Challenges Associated with Scaling up Artemisinin Combination Therapy in Sub-Saharan Africa A Review Article

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Abstract

Malaria is the leading cause of morbidity and mortality in Sub-Saharan Africa. One key strategic intervention is provision of early diagnosis and prompt effective treatment. A major setback has been the development of drug resistance to commonly used antimalarials. To overcome this, most countries in Sub-Saharan Africa have adopted Artemisinin Combination Therapy (ACT) as a first line treatment for uncomplicated malaria. Artemether Lumefantrine (AL) and Artesunate Amodiaquine (ASAQ) are the main drugs of choice. There are key implementation issues, which may have a bearing on the scaling up of this new treatment. This article reviewed the published papers on ACT with focus on sustainability, compliance, and diagnosis. ACTs are costly, but highly effective. Their scaling up is the most cost effective malaria intervention currently available. Most countries rely heavily on the Global Fund for their scaling up. AL has a short shelf life, a complicated six-dose regimen that requires intake with fat to ensure sufficient bioavailability. High rates of adherence have been reported. Use of parasitic diagnosis is advocated to ensure rational use. Parasitic diagnostics like rapid test and microscopy are currently inadequate. The majority of malaria cases may continue to be diagnosed clinically leading to over prescription of drugs. ACTs are currently not available at the community level for home based management of malaria. Issues related to safety and rational use need to be addressed before their use in the informal health sector like community drug sellers and community health workers. The majority of malaria cases at the community level could go untreated or continue to be treated using less effective drugs. We conclude that ACTs are highly effective. A major challenge is ensuring rational use and access at the household level. It is hoped that addressing these issues will increase the likelihood that ACT achieves its intended goals of reducing morbidity and mortality due to malaria, and delaying the onset of drug resistance.

Key words: artemisinin combination therapy, antimalaria, Sub-Saharan Africa, malaria, plasmodium.

Malaria Burden

Malaria can be an acute or a chronic disease. It is caused by intracellular protozoa of the genus Plasmodium that are transmitted by the bite of an infected female Anopheles mosquito. Anopheles gambiae is the most important vector in Africa and is among the most efficient for transmission of the disease [1]. There are 120 Plasmodium species, of which four are of consequences to humans: P. falciparum, P. vivax, P. malariae and P. ovale. These share a common basic life cycle, though there are differences in their pathogenicity and epidemiology. It is P. falciparum which causes nearly all the mortality in cases of malaria infection [1,2].

Globally, it is estimated that one million children die from malaria annually [1,2,3]. An estimated 90% of all global deaths due to malaria occur in Sub-Saharan Africa [2,4]. Children under five and pregnant women are most at risk. It is estimated that malaria accounts for 30-50% of inpatient admissions and 50% of total outpatient visits in children under five [3], and nearly 25% of all childhood mortality in Africa [4]. Malaria has been linked to poverty [5]. It has slowed economic growth in African countries by 1.3% per year resulting in a gross domestic product which is 32% lower than it would have been had malaria been eradicated from Africa in 1960. Malaria accounts for 40% of public health expenditure and is estimated to cost Africa more than US$ 12 billion every year in lost GDP [5].

Global response

In 1998, the World Health Organisation, the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), and the World Bank joined forces to create the Roll Back Malaria Partnership (RBM). The aim of this initiative is to reduce malaria mortality by 50% by the year 2010 and achieve the malaria-related Millennium Development Goals (MDGs) by 2015. This partnership has increased with the addition of a wide range of partners. The mission of the RBM is to enable sustained delivery and use of the most effective prevention and treatment interventions for those affected most by malaria [6]. These interventions include use of insecticide treated nets, vector control, indoor residual spraying, presumptive treatment of pregnant women and prompt effective treatment of malaria cases.

