the quality of care. Stock outs are caused by multiple factors, but often reflect weaknesses in medicine and supplies procurement, management and distribution practices. The commonest cause of stock outs in Uganda are inadequate and delayed funding, delayed drug deliveries and poor quantification and forecasting of commodity needs. These shortcomings must be corrected to bring about substantial improvement in malaria control.

4.3. Improving the management of severe malaria

Severe malaria is a neglected aspect of malaria control. The management of severe malaria requires relatively skilled health workers and hence the need for efficient referral networks, yet the latter are poorly developed in Uganda. A recent study in Uganda observed that practices related to severe malaria case management were deficient in many areas, including patient evaluation for the presence of danger signs, diagnosis and correct treatment and dosing (Achan et al., 2011). Further, none of the studied inpatient health facilities had all the components of a basic care package for severe malaria management in place. To improve management of severe malaria, priority interventions should be implemented at the different points of patient care, including improved patient assessment, referral practices, quality of diagnosis, triage and emergency care, treatment practices, availability of medicines and

supplies, health worker training and support supervision. In addition, regular clinic audits will be required to track the quality of severe malaria management.

5. Improving the coverage of malaria control interventions: malaria prevention

5.1. Increasing coverage and use of insecticide treated nets (ITNs)

The efficacy and effectiveness of ITNs has been widely studied and confirmed, their cost-benefit certified, and their social acceptability proven (Lengeler, 2004). Studies in Burkina Faso, The Gambia, Ghana, Tanzania and Zaire reported reductions of 30-63% in malaria morbidity rates following the introduction of ITNs in households (D'Alessandro et al., 1995; Lengeler, 2004; Lyimo et al., 1991; Nevill et al., 1996; Sexton et al., 1990; Snow et al., 1987; Stich et al., 1994). However, despite the overwhelming evidence that this strategy can prevent childhood illness and deaths, ITN coverage and utilization presently falls short of targets in Uganda. According to the first Uganda Malaria Indicator Survey conducted in 2009, only 33% of children under 5 years of age and 44% of pregnant women reported sleeping under a bednet on the night prior to the survey (Uganda Bureau of Statistics, 2010). This dismal coverage was largely due to an initial strategy of experimenting with various public, private and mixed models for ITN delivery. While approaches for the delivery of ITNs skewed to the private sector are useful for improving coverage of ITNs long-term, they have been sub-optimal in achieving ITN coverage targets in Uganda, in part because they require commensurate improvements in household income to allow procurement of ITNs. Therefore, the scale up of ITN coverage, especially among the most vulnerable groups (children under five years old and pregnant women) requires the use of public sector skewed models. In the short-to medium-term, the Uganda ITN strategy should facilitate implementation of mass campaigns for net distribution such as National Net Weeks. For example, using a campaign linked to measles immunization, Rwanda and Zambia achieved their ITN targets. Integrating with other ongoing campaigns such as child health days or measles campaigns could help leverage scarce logistics and human resources for ITN distribution. However, the campaign approach requires that ITNs are free or very highly subsidized and in adequate supply. Once targets are achieved, private, mixed and public delivery models could run in parallel to sustain coverage.

5.2. Scaling up targeted indoor residual spraying (IRS)

A large investment has been made toward IRS in Uganda since 2006, when the first program in a number of decades was initiated. However, IRS is very expensive, and only a limited number of communities have been targeted. Initially, the strategy was restricted to high elevation epidemic prone districts in western Uganda. The epidemic prone areas have been mapped, and IRS has been conducted before the main malaria transmission season. More recently, IRS targeting high transmission districts in the northern part of Uganda was added under the U.S. President's Malaria Initiative, achieving very high entomological impact, although the epidemiological impact of this practice is yet uncertain (Pluess et al., 2010). New guidance from the WHO supports the use of IRS in high transmission settings, but its impact on ITN use in the same setting is still a subject for scientific debate (Kleinschmidt et al., 2009). Indeed, due to concerns regarding cost effectiveness and the impacts of each intervention on the other, we caution against the combined use of IRS and ITNs in the same setting. Rather, we propose that Uganda should scale up either ITNs or IRS before attempting to combine the two. However, we propose an IRS strategy for boarding schools and institutions, and also for internally displaced persons and refugee camps irrespective of whether they are located in low or high malaria transmission settings.

5.3. Prevention of malaria in pregnancy

The scale up of malaria prevention in pregnancy should be addressed as a package which includes ITNs, intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP), management of malaria and anemia in pregnancy, and monitoring and evaluation. Ideally, malaria control measures should be integrated with other resources directed at reproductive health. A critical issue that will arise as the burden of malaria decreases is the continued usefulness of IPTp; decisions regarding continuation of this policy should be informed by the level of malaria transmission intensity and the effectiveness of the drugs being used (ter Kuile et al., 2007). Indeed, there is concern about the spread of resistance to SP, which impacts upon its efficacy when used for IPTp. Monitoring the efficacy and effectiveness of IPTp with SP is needed through clinical studies and the tracking of known molecular markers of SP resistance. Alternative drugs, dosing schedules and adherence strategies for IPTp should also be evaluated.

