Counterfeit Antimalarials and the Commodification of Health

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Counterfeit and substandard medicines are a persistent threat to the global control and eradication of infectious diseases. The issue is particularly acute in developing countries due to a lack of local and international pharmaceutical surveillance networks. In this context, the inability to fulfill the fundamental right of individuals to access life-saving essential medicines is a critical public health challenge. Accordingly, this analysis focuses on the crisis of counterfeit and substandard antimalarials in sub-Saharan Africa through a multidimensional framework. Of primary importance is healthcare system vulnerability to market-driven forces, which facilitates the emergence and sustainability of barriers in accessing high-quality antimalarials. Consequently, the informal drug market thrives because of the dire need for affordable malaria treatment. The impact of counterfeit antimalarials cannot be understated, ranging from increased morbidity due to adverse effects from substandard product ingredients to heightened resistance to the final line of antimalarial treatment (artemisinin-combination therapy). The ability of international humanitarian organizations and various levels of government to combat counterfeit medicines remains a daunting task, as the right to health has become a costly commodity.

Introduction

A threat to global health is the proliferation of counterfeit and substandard medicines that compromise the control of infectious diseases, particularly within the healthcare systems of developing countries. Access to essential medicines is an indicator of a country's healthcare infrastructure quality: medicines must address the health priorities of the population and be consistently available in the correct amounts and at an affordable cost (UN Millennium Project, 2005; WHO, 2010). The right to health is a human right identified by the United Nations (2005) and almost two billion people are unable to regularly access life-saving medicines (WHO, 2004) with only approximately 35% availability of these medicines in the public sector of developing countries (WHO, 2009). This creates a

thriving industrial-complex of counterfeit and substandard drugs encouraged by the high cost of medicines along with their desirability, thereby presenting economic incentives where profits are gained by the loss of life (Brezis & Wiist, 2011; Chika, Bello, Jimoh, & Umar, 2011; Marks, 2009; Newton et al., 2006). The globalized economy and vulnerability of health to market forces create a dangerous situation of poor quality medicines (Brezis & Wiist, 2011; Chika et al., 2011).

The number of global annual deaths from malaria in 2012 was 627,000 individuals (WHO, 2014). Of the *Plasmodium* species infectious to humans *P. vivax*, *P. ovale*, and *P. malariae* are considered the most benign forms, whereas *P. falciparum* is the most virulent. Africa bears 91% of the global malaria burden and in sub-Saharan Africa *P. falciparum* is the predominant parasite,

exhibiting a highly stable endemic transmission pattern disproportionately affecting young children and pregnant women (Osamor, 2010; RBM, 2011; Warsame, Olumese, & Mendis, 2010). The question remains why malaria still exerts significant morbidity and mortality in sub-Saharan Africa as the disease is preventable and curable in 90% of cases (Osamor, 2010; RBM, 2011).

This analysis demonstrates the commodification of health as directly contributing to the proliferation of substandard and counterfeit antimalarials in sub-Saharan Africa, combining to create a global health threat of emerging malaria parasite resistance to the last line of pharmaceutical treatment. The underlying mechanisms of this multidimensional health crisis are: the decentralization of health infrastructure in Africa during the 1980s and 1990s, global governance mechanisms restricting pharmaceutical access and incentivizing market-based approaches to healthcare, local health systems manifesting access barriers due to contradictions between market-driven health and needs-driven health, and the implementation of artemisinin-combination therapy (ACT) as the current frontline treatment driving malaria resistance by compromising affordability and treatment-seeking behaviour.

Decentralized Health Infrastructure and the Global Economy

Neoliberal market principles dominate the global economy, and over the last few decades the distribution of wealth and life chances has become increasingly unequal (Benatar, Gill, & Bakker, 2009; Buckley & Baker, 2008; Koivusalo, 2006). The decentralization of health infrastructure in Africa in the 1980s and 1990s exemplifies an initial phase of forced integration into the global economy through interventions by the International Monetary Fund (IMF) and World Bank (Benatar, 1998; Buckley & Baker, 2008; Stein, 1992). The structural adjustment programmes, introduced by international financial institutions as a strategy of industrial alignment, demonstrated the core principles of neoliberalism:

promoting free markets, privatizing services and deregulating the government and economy (Meier & Steel, 1987; Pfeiffer & Chapman, 2010). The underlying assumption was that the benefits of a free market automatically reduce poverty and improve healthcare, thereby enhancing quality of life in developing countries (Buckley & Baker, 2008; IMF, 2007; Pfeiffer & Chapman, 2010). However, the implementation of such alignment strategies ultimately disengages local governments from providing critical and essential services.