In Sub-Saharan Africa, malaria has for a long time been treated using cheap and effective drugs like Chloroquine, Sulphadioxine pyrimethamine, and Amodiaquine. The malaria parasite has gradually developed resistance to these drugs, decreasing their effectiveness. A study in a holoendemic area in western Kenya in 1993 found a resistance of 35% to Amodiaquine and 34.5% to Sulphadioxine pyrimethamine [7]. WHO recommends a change in the first line treatment if total failure proportion exceeds 10% [8]. Many countries have adopted Artemisinin Combination Therapy (ACT) as the first line drugs for the treatment of uncomplicated malaria.

The objectives of any national malaria treatment policy is to provide access to safe, good quality, effective, affordable, and acceptable antimalarial drugs; ensure rapid and long lasting cure, and delay development of resistance to antimalarial drugs. ACT partly fits this bill as they are highly efficacious but costly. An open label study in Kenya, Tanzania, and Nigeria assessed the efficacy and safety of ACT in infants and children with acute, uncomplicated falciparum malaria showed that treatment was safe and well tolerated with an overall 28-day cure rate of 86.5% and 93.9% when corrected by Polymerase Chain Reaction for re-infection [9]. The aim of the study was to explore and highlight potential implementation issues in the scaling up of ACTs with more emphasis on artemether-lumefantrine, as the first line anti-malaria treatment in Sub-Saharan Africa, and the study focused on the key implementation issues e.g. sustainability, access, and compliance with regard to the scaling up of ACT in Sub-Saharan Africa.

Rationale for Implementation research

It has been argued that implementation research should not stop after demonstration of proof that an intervention is efficacious. Implementation research should go further and solve major implementation problems. Implementation research is borne out of the realisation that many interventions have been successfully researched and developed, and yet had little impact due to implementation issues. The overall goal of implementation research is to significantly improve access to efficacious interventions against tropical diseases by developing practical solutions to common critical problems in the implementation of these interventions [9].

Combination Therapy

Combination therapy is not a new phenomenon. It has been deployed in the treatment of diseases like TB, leprosy, and AIDS. It delays emergence of resistance and increases efficacy [10]. Antimalarial combination therapy is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and thus unrelated biochemical targets [8]. Artemisinin and its derivatives (Artesunate, Artemether, Artemotil, and Dihydro-Artemisinin) produce rapid clearance of parasitaemia and rapid resolution of symptoms. They reduce parasite numbers by a factor of 10-100 times when compared to other antimalarials. Artemisinin compounds are active against all the four species of Plasmodium that infect humans [8].

A public health advantage of ACT is that they reduce gametocyte carriage and thus transmissibility of malaria [1]. This plays a prominent role in malaria control in areas of low transmission, though this may not be so in areas of high transmission intensity where a large reservoir exists in asymptomatic people [1]. A major potentially serious adverse effect reported with ACT is type I hypersensitivity reactions in approximately 1 in 3,000 patients [12], though phase IV trials are yet to be carried out and the possibility of other adverse reactions cannot be ruled out [13]. WHO currently recommends four ACTs. These are Artemether-Lumefantrine, Artesunate + Amodiaquine, Artesunate + mefloquine, and Artesunate + Sulfadoxine-pyrimethamine. The choice of ACT depends on the level of resistance of the partner drug in the combination and transmission intensity [8.[

Artemether- lumefantrine

Artemether- lumefantrine is one of the ACT drugs being used by most countries in sub-Saharan Africa. It was the first ACT available in combination dose and whose manufacturer, Novartis Pharma, has been vetted by WHO as having good manufacturing practices. It is a combination of the Artemisinin derivative: Artemether and Lumefantrine (previously called benflumetol) in a 1:6 ratio. It is a new, effective, and well-tolerated drug [14]. It achieves its antimalarial effect through the initial large reduction in parasite biomass by artemether and subsequent removal of all the remaining viable parasites by the less active but more slowly eliminated lumefantrine [15]. The combination also provides mutual protection of the two antimalarial drugs from the development of resistance, as parasites are never exposed to artemether alone and relatively few are exposed to lumefantrine [15].