6. Monitoring and evaluation

6.1. Public health surveillance and information systems

Strengthening surveillance and health information systems has previously been underfunded, but should be a priority for malaria control in Uganda. Uganda had its first malaria indicator survey in 2008. Regular population-based surveys will be important for national and regional assessment of coverage of interventions and disease burden indicators. This will facilitate tailoring interventions at the district level to the local epidemiological context. Institutionalizing the conduct of population and facility based quality of care surveys and strengthening integrated disease surveillance, including formal Health Management Information Systems, is of crucial importance. A requirement for effective periodic evaluation should be the development of a comprehensive monitoring and evaluation framework that articulates how performance assessment will be measured for each of the key strategies at national and local levels.

6.2. Drug resistance surveillance

Malaria drug efficacy monitoring has been ongoing in Uganda since 1997 under the East African Network for Monitoring Antimalarial Treatment (EANMAT). EANMAT initially included NMCPs from Tanzania, Kenya and Uganda, and was later joined by those from Zanzibar, Rwanda and Burundi. The goal of EANMAT was to facilitate the implementation of rational and evidence based malaria treatment policies in East Africa by providing high quality data on antimalarial drug treatment efficacy for policy makers. Before going into abeyance, as efficacy monitoring became a lower priority compared to the scale up of new artemisinin-based combination therapies (ACTs), EANMAT set up and supported multiple sentinel sites at health facilities in each member country, disseminated drug efficacy data and organized valuable sub-regional and international policy debates.

In Uganda, in addition to EANMAT activities, drug efficacy testing has been supported since 2001 through the Uganda Malaria Surveillance Program, a collaborative project between the NMCP, Makerere University, and the University of California, San Francisco, funded initially by the Centers for Disease Control and Prevention, and more recently by the President's Malaria Initiative. Six sentinel sites with wide variation in malaria transmission intensity (Okello et al., 2006) are currently operational, and efficacy data from these sites has been instrumental in guiding national treatment policy. Specifically, these data have demonstrated unacceptable efficacy of chloroquine-sulfadoxine-pyrimethamine (Bakyaita et al., 2005; Kamya et al., 2002; Talisuna et al., 2002; Yeka et al., 2005), a combination of older drugs that was the national first-line regimen for uncomplicated falciparum malaria

from 2001 to 2004, and excellent efficacy of ACTs, in particular the new national first-line regimen, AL (Dorsey et al., 2007; Staedke et al., 2004; Yeka et al., 2005) .

Drug resistance surveillance remains an urgent priority for Uganda for the following reasons. First, ACTs vary in efficacy (Dorsey et al., 2007), and it is important to monitor the clinical efficacies of different regimens to assure that optimal therapies are used. Second, there is great concern regarding the spread of parasites with decreased sensitivity to artemisinins, as recently seen in Cambodia (Dondorp et al., 2009), to Africa. Surveillance to recognize the spread of these parasites, using measures of in vitro drug efficacy and, if available, molecular markers of resistance, is an urgent priority so that, if the spread occurs, it can be managed by prompt adjustments in treatment strategies. Third, ACTs rely on artemisinin partner drugs, and these drugs, which all have longer half-lives than artemisinins, are under strong selection for resistance as ACT usage increases. Efficacies of partner drugs can also be studied with in vitro methods, and for some partner drugs (e.g. lumefantrine and amodiaquine), molecular markers that predict decreased efficacy are known and quite simple to assess. Changes in sensitivity to partner drugs may mandate changes in treatment policies. Fourth, SP remains, despite partial parasite resistance, the standard regimen for IPTp in Uganda. Surveillance for mutations that lead to high-level SP resistance is important, as additional mutations may block any utility of SP for the prevention of malaria. In summary, it is imperative that Uganda moves beyond recent apathy toward monitoring antimalarial drug efficacy, as evidenced by the collapse of EANMAT and other regional networks, and rather places surveillance as a high priority.

6.3. Pharmacovigilance

Pharmacovigilance, the monitoring of drug safety and efficacy after product registration, is critical, as important drug limitations may not be recognized during preclinical development and clinical trials involving relatively small numbers of individuals. In the last few years, therapy for malaria has shifted from older drugs with established safety but waning efficacy, to ACTs. Although ACTs have demonstrated good safety profiles in clinical trials, post-marketing data are limited, especially outside southeast Asia. Yet, millions of doses of ACTs are now being used each year in Africa. Pharmacovigilance to identify unforeseen problems with ACTs is thus an urgent priority. A related concern is the safety of ACTs and other treatments in the context of co-infections, and thus co-treatment for HIV infection, tuberculosis, or other infections. Similarly, safety in the context of malnutrition deserves attention. Lastly, safety profiles of ACTs and some other drugs during pregnancy are poorly appreciated.