The justification for intervention in Africa centred on the country's economic stagnation and debt crisis, attributed to the low output of an unsustainable industrial sector and a lack of foreign investments due to government price controls on imports (Buckley & Baker, 2008; Meier & Steel, 1987; Stein, 1992). The industrial alignment strategy devalued the country's currency, removed government controls on trade and imports, and refocused the economy as export-oriented (producing materials for distribution in developed countries) (Meier & Steel, 1987; Riddell, 1992; Stein, 1992). Although foreign aid and investments increased, funds were directed to debt repayment and not to strengthening health infrastructure; consequently, the IMF and World Bank strategy worsened existing inequalities, as the liberalization of the market increased the cost of essential goods and services (Breman & Shelton, 2007; Buckley & Baker, 2008; Pfeiffer & Chapman, 2010).

Free market practices and principles detrimentally affected the health sector, primarily through privatization and commercialization of healthcare. The strategy imposed user fees, removed price controls and subsidies that the African government implemented to lower the cost of living, and enabled non-governmental organizations or other private sector entities to provide health services as the government was removed from investing in public health (Maclean & Maclean, 2009; Riddell, 1992; Sanders, Todd, & Chopra, 2005). Prior to the 1980s, essential drugs were free at community health centres throughout Africa; however, the implementation

of user fees liberalized the sale of drugs and increased costs of essential medicines, leading to declines in consumption as an individual's ability to pay became a determinant of accessing health services – a barrier remaining to this day (Benatar et al., 2009; Maclean & Maclean, 2009; Sanders et al., 2005). The financial incentives of a deregulated African economy permitted brand-name drug manufacturers to operate at low costs and replace domestic manufacturers, further contributing to the increased price of medicines (Buckley & Baker, 2008; Riddell, 1992; Sanders et al., 2005). The resultant shift in health sector resources marginalized individuals in rural or remote areas, as development was concentrated on urban health centres and the delivery of health services was unregulated (Konde-Lule et al., 2010; Tumushabe & Mugabe, 2009). Accordingly, the provision of healthcare to the market fostered social inequality and economic vulnerability, demonstrating the inability of neoliberal principles to improve the health and economic status of those in sub-Saharan Africa.

As a particular example of the detrimental effect of market-fostered healthcare, the structural adjustment program introduced in Tanzania during the 1980s benefited the economy, but reduced quality of life due to the absence of public healthcare expenditure (Buckley & Baker, 2008; Turshen, 1999). Government spending on healthcare was 7.5% in 1978 and dropped to 3.9% in 1989, due to the recovery strategy implemented by the IMF and World Bank (Kumaranayake, Lake, Mujinja, Hongoro, & Mpembeni, 2000; Turshen, 1999). Similar to other sub-Saharan African countries, Tanzania is currently focused on restoring the neglected health system, but funding remains inadequate to address priority diseases (e.g., tuberculosis, AIDS and malaria) as only 46% of healthcare expenditure is publicly funded (Buckley & Baker, 2008; Kumaranayake et al., 2000). Currently within Africa, a vulnerable healthcare infrastructure is a related outcome of the international financial institutions' alignment strategies, manifesting through health service fragmentation and unequal access.

Global Governance Mechanisms

Global governance mechanisms, such as international trade agreements, significantly influence the availability of pharmaceuticals in developing countries. The erosion of public health due to market liberalization provided the business sector with opportunities to influence the global health research agenda, particularly protecting the financial investments of pharmaceutical companies, rather than addressing social complexities of disease (Benatar et al., 2009; Maclean & Maclean, 2009; Tumushabe & Mugabe, 2009). One such detrimental market-promoting international agreement is the World Trade Organization's (WTO) Trade Related Aspects of Intellectual Property Rights (TRIPS), which strengthens the standards for the protection of patents (Benatar et al., 2009; Reddy, 2011; WTO, 2012). The agreement is mandatory to enforce by all WTO members by 2016, where 47 of the 142 members are African countries (Sterckx, 2004; WTO, 2012), and raises concerns regarding the beneficiaries of market-based approaches to health.