Overall cure depends on the presence of adequate lumefantrine to eradicate residual biomass left by artemether, and this in turn is reliant on adequate bioavailability. The oral bioavailability of lumefantrine is reduced significantly in the acute phase of malaria. Patients with acute malaria are reluctant to eat and often vomit. The more severe the infection, the less likely the will to eat. Lumefantrine is poorly water-soluble and highly lipophilic [16]. Oral bioavailability increases substantially after a meal rich in fat. A healthy volunteer study compared absorption in fasted subjects and subjects who took the drug with a high-fat meal showed that artemether bioavailability increased two-fold and Lumefantrine bioavailability increased 16-fold in those who took the drug with food [16]. Ashley et al conducted a multiple crossover pharmacokinetic study to compare the area under the plasma concentration-time curve (AUC) for lumefantrine after administration of a single dose of AL in fasting state with varying amounts of fat. The population means estimated the volume of Soya milk required to obtain 90% of maximum effect (in terms of lumefantrine AUC) to be 36 milliters or 1.2 grams of fat [17]. This will be a challenge in the scaling up of ACTs since achieving high cure rates requires the achievement of sufficient bioavailability. Ensuring consistent intake with a fatty meal in unsupervised settings may not be easy. To increase lumefantrine absorption, doses should be taken at the required intervals accompanied by food. An interval of 8 hours between the first and the second dose, 24 hours between the first and the third dose, and 12 hourly intervals between doses thereafter is recommended.

Diagnosis of malaria

Microscopy

Light microscopy is the most efficient method for parasitological diagnosis of malaria. It is done by examining a stained thick or thin blood smear for the presence of malaria parasites. Thin films are recommended for species identification. Light microscopy is considered to be the 'gold standard' against which the sensitivity and specificity of other methods must be assessed [18]. A skilled microscopist is able to detect asexual parasites of densities of fewer than 10 parasites

per micro litre of blood but under typical field conditions the limit of sensitivity is approximately 100 parasites per micro litre of blood [18]. Light microscopy has important advantages. These include low direct costs if the infrastructure to maintain the service is available; high sensitivity if the quality of microscopy is high; it can differentiate between plasmodia species; it can determine parasite species and can be used to diagnose many other conditions [8]. There are constraints to ensuring good quality microscopy. These include inadequate training and supervision of laboratory staff; the need to rely on electricity at night time; delays in providing results to patients and the need for maintaining quality assurance and control of laboratory services [8].

In research set ups, the quality of microscopy is quite high. A sensitivity of 99.6% and a specificity of 100% have been attained [19]. In non-research settings, diagnostic accuracy varies. A cross-sectional survey to evaluate accuracy of routine malaria microscopy was conducted in 17 health facilities found in two districts in Kenya. After comparing initial microscopy readings to expert readings, the sensitivity and specificity of routine microscopy was 68.6% and 61.5% respectively. The positive predictive value was 21.6% and negative predictive value 92.7% [20].

Microscopy can play a key role in promoting rational use of ACT because it enables the clinicians to distinguish febrile episodes caused by the malaria parasite from those arising from other causes. In a prospective study in Uganda, use of microscopy and withholding antimalarial therapy in febrile children with negative blood smears was found to be safe and saved over 1600 antimalarial treatments in 601 children over an 18 month period [19]. In Kenya microscopy is not widely available. It has been estimated that functional microscopy exists only in 24% of all government health facilities [20]. In Zambia, microscopy was found to be available at 39% of health facilities [21]. Malaria treatment guidelines by WHO, state that in high malaria endemic areas, any child with fever or history of fever is presumptively classified and treated as malaria. Parasitological diagnosis is not a pre-requisite. In low malaria endemic areas, any child with fever or history of fever in the absence of measles, running nose or any other identifiable cause of fever is to be presumptively classified and treated as having malaria. Use of parasitological diagnosis is recommended. In all patients aged 5 years or above with fever or history of fever, the use of parasitological diagnosis is recommended. Where diagnostics are lacking, presumptive treatment is carried out [8].