Despite the keen interest for pharmacovigilance in Africa, approaches remain problematic. Passive reporting of adverse events is notoriously poor in developing countries and largely nonexistent in Africa. Thus, in Uganda, multiple pharmacovigilance systems should be piloted, and successful programs implemented. Promising approaches include facilitation of passive reporting of adverse events; detailed prospective surveillance for recent adverse drug reactions; use of hospital- or population-based pregnancy registers to follow-up of deliveries considering drug exposure histories; hospital-based case-control studies to detect possible drug-related side effects; and continuous demographic surveillance systems at selected sentinel sites to identify and investigate deaths in sentinel populations. For each of these approaches, standardized tools need to be developed. Furthermore, a reporting hierarchy and organizational framework for pharmacovigilance needs to be clearly outlined for stakeholders in Uganda.

6.4. Monitoring insecticide resistance and mapping vector distribution

In Uganda, as in most of sub Saharan Africa, important efforts are being made to scale up use of ITNs (President's Malaria Initiative, 2010). However, ITNs remain highly dependent on a single class of insecticide, synthetic pyrethroids. Recently a renewed interest in IRS has been seen (President's Malaria Initiative, 2010). This intervention offers a greater choice than ITNs in the use of insecticides, but it too is potentially jeopardized by insecticide resistance to pyrethroids, DDT, and other agents. Knowledge of changing trends of resistance in target vector species is a basic requirement to guide insecticide use in malaria control programs. Until recently, no data were available on insecticide resistance in the main malaria vectors in Uganda, and available information remains severely limited. Therefore regular insecticide resistance surveillance, including bioassays and assessments for molecular markers associated with resistance at selected sentinel sites is a high priority. In addition there is a need for regular surveillance for predominant malaria vectors, as changes in vector species may impact importantly on malaria transmission. Regular surveillance for resistance and vector species should provide data to guide policy makers as they choose between limited and expensive interventions for vector control.

7. International Center for Excellence in Malaria Research (ICEMR)

In 2010 the United States National Institutes of Health established 10 International Centers of Excellence for Malaria Research (ICEMRs), forming a global network of independent research centers in malaria-endemic settings, to provide the knowledge, tools, and evidence based strategies crucial to understanding, controlling, and, ultimately, preventing malaria. The center representing the East African region is based in Uganda and named PRISM - Program for Resistance, Immunology, Surveillance and Modeling of Malaria. PRISM collaborating institutions include the University of California, San Francisco, the Uganda Infectious Diseases Research Collaboration, the Makerere University Faculty of Medicine, the London School of Hygiene and Tropical Medicine, the Liverpool School of Tropical Medicine, and the University of Florida.

The overall purpose of the PRISM program is to perform comprehensive surveillance studies aimed to improve our understanding of malaria and measure the impact of populationlevel control interventions. Uganda provides an ideal environment for this program, where malaria covers a wide range of epidemiological settings. Studies will be conducted in six sentinel sites, ranging from areas of relatively low transmission intensity to areas with some of the highest transmission intensities recorded in the world. This comprehensive approach to surveillance will bring together expertise from multiple disciplines to collect data across multiple levels, reflecting the complex nature of interactions between the mosquito vector, malaria parasite and human host. The program will consist of 3 research projects linked together in an integrated manner to maximize scientific discovery. Research project 1 will compare different malaria surveillance methodologies and measure the impact and cost-effectiveness of control interventions. Research project 2 will investigate the role of immunological assays for estimating transmission intensity and predicting disease risk. Research project 3 will identify markers of antimalarial drug and insecticide resistance and investigate the role of these markers as malaria surveillance tools. In addition to the research activities described above, the program will place a strong emphasis on local training and capacity building, the transfer of technology, and building strong relationships between researchers and policy makers. The Uganda PRISM program is a valuable addition to malaria surveillance activities, and it should provide important data to help guide malaria control efforts in the coming years.

8. Conclusion

In this paper we have presented perspectives for the future of malaria prevention and control in Uganda. Key summary points are as follows. First, although malaria elimination is increasingly discussed, for Uganda and other African countries with very high malaria transmission intensity and major health systems challenges, attention is now best focused on improving coverage of interventions for malaria control. Second, an important component of improved malaria control will be overall improvement in health systems, including enhancements in leadership, management, and community initiatives. Third, specific actions are needed to improve coverage of key interventions for malaria case management (diagnostics, access to ACTs, management of severe malaria) and prevention (ITNs, IRS, IPTp). Fourth, improved monitoring and evaluation will be essential for scaling up malaria control, including improved health information systems, surveillance for drug and insecticide resistance, and pharmacovigilance. The challenges for malaria control in Uganda are great, but so are the opportunities. It is hoped that recent international enthusiasm for malaria elimination can be channelled in Uganda to improved focus on validated measures that, with attention to the strategies detailed in this report, can be expected to lead to major decreases in malaria morbidity and mortality in the coming years.

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Research highlights

Yeka, et al.: Malaria in Uganda: challenges to control on the long road to elimination. I. Epidemiology and current control effort

- Uganda bears a particularly large burden from malaria.
- Our understanding of malaria in Uganda is limited by a lack of reliable data.
- Uganda has made progress in implementing key malaria control measures.
- There is no convincing evidence that the malaria burden has decreased recently.
- There remain major challenges to malaria control in Uganda.

Uganda bears a large malaria burden. It has made progress in implementing key control measures, but there is not yet convincing evidence that the burden has decreased. We summarize malaria epidemiology, control efforts, and challenges to control.