Less restrictive patent systems in developing countries, such as those in Africa, were the impetus for TRIPS; pharmaceutical products were previously excluded from requiring patents, in contrast to the rigid protection standards of industrialized countries (Barton, 2004; Benatar et al., 2009; Reddy, 2011). However, in the pharmaceutical business model, profits are necessary to recover the expense of research and development, and countries with weak patent systems do not provide incentives for pharmaceutical innovation as generics, rival pharmaceutical companies, or government price control measures threaten the ability to maximize profits (Min, 2012; Reddy, 2011; Tumushabe & Mugabe, 2009). In sub-Saharan Africa, only the process for manufacturing a pharmaceutical was patentable; however, under TRIPS, the final product is also patentable (Sterckx, 2004; Zainol, Amin, Jusoff, Zahid, & Akpoviri, 2011). This effectively stifles desirable social outcomes attainable by providing affordable drugs, since the pharmaceutical company retains control in

directing distribution of the product (Sterckx, 2004; Tumushabe & Mugabe, 2009; Zainol et al., 2011). Furthermore, no formal criteria are required to patent a drug, and this undermines the ability of developing countries to maintain quality control measures by selectively granting patents on the drugs that will eventually circulate (Brock, 2001; Sterckx, 2004; Zainol et al., 2011).

The problem of accessing essential medicines in sub-Saharan Africa due to the unprofitable market is exacerbated by intensification of the patent system. Patent protection is argued to help establish local pharmaceutical industries, but in sub-Saharan Africa there has been an inequitable distribution of health-related research and development over the decades (Benatar et al., 2009; Tumushabe & Mugabe, 2009). The situation is unsustainable for investment by pharmaceutical companies, as consumers in Africa are perceived to hold limited purchasing power since many are unable to purchase drugs, and the market itself is unappealing due to high import taxes, debt burden, and the absence of trained personnel in communities (Whitty, 2011; Zainol et al., 2011). Approximately one billion dollars in profit is necessary for a company to assume the risks involved in the production and marketing of drugs related to any particular disease (Pies & Hielscher, 2011; Whitty, 2011). If the market is not viable in sub-Saharan Africa, the ability to generate profits is a high risk venture.

The development of innovative drug treatments is another presumed advantage of the strengthened patent system. However, the fact that only 13 of the 1,393 drugs produced between 1975 and 1999 were exclusively relevant for diseases occurring in African countries demonstrates that Africa has not benefitted (Sterckx, 2004; Zainol et al., 2011). Similarly, from 2000 to 2012, of the 101 new drugs for immunological or infectious diseases approved by the Food and Drug Administration only 20 were related to priority diseases in Africa (CentreWatch, 2012). The under-development of pharmaceutical innovation is evident in the United Nations Development Programme, Human Development Report (2001) where 12 African countries ranked last with the lowest expenditure on research and development, a limited ability to adopt new technologies, and a significant disease burden compromising technological uptake (Tumushabe & Mugabe, 2009; UNDP 2001). For example, in Rwanda the malaria burden is 20,310 cases per 100,000 people with only 35 scientists or engineers per 100,000 people, indicating a lack of capacity to support innovative health research and development (Tumushabe & Mugabe, 2009; UNDP 2001). Fragmentation of the health sector, limited public health expenditure, and vulnerable infrastructure preclude implementing large-scale initiatives to strengthen the industrial capacity of sub-Saharan Africa and encourage foreign investments.

Enhanced patent protection measures have not yet resulted in the provision of affordable drugs. A component of TRIPS protects pharmaceutical patents for 20 years, which benefits the drug companies by generating profits but also prohibits manufacturing generic brand drugs until the expiry of the patent term (Barton, 2004; Lucyk, 2006; Marks, 2009). This does not lead to desirable social outcomes, as developing countries are unable to offer lower cost generic medicines until the patent expires. Similarly, the patent holder (e.g., the pharmaceutical company) controls the price of drugs, and this may result in increases of up to 200% in developing countries such as sub-Saharan Africa where artemisinin combination therapy is $6.00, a 60% increase from the manufacturer price (Turshen, 1999; Zainol et al., 2011). There is a clear differential between the initial price set by the manufacturer and the price paid by consumers which varies from one country to another, attributable to the liberalized pharmaceutical market (Barton, 2004; Min, 2012).