Rapid diagnostic tests (RDTs)

RDTs are immunochromatographic tests based on detection of specific parasite antigens, either Plasmodium lactate dehydrogenase (pLDH) activity or the presence of Histidine-Rich-Protein (HRP). Most of the RDTs available are specific for Plasmodium falciparum. RDTs are simple to use and are sensitive in detecting low parasitaemia [4]. Use of RDTs is not recommended for follow up, as most of the tests remain positive for up to 2 weeks following effective antimalarial and clearance of parasites. They also cannot be used to determine parasite density [4], and they are relatively more expensive than microscopy. Their key advantage is that they can be used in a wide range of setups from hospitals to field laboratories, users require minimal training compared to microscopy, and can be taught to low cadre workers [8]. Some RDTs are susceptible to heat induced damage and may not perform well under the high temperatures prevalent in the tropics [22]. Most manufacturers of RDTs recommend that their products be stored at temperatures below 30 °C. These recommendations may not be maintained during the shipment and use of RDTs in field labs.

Clinical diagnosis

Clinical diagnosis is through the detection of signs and symptoms. These include fever, chills, headache and anorexia. These per se are not specific to malaria but apply to many diseases. Clinical diagnosis if not supplemented by parasitological diagnosis, tends to overestimate malaria cases. A review by Amexo et al. found that clinical diagnosis by health professionals overestimates malaria (number of cases with negative microscopy over the number of malaria clinical diagnosis) by an average of 61%, ranging from 28% to 96% [23]. Among children, bacterial diseases tend to be misdiagnosed as malaria and in one study bacterial diseases may have been responsible for more deaths in children than malaria in a malaria endemic area [24]. In a prospective study in Kampala, malaria was responsible for only 32% of febrile episodes in children [19]. A study in Kenya found out that the children had an average of around 7 episodes of fever per year, of which only 2.5 were due to malaria [25]. This leads to children being treated for the wrong diseases which could be harmful. One study concluded that the probability of dying was two times higher in children diagnosed to have malaria but with a negative blood slide compared to those with a positive blood slide [26]. One factor leading to an overestimate of malaria among adults in some areas is the prevalence of HIV/AIDS. A study in Malawi found that fever was much more likely to be associated with HIV infection than with malaria parasitaemia [27]. There have been attempts to develop clinical algorithms, with limited success as a review that their use in highly endemic areas resulted in a high risk of failure to treat malaria. The best clinical algorithms were site specific [28].

Diagnostics

Clinical diagnosis without any parasitological diagnosis has been the norm in many African countries. In the advent of ACT this has to change. Presumptive treatment may only be acceptable in children under 5 years. Studies have shown that there is a three fold higher rate of malaria cases among children aged 0-4 years compared to those aged 5- 14 years [1]. In Kwa Zulu Natal (KZN), AL was introduced in 2000 (29). Prior to this, rapid immunochromatographic card tests were introduced in 1996 to ensure definitive malaria diagnosis in all public-sector health-care facilities. Thus only definitive cases were treated in KZN and this was a major factor in attaining the estimated cost savings of US$ 201,065 in 2002 alone for the sub- district studied [29]. In most countries, both ACT and malaria related diagnostic tests are being scaled up simultaneously and overdiagnosis cannot be ruled out. Provision of diagnostics must be accompanied by adequate quality control. This is considering that high temperatures may affect RDTs. A

study in Kenya found that microscopy in government health facilities had positive predictive values (21.6%). This means that four out of every five slides reported as positive were indeed negative [20]. A major challenge is scaling up diagnostics concurrently with ACTs and ensuring quality control is maintained.

Changing prescribing patterns

Changing clinicians' prescribing patterns after transition to a new drug is also a challenge. Zambia was the first African country to change its policy towards using more expensive Artemether-Lumefantrine (AL), characterised by a 'complex dosing regimen, complicated procurement and distribution; and little national prescribing experience' [21]. A study was done to evaluate treatment practices for uncomplicated malaria after the policy change in 4 districts. Among children weighing 10 kilograms or more, Sulphadoxine pyrimethamine (SP) was commonly prescribed (68%) whereas the recommended AL was prescribed for only 11% of children. Among children weighing more than 10 kilograms seen at facilities where AL was available, AL was prescribed for 22% of children and SP for 54% [21]. A follow-up survey two years later found significant improvements in malaria case management. The proportion of children weighing 5-9 kilograms treated with AL rose from 1% to 27%, and from 11% to 42% among those weighing 10 kilograms or more [30].