The protection of private property rights from a financial perspective directly opposes the moral or social desirability of ensuring the availability of low cost essential medicines. The flow of essential goods and services to Africa is controlled by its position in a particular political-economic structure where governments are unable

to exert influence on the costs of goods or essential medicines entering the country (Min, 2012; Turshen, 1999; Zainol et al., 2011). Consequently, global mechanisms are driving profitable pharmaceutical research in economies guaranteeing a return on investments, which is detrimental to social- or needs-driven investments necessary in countries such as those in sub-Saharan Africa without such similarly marketable economies.

Emergence of the Informal Market

The institutionalization of neoliberal policies over the decades and the restrictive power of international trade agreements contributed to an underfunded public health sector in sub-Saharan Africa without the ability to provide affordable and equitable care. A consequence of this marketization of health is a shift in the boundaries of expertise and in the gap left by the formal market (e.g., hospitals, clinics and health centres). The informal market provides 75% of the healthcare services through private pharmacies, retail shops, illegal drug vendors, or international aid agencies (Conteh & Hanson, 2003; Newton et al., 2006; Onwujekwe et al., 2010a; Tetteh, 2008).

In sub-Saharan Africa, the informal market is often the first point of access for many individuals; healthcare expenditures are out-of-pocket, which affects the decision-making process in seeking treatment (Okeke, Lamikanra, & Edlman, 1999; Onwujekwe et al., 2010a). The cost of treating an episode of malaria consumes 60% of a household's total budget for the year, deterring individuals from seeking treatment in the high-cost formal sector facilities and promoting self-treatment for approximately 66% of sub-Saharans (Buabeng & Matowe, 2010; Okeke et al., 1999; Whitty, Chandler, Ansah, Leslie, & Staedke, 2008). Oladepo and colleagues (2007) demonstrated that rural dwellers in Nigeria often delay treatment at primary health centres until absolutely necessary (e.g., complications arise or the individual is near death); however, these choices also increase morbidity and mortality of malaria due to untimely treatment interventions. The geographical accessibility of informal providers in these rural areas is also an incentive, where despite the lower quality of services, the advantage of proximity outweighs the financial and health costs associated with public sector facilities (Oladepo et al., 2007; Onwujekwe et al., 2010a). Additional benefits include the ability of individuals to negotiate the price of antimalarials based on what is affordable, and the absence of transportation or nonmedical costs (Bloom et al., 2011; Granado, Obrist, Manderson, & Tanner, 2009). For example, Granado and colleagues (2009) indicated that rural patients in Cote d'Ivoire visited private pharmacies, shops, and herbalists more consistently than public sector facilities as treatment was obtained without question from the pharmacist or retailer and in affordable dosages. In this context, patients exercise choice in directing treatment rather than simply accepting the diagnosis of healthcare workers (Granado et al., 2009). These community-based distributors are also potentially capable of enhancing accessibility to medicines in rural areas, such as in Kilifi (Kenya), where a training program for shopkeepers on the symptoms of malaria, which antimalarials to sell, and the dosage was successful in improving the correct use of antimalarials (Goodman, Mutemi, Baya, Willets, & Marsh, 2006; Marsh et al. 2004). Matovu, Nanyiti, and Rutebemberwa (2014) similarly advocate community-based programs in rural areas of Uganda (in the gap left by the formal health sector) to facilitate prompt treatment and reduce the severity of illness.

However, there are consequences of the widespread informal sector distribution of drugs. Proprietors are not always adequately trained in pharmaceutical dispensing practices and may not follow government treatment guidelines for malaria by providing substandard medicine dosages or treatment regimes without patient information (Foster, 2010; Okeke et al., 1999). In this manner, practices contraindicated by the WHO to facilitate control of malaria occur, such as only 9% of Nigerian retail shops recommending the current treatment of ACT; however, consumer demand is high for affordable

malaria treatments (e.g., sulphadoxine-pyrimethamine (SP), chloroquine (CQ) or artesunate as a monotherapy) (Bloom et al., 2011; Foster, 2010; Tipke et al., 2008). This informal market is unregulated, with sale and dispensation of drugs beyond the control of the government, and it is at this point where counterfeit and substandard drugs are increasingly entering the drug distribution network in sub-Saharan Africa (Bloom et al., 2011; Tipke et al., 2008; Zainol et al., 2011).

Counterfeit and Sub-standard Antimalarials

Medicines are manufactured commodities, becoming objects that are produced, marketed, purchased, and consumed (Applbaum & Oldani, 2010). Poor quality drugs are classified as counterfeit, substandard, or degraded and present a critical yet underreported problem as only 5-15% of the 191 WHO member states report counterfeit drugs (Newton et al., 2006; WHO, 2012). A counterfeit medicine is deliberately mislabelled, applying to brand-name and generic drugs that may contain the correct active ingredients or the wrong ones, have no or insufficient therapeutic levels of active ingredients, as well as have fake packaging (Glass, 2014; Newton et al., 2006; Wondemagegnehu, 1999). Substandard drugs are genuine products that do not meet quality specifications due to insufficient manufacturing practices or a lack of expertise (Primo-Carpenter, 2004; WHO, 2012). Degraded drugs are initially of good quality but due to inadequate storage subsequently lose efficacy, which is common in the climate of sub-Saharan Africa (Caudron et al., 2008; Keoluangkhot et al., 2008). Globally, illegal trade of substandard and counterfeit drugs is a highly profitable and structured industry in developing countries, generating an estimated 70 billion dollars a year as pharmaceuticals are easily transportable, have a high cost per unit, and the lack of diagnostic laboratories ensures the quality of these drugs is not recognizable by frontline health workers (Glass, 2014; Tipke et al., 2008; WHO, 2012). There is no linear supply chain between manufacturers, distributors, and pharmacies; as such, physicians or healthcare providers, the purchaser (public or private markets), and the consumer or patient are separate entities (Applbaum & Oldani, 2010; Caudron et al., 2008; Min, 2012). Malfunctions in various facets of this chain have devastating impacts on population health, while undermining the capability of governments to address imbalances in the health system (Min, 2012; Tumushabe & Mugabe, 2009).

A confluence of factors facilitates proliferation of the substandard and counterfeit drug industry in sub-Saharan Africa where approximately 20-90% of the antimalarial drug supply is compromised (Caudron et al., 2008; Min, 2012; Nugent, Pickett, & Back, 2008). The export of pharmaceuticals from developed to developing countries is not subject to rigorous quality assurance protocols, and pathways of counterfeit drug infiltration into Africa proceed along trade routes of southern China, Burma, and Vietnam, providing an ease of entry for poor quality drugs (Caudron et al., 2008; Keoluangkhot et al., 2008; Newton et al., 2006, 2010). The high cost of genuine medicines such as ACT, or inexpensive medicines such as CQ, provide economic incentives to counterfeiters, largely due to high demand (Newton, Green, & Fernandez, 2010). Lack of legislation against the counterfeit drug trade, light penalties, and complex international trade agreements enable the clandestine movement of counterfeits across transnational borders, creating a low risk but profitable venture (Newton et al., 2006, 2010; Nugent et al., 2008). The vulnerability of health to market forces within the infrastructure of sub-Saharan Africa is attributed to detrimental neoliberal economic policies and the absence of a pharmacovigilance framework, creating a sub-optimally regulated environment where poor quality drugs are not detected in the distribution network (Caudron et al., 2008; Min, 2012). As a result, the burden of ensuring drug quality and safety is on local medical staff as informal surveillance, in a context of resource constraints on quality assessment frameworks and diagnostics (Caudron et al., 2008; Newton et al., 2010).

Although counterfeit antimalarials contribute to increased treatment failure and mortality, confounding country-wide distribution patterns of malaria, it is difficult to discern whether morbidity and mortality rates are attributable solely to malaria or to poor quality drugs with severe side effects (Caudron et al., 2008; Newton et al., 2006, 2008). A related challenge is identifying whether patients are aware of the likelihood of purchasing counterfeit or substandard drugs and the consequences of consuming these medicines, however, such information is scarce (Burki, 2010; Min, 2012). If treatment fails individuals may alter treatment seeking behaviour, but the extent to which the behaviour is modified and the sources patronized is unknown.