A study in Kenya indicated that 79.3% of patients with a negative result were treated for malaria [20]. Studies have shown that in the midst of this over-prescription at health facilities, there are genuine malaria cases that are misdiagnosed and subsequently not treated for malaria. A study in Zambia estimated this to comprise 17% of children with uncomplicated malaria, and 18% in Kenya [21]. Changing clinicians prescribing behaviour is possible but requires investment to ensure adequate quality assurance, regular training and supervision [31].

Adherence to ACTs

A study done on adherence to a six-dose Artemether-lumefantrine regimen found that adherence was high at 90% [32]. Lack of formal education was the only factor associated with non-adherence after controlling for confounders (odds ratio = 3.1) and the most commonly missed dose was the sixth dose (41.7%). A study on adherence in a refugee settlement in Zambia found higher rates of non-adherence, with 60.6% of patients probably non-adherent. Non adherence was highly associated with insufficient explanation by the dispenser [33]. This study used strict definitions and a patient who took all tablets was classified probably non-adherent if the day of intake was incorrect. The drugs were also given out in loose sachets [33]. A study on adherence to AL in southern Sudan found that 18.3% of patients were non-adherent [34]. In another study, high cure rates irrespective of whether AL was given under supervision with food or under conditions of routine clinic practice were observed. Day-28 cure rates were 97.7% and 98.0% in the supervised and unsupervised groups, respectively [35]. A study in Tanzania found that complete adherence measured at 48 hours was 75.0%, based on self-report and tablet counts [36]. Counselling by health workers is important as it plays a key role in ensuring adherence. This is more so given the need for fat intake to ensure sufficient bioavailability. AL comes already pre-packaged in blister packs, which contain pictorial instructions on how to take the drug. This is intended to discourage resale and improve compliance, as non-literate people will be able to follow instructions. A potential problem is that the rapid resolution of symptoms may make some patients discontinue treatment and save the remaining drugs for future use. In one study, 13.7% of caretakers stopped treatment once the child appeared to have recovered [33].

Use of ACT in home management of malaria (HMM)

In Africa, the majority of malaria cases are treated outside the formal health sector. This is because provision of health services is inhibited by factors like inadequate funds, drug stock-outs, inaccessibility, poor management and demoralized staff. In addition, optimal utilization of services is hampered by the relationships between providers and clients [37]. This leads to government health facilities being underutilized, for example in Mali the utilization rate is 0.15 new cases per inhabitant per year, Ivory Coast 0.12 and Benin 0.24 [38]. Home Management of Malaria (HMM) is an intervention geared towards improving access to antimalarial treatment close to homes. It includes training both health staff, community members, a campaign for behavioural change, and the production and distribution of user friendly, pre packaged drugs at community level. It utilises trained community based agents (CBA) who treat febrile cases using the pre-packaged medicines. CBA include community health workers, shopkeepers and teachers. In Kenya, the training of shopkeepers led to an increase in the proportion of over the counter drug users receiving an adequate dose from 8% in 1998 to 64% in 2001(39). HMM plays a key role in attaining one of the targets of roll back Malaria, which is 60% of people with malaria have access to effective drugs within 24 hours of onset of symptoms [40]. In Kenya, it was estimated that only 5.3% of fevers in children under 5 years were treated with an antimalarial drug within the first 24 hours, and only 2.3% were treated with SP which was the recommended drug then [41]. HMM has been proven to be effective. In an often quoted study in Ethiopia, mother co-ordinators were trained to teach other local mothers on recognition of malaria symptoms and to promptly give choloroquine. Under 5 mortality declined by 40% in the intervention localities [42].