Considerable proliferation of the counterfeit and substandard drug industrial complex in the informal market indicates the absence of quality assurance frameworks in sub-Saharan Africa; however, the question remains why individuals are compelled to seek treatment in this sector given the risks of poor quality antimalarials and the potential negative outcomes on health. The public health sector or formal market manifests systemic access barriers due to the contradictions inherent in market-driven and needs-driven health. Geographic barriers influence proximity and feasibility of accessing appropriate antimalarials where significant disparity exists between urban and rural areas, as urban residents have improved access to quality formal health sector services due to the over-concentration of private sector funding over the decades (Abuya et al., 2007; Caudron et al., 2008; Chuma et al., 2010). For example, rural populations in Nigeria were more likely to seek treatments through traditional healers, medicine vendors, and community health workers due to the low costs of medicines (Onwujekwe et al., 2010a). Availability of appropriate care is an ongoing challenge as hospitals, clinics, and health centres experience stock-outs of antimalarials (Bate, Coticelli, Tren, & Attaran, 2008; O'Connell et al., 2011). The issue of maintaining sufficient stocks is due to delays in drug deliveries and the

inability to account for seasonal fluctuations in malaria disease burden (Chuma et al., 2010; Goodman et al., 2007). In a survey of health facilities in Kenya, 36% experienced stock-outs of antimalarials, which compromises predictable and sustained access to these drugs and ultimately becomes a deterrent for those seeking treatment from rural or remote areas (Amin et al., 2007; Bate et al., 2008; O'Connell et al., 2011).

One type of financial barrier is the potential for informal or under-the-table payments sought by health service providers under the guise of pretending drug shortages, offering to reduce wait times, or offering improved services, consequently consuming 10% to 45% of the total out-of-pocket patient costs for healthcare (O'Connell et al., 2011; Onwujekwe, Dike, Uzochukwu, & Ezeoke, 2010b). Many individuals live on one or two dollars per day (Maestad & Mwisongo, 2011; Onwujekwe et al., 2010b) and informal payments lead households to incur detrimental treatment expenditures, acting as an obstacle for those lacking the means to access the health service system. For example, public hospitals in Nigeria exhibited an average expenditure for malaria treatment between $6.30 and $6.40 for patients; however, the price indicated by providers was only $2.20 per treatment, indicating informal payments ranging from $4.10 to $4.20 per malaria episode (Onwujekwe et al., 2010b). The costs of antimalarial treatments without consideration of informal payments are unaffordable to a significant portion of the sub-Saharan population. Despite the availability and subsidization of ACT, 44% of customers in Tanzania opted to purchase alternative and affordable treatments in private shops (Bate et al., 2008; Caudron et al., 2008). Although the quality of drugs may be higher in formal sector facilities, the cost of access may inadvertently lead individuals to treatment choices involving substandard drugs.

Cultural perceptions of illness and the quality of care in the formal sector also deter individuals seeking treatment. With regards to perceptions of health worker attitudes, older clients in Kenya were reluctant to accept

treatment from young healthcare providers as they were thought to be inadequately trained (Amin et al., 2007; Chuma et al., 2010). Similarly, operating hours of facilities are inconvenient in the public sector. Facilities in Kenya were open from 8:00am to 4:30pm but closed on weekends, forcing individuals to seek treatment from private shops or suffer throughout the weekend (Amin et al., 2007; Chuma et al., 2010). Cultural conceptions of illness are also integral to understanding treatment-seeking behaviour. In Burkina Faso, sumaya and kono are the local illness concepts, resembling uncomplicated malaria and cerebral malaria, respectively (Beiersmann et al., 2007). Perceptions affect treatment and provider selection as sumaya is treated with traditional and modern methods, while kono (the most severe form of malaria) is treated by traditional healers (Beiersmann et al., 2007). The complexity of cultural or personal perceptions further confounds the ability of health systems to be appealing for patronage by all patients.