The use of ACT in HMM is currently a contentious issue. The above mention study from Ethiopia in support of HMM, was done in an area of low, seasonal malaria transmission. Tigray area also has an effective community based primary health care programme characterised by frequent supervision of Community Health Workers (42,43(what are these numbers? Some experts have argued it should not be used as the negative consequences will outweigh benefits. These include poor compliance, over-prescription and cost implications [43]. Amanua et al found use of AL to be feasible and acceptable in Ghana with 92.5% of children being treated with an adequate dose of AL, and delay in seeking treatment declined from 3 to 2 days after onset of symptoms [44]. Though such an intervention cannot be implemented on a large scale as this intervention was carried out for only four months, supervision was high and the number of children treated was low. The authors did

note that for the program to be sustainable the Community based Agents (CBAs) need to be paid.

ACT is given by prescription only and is not available over the counter. Thus it cannot be sold by informal sellers like shopkeepers [45]. AL is being provided free of charge at health facilities and this creates no incentive for shopkeepers to stock such a drug, even if it was possible for them to do so. Health education including mass media campaigns are being utilised to persuade people to go for treatment directly at the health facilities, the underlying assumption being that they are accessible. This will in effect create a two-tier drug system, with the ACTs being available in health facilities and less effective antimalarials being available at the community and household levels [46].

Sustainability of ACT treatment

Cost has been cited as a major impediment in the scaling up of ACT [47,48], with ACTs costing close to ten times more than other antimalarials. Introduction of AL in Zambia was estimated to have caused a six fold increase in the amount of funds normally spent on the purchase of antimalarials, and use of AL was estimated to result in an incremental cost-effectiveness ratio of US$4.10 compared to SP [48].

In 2002, the US Agency for International Development commissioned the Institute of Medicine (IOM) to recommend global actions to ensure the broadest possible access to ACT. In a report issued in 2004, the IOM Committee on Economics of Antimalarial drugs recommended a global subsidy of US$ 300- 500 million per year to replace the increasingly ineffective drugs with coformulated ACT therapies. This international subsidy would discourage the distribution of monotherapies, such as solo artemisinins. This would prevent the development of drug resistance to ACT [49]. In 2001, WHO entered into a special pricing agreement with Novartis, in which Coartem® will be made available at a negotiated price ranging from US$ 0•9 in the smallest children to US$2•40 for an adult course. These prices represent the production costs only incurred by Novartis and are subject to periodic reviews to ensure that they constantly reflect production costs only [50]. The drug comes pre-packaged in a blister pack. There are 4-age specific blister packs, which contain 6, 12, 18 or 24 tablets respectively, according to the 6-dose regimen recommended by WHO. This agreement allows Novartis to forecast demand and plan production schedules more efficiently [50]. This is important as the artemisinin component is derived from the plant Artemisia annua. The cycle of planting, harvesting, extraction of artemisinin and further processing to Artemether requires 10 months. Novartis requires a period of 4 months from the time it receives an order from WHO to when it ships the product, though a 6 months period is recommended [50].

The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) is the financial engine behind the scaling up of ACT [18,22]. Since the establishment of the GFATM in 2002, a total of US$ 230 million have been allocated for malaria programmes, mainly for the procurement of ACTs, and mostly for African countries. The GFATM grants enable countries to scale up their fight against malaria. These grants enable the countries to purchase ACTs directly or indirectly through WHO which acts as a broker [45,50]. Most countries rely heavily on the Global Fund to implement this new treatment. Delays in cash flow after grant approval has led to 43 countries adopting ACT but only nine implementing it by 2005 [47]. Sustainability of the treatment has been questioned. Kenya, for example, typically spends 10 million US dollars on essential drugs in one year [11]. The annual cost of ACT required is over twice this amount. In 2006, the Global Fund announced that a new round of funding (Round 6) could be jeopardized by lack of finances [40]. At the global level, other sources of funding are available and may facilitate scaling up of ACT. These include the World Bank's Booster Programme for Malaria Control, which amounts to between US$500 million and US$1 billion over the next five years, and USA's President's Malaria Initiative (PMI) for US$1.2 billion over five years for 15 countries [6]. This is good, though relying on donor support for long term financial support may not augur well for sustained scaling up [47,48].