ACT Implementation and Compromised Affordability

The last three decades demonstrated an ongoing evolution of resistance in malaria parasites to a variety of antimalarials (Bassat & Alonso, 2010; Keoluangkhot et al., 2008; Talisuna, Bloland, & D'Alessandro, 2004). For example, between 2001 and 2004, CQ and SP had a significant treatment failure of 22% to 77% throughout Uganda (Caudron et al., 2008; Nanyunja et al., 2011). The discontinuation of monotherapies (single-drug regimes) such as CQ and SP shifted to a focus on combination drug treatment, and in 2005 the WHO switched to ACT as the frontline malaria treatment (Lindsay, 2010; Talisuna et al., 2004; WHO, 2010). To ensure the effectiveness of ACT and avoid fostering resistance, the use of artemisinin or its derivatives (artemether and artesunate) as monotherapies are contraindicated by the WHO; however, monotherapies are still widely available in both the informal and formal sectors in sub-Saharan Africa and Southeast Asia, raising opportunities

of creating resistance through the inappropriate consumption of antimalarials (Bate et al., 2008; Lindsay, 2010; Warsame et al., 2010).

The high cost of ACT, as much as $6.00 per treatment regime, compromises treatment affordability. In Africa, government expenditure on health per person is approximately $6.00, which must cover all aspects of health, not solely antimalarial medications (Bassat & Alonso, 2010; Caudron et al., 2008; Talisuna et al., 2004). The adoption of ACT faced significant challenges in sub-Saharan Africa, as efforts had to ensure this drug was produced and available in sufficient quantities for distribution, as well as secure increases in national health ministry budgets and external donor funding to afford the cost-prohibitive replacement treatment (Newton et al., 2010; O'Connell et al., 2011). There are difficulties in implementing a policy change that replaces an inexpensive but popular and widely available antimalarial such as CQ or SP with one that is of limited availability (by prescription only) and beyond the means of affordability for many individuals (Amin et al., 2007; O'Connell et al., 2011; Warsame et al., 2010). As a result, the Global Fund to Fight Against AIDS, Tuberculosis and Malaria (GFATM), launched in 2002, became the main financier of these drugs (Amin et al., 2007; Foster, 2010; GFATM, 2012). With this incentive, nearly all sub-Saharan countries endemic for *P. falciparum* revised national health policies where ACT became the frontline antimalarial (40 out of 44), although there was a considerable time lag between the adoption and deployment of the treatment regime (Caudron et al., 2008; Nanyunja et al., 2011; Warsame et al., 2010).

As a particular example, Uganda received funding from GFATM in 2005, but encountered rampant ACT stock-outs in formal sector facilities 16 months into program implementation. ACT treatment was only prescribed in 64% of the cases by healthcare workers, with a CQ/SP combination treatment comprising the remainder as it was still perceived as effective (Konde-Lule et al., 2010; Nanyunja et al., 2011). As a result, Uganda's funding was suspended by the Global Fund only

to be reinstated months later, further compromising the incorporation of ACT into the country's treatment regime (Konde-Lule et al., 2010; Nanyunja et al., 2011). Similarly, in Burkina Faso ACT treatment cost $6.50, and as this was cost prohibitive the country maintained the affordable CQ as the frontline treatment, contradicting the WHO recommendation (Beiersmann et al., 2007; Okeke et al., 1999). The lack of predictability, sustainability, and alignment of strategies (such as the Global Fund) with national deployment strategies hampers implementation, highlighting the systemic health infrastructure challenges in sub-Saharan Africa, particularly weak stock management, limited diagnostic capacity, and inadequate healthcare worker training (Amin et al., 2007; Nanyunja et al., 2011).

The high cost and limited availability of ACT creates an ideal situation for the proliferation of counterfeit antimalarials, increasing the risks of morbidity and mortality. Individual treatment choice is constrained and forces the maintenance of older ineffective therapies or monotherapies that are partner drugs in ACT treatment, increasing the opportunity for antimalarial resistance but maximizing profits to the detriment of population health (Caudron et al., 2008; O'Connell et al 2011; Warsame et al 2010). The WHO requested pharmaceutical companies to cease production of artemisinin-derived monotherapies after implementation of ACT; however, only 13 of the 23 companies agreed (Bassat & Alonso, 2010; O'Connell et al., 2011). Private sector pharmaceutical markets are unregulated in developing countries and are not legally bound to adhere to WHO guidelines to remove monotherapies that are still generating profits by exploiting the high demand for inexpensive therapies (Newton et al., 2010; Osamor, 2010). In Cameroon, despite partial government subsidies for ACT, monotherapies actively marketed by the pharmaceutical industry remain in the state supply chain through private pharmacies (Ongolo-Zogo & Bonono, 2010). Even if pharmaceutical companies withdraw monotherapies, there is still a market where other companies exploit purchasers by manufacturing substandard or contraindicated products (Newton et al., 2010; Osamor, 2010).

It is the absence of regulatory measures to remove expired or non-recommended drugs that ensures accessibility at affordable prices, but if these drugs are removed from the market it simultaneously denies access to life-saving treatments that are otherwise unaffordable (Caudron et al., 2008; Newton et al., 2008; Okeke et al., 1999; Ongolo-Zogo & Bonono, 2010). A government-implemented ban to remove the popular and affordable CQ from the informal sector in Kenya and Nigeria was suggested; however, this prompted protests from healthcare workers and individuals due to the high cost of ACT and limited availability of this treatment (Bassat & Alonso, 2010; Osamor, 2010). Similarly, healthcare workers' perceptions also influence whether frontline treatments are implemented. Seventy-six percent of providers in Nigeria continued to use CQ despite the mandate to discontinue its use as a monotherapy, as ACT was argued to be unaffordable to patients (Udezi & Oguagbaka, 2011). Accordingly, there is a strong incentive for individuals to choose inappropriate and ineffective antimalarials given the significant costs of treatment, further proliferating inexpensive therapies.

The Global Threat of Antimalarial Resistance

Antimalarial resistance is a response to systematic breakdowns in sub-Saharan Africa's health infrastructure, where the global pharmaceutical market, regulatory, and trade regimes subsequently influence drug resistance (Newton et al., 2008; Nugent et al., 2008). The contribution of counterfeit and substandard drugs is significant in driving antimalarial resistance in sub-Saharan Africa. Accelerated drug resistance is evident due to weak drug regulation bodies, poor management of the supply chain (e.g., informal sector drug availability contravening national guidelines or counterfeit drug presence), lack of knowledge or training among providers, and insufficient resources to provide drug monitoring and surveillance (Amin et al., 2007;

Caudron et al., 2008; Nugent et al., 2008). It is a fundamental challenge for sub-Saharan governments to control the spread of antimalarial resistance by regulating the private or informal sector (Bloom et al., 2011; Osamor, 2010).

Accordingly, access to affordable drugs and adherence to treatment regimes are compromised by the market for health commodities in developing countries without a concomitant strengthening of infrastructure to support an efficient regulatory environment (Newton et al., 2010; Nugent et al., 2008). In this context, the inappropriate use of antimalarials can have widespread consequences due to the transboundary nature of drugs (Newton et al., 2010; Nugent et al., 2008). The rapidity by which antimalarials are rendered ineffective by increasing parasite resistance is critical, as the rate of drug loss is not matched by the rate of replacement into the health market (Bassat & Alonso, 2010; Warsame et al., 2010).

High failure rates of ACT in Southeast Asia have consequences for Africa, as resistance historically originating in Southeast Asia migrates to Africa (Maude, Woodrow, & White, 2010; Rogers et al., 2009). The independent evolution of CQ and SP resistance in Southeast Asia, during the 1950s and 1970s respectively, eventually spread to Africa in the 1980s and 1990s, eliminating previously effective antimalarials (Maude et al., 2010; Rogers et al., 2009; Talisuna et al., 2004). The relationship between counterfeit or substandard drugs and resistance is a challenging issue; however, it is acknowledged that there is significant risk if resistance reaches Africa (Burki, 2010; Newton et al., 2008). The absence of a drug regulatory authority to control the quality of drugs entering and being distributed in sub-Saharan Africa, the limited government and health infrastructure, and the unregulated informal market combine to create an ideal environment for the rise of antimalarial drug resistance.

Conclusions

The availability and accessibility of essential medicines determines the degree to which sub-Saharan Africa can successfully confront the morbidity and mortality of malaria by focusing on initiatives to address inherent vulnerabilities in healthcare infrastructure. The prominence of substandard and counterfeit drugs due to international economic and trade policies renders antimalarial treatments cost-prohibitive and constrains treatment seeking to the informal sector. The absence of sufficient research and development into priority diseases further contributes to a multidimensional challenge of inequitable access, enabling the irrational consumption of antimalarials and driving global malaria resistance.

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