The drug is single sourced, as WHO only prequalified Novartis as the sole manufacturer. This was aimed at ensuring quality and avoiding counterfeit drugs, which account for 25% of all drugs in developing countries [51]. On the other hand, it leaves no room for cheaper generics or competitive bidding, which is contrary to public procurement rules [45]. This also locks out local pharmaceutical companies from this lucrative market despite Artemisia annua being grown in these countries [45,47]. AL has a short shelf life of 2 years and Novartis normally freights the drug. This is cost-effective, as it allows the drug to have at least 18 months lead time before expiry. If the drug was manufactured locally, they would be savings on the freight charges and more lead time to expiry. The logistics in place should ensure effective distribution so as to avoid the drugs running out or expiring [50]. In Zambia 8% of health facilities had in their possession expired AL and they also suffered from stock-outs 30% of the time [21].

The patent for Coartem expires in 2010 and is held by Novartis, though Cipla does manufacture artemether and lumefantrine in bulk but not in combination. Other less expensive ACTs are currently being developed. In March 2007, Drugs for Neglected Diseases Initiative and Sanofi Aventis Pharmaceuticals launched a less expensive ACT, artesunate Amodiaquine (ASAQ). An adult dose costs US$1 dollar and a child dose costs US$ 0.5. It also has a simple dosing formula compared to AL as an adult takes only two tablets a day and a child one tablet. ASAQ is not patented and is a cheaper but still effective alternative to AL [52.[

Cost effectiveness of ACT

Despite being costly, ACT was found to be the most cost effective strategy for control of malaria in most countries in sub-Saharan Africa with a net effectiveness of 63% reduction in case fatality [53]. Muheki et al explored the economic aspects of the implementation of Artemether-Lumefantrine to replace SP in the Kwa Zulu Natal province in South Africa. The number of outpatient malaria cases and inpatient admissions both declined by 94% between 2000 and 2002. After accounting for the role of concurrent improvements in vector control, it was conservatively

estimated that 36% of the decline in outpatient cases and 46% for inpatient admissions was attributable to changing the first line drug to AL [29].

A cost-effectiveness study of antimalarial combinations in Tanzania found AL to be the most cost-effective. From a societal perspective AL was most cost-effective at day 14; resulting in a gross saving of US$1.51 or a net saving of US$22.24 per case averted [54]. In Zambia, the average cost-effectiveness ratio, defined as the total treatment cost divided by the total number of cases successfully treated (i.e. cost per cured case), has been estimated at US$8.57 and US$10.65 for AL and SP respectively [48].

ACT has a high cure rate thus relatively fewer patients will develop complicated malaria. This results in cost savings due to decline in hospital admissions and treatments using expensive second line drugs. This superiority comes with a price. This extra or incremental cost of producing one extra successful cure of an episode of malaria is known as the incremental cost-effectiveness ratio, which was estimated to be US$4.10 [48]. This is the amount that it costs to achieve one extra successfully treated case using AL in relation to Sulphadoxine pyrimethamine.

It has been argued that there is a need to shift from a narrow disease based focus to comprehensive integrated health services. This will make health services more accessible and will facilitate better malaria control [55].

Conclusion

Donor funding is fickle and may not prove reliable in the long run, therefore governments must increase their health sector funding in line with the Abuja declaration so as to attain a minimum 15% of total government expenditure. This will enable them to cover for any shortfalls in the donor funding. Single sourcing is bad for prices and runs contrary to public sector procurement rules. This has to be done away with and there is hope that Chinese and Indian pharmaceutical firms will produce cheaper ACT's.

There is need to strengthen health systems by better disease prevention and control and finding new ways of treatment, to secure less resistance and better effect for the drugs.

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