HEALTH COMMUNICATION CAPACITY COLLABORATIVE

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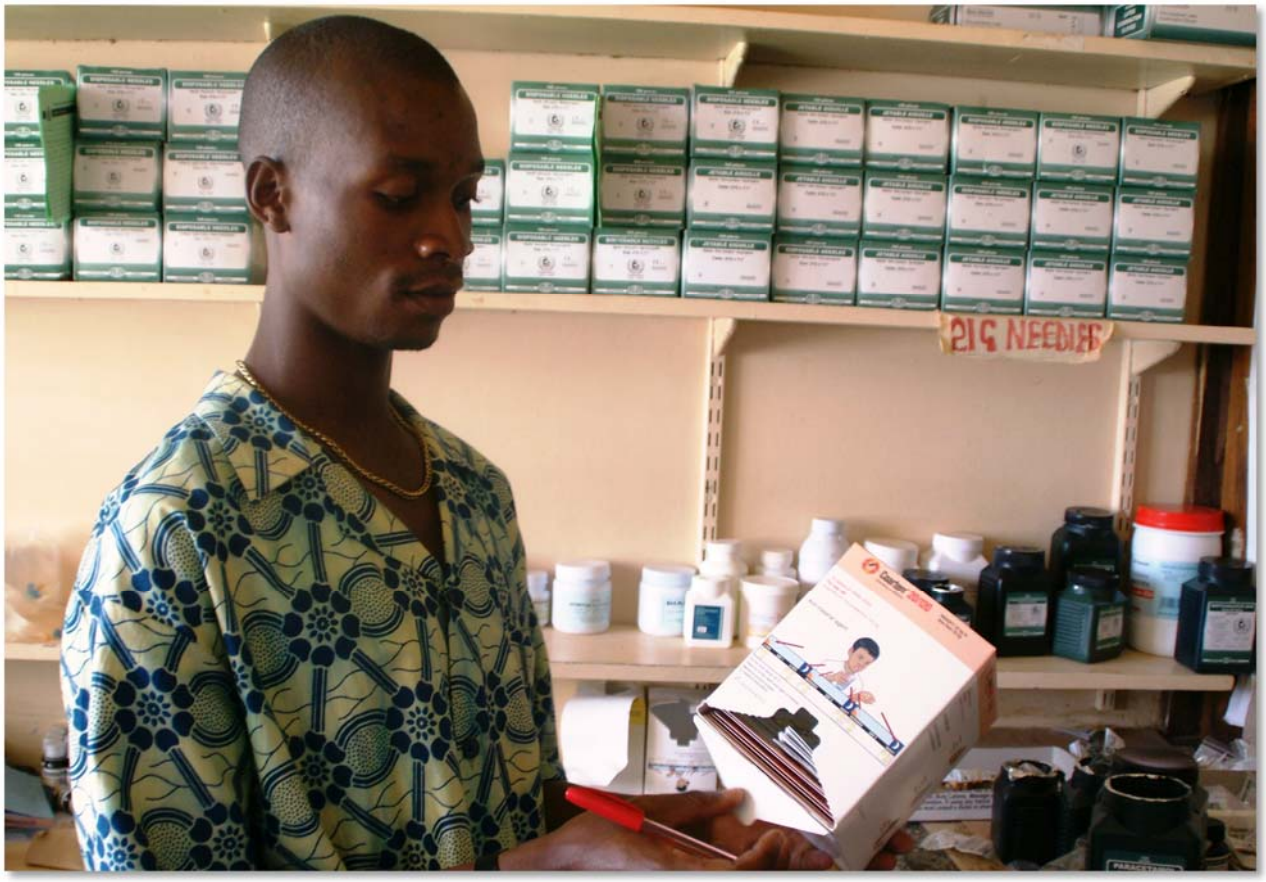
U.S. President's Malaria Initiative

Global Landscape of Antimalarial Medicines

Global Situational Analysis of Substandard and Falsified Antimalarial Medicines



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Acronyms

ACT	Artemisinin-based Combination Therapy
AMFm	Affordable Medicines Facility-malaria
API	Active Pharmaceutical Ingredients
CePAT	Center for Pharmaceutical Advancement and Training
FDA	U.S. Food and Drug Administration
IMPACT	International Medical Products Anti-Counterfeiting Task Force
GPHF	Global Pharma Health Fund
GMP	Global Malaria Programme
JIATF	Joint Inter-Agency Task Force
MQDB	Medicines Quality Database
PSI	Pharmaceutical Security Institute
PQM	Promoting the Quality of Medicines
SSFFC	Spurious, Substandard, Falsified, Falsely-Labeled and Counterfeit Medicines
SRA	Stringent Regulatory Authorities
RAS	Rapid Alert System
USP	U.S. Pharmacopeial Convention
WHO	World Health Organization
WHO PQP	World Health Organization Prequalification Programme
WWARN	WorldWide Antimalarial Resistance Database
USAID	United States Agency for International Development
UNODC	United Nations Office on Drugs and Crime

Introduction

Malaria is a preventable and treatable disease that affects almost half of the world's population. Fortunately, the massive scale-up of malaria prevention and treatment programs has improved the global malaria burden – contributing to a 37 percent global reduction in malaria incidence (42 percent in Africa) and 60 percent global reduction in malaria mortality between 2000 and 2015 (World Health Organization or WHO, 2015a). Access to safe and effective antimalarial medicines is a central component of current evidence-based malaria strategies (WHO, 2011). As such, increased donor efforts have been used, in part, to increase availability and accessibility of artemisinin-based combination therapy (ACT), resulting in an ACT procurement increase from 11 million to 392 million between 2005 and 2013. In 2013, 70 percent of patients with malaria who sought care were treated with ACTs (WHO, 2014b).

Unfortunately, this progress is threatened by the widespread availability of poor quality malaria medicines – or "SSFFC" medicines, an acronym for the comprehensive term "substandard, spurious, falsified, falsely-labeled, and counterfeit." In some cases, SSFFC medicines – whether generic or brand name – do not meet the legal standards determined by manufactures and regulators. In other instances, they carry a false representation, identity or source (Institute of Medicine or IOM, 2013). Poor quality medicines are pervasive throughout Africa and Asia, and cause undue harm by contributing to treatment failure, growing artemisinin drug resistance and, in some cases, death (WHO, 2011; Bate et al., 2012).

While estimates around the prevalence of poor quality antimalarials vary depending on sampling and analytical methods, a recent meta analysis of quality medicine surveys from 21 countries in sub-Saharan Africa show that "35 percent of samples failed chemical analysis" (Bassat et al., 2016; Nayyar et al., 2012). Malaria medicines are particularly at risk for quality issues and represent the medicine type with the highest quality failure rate in a recent U.S. Pharmacopeial Convention (USP) Medicines Quality Monitoring study in Africa, Asia, and South America. An analysis of the medicine samples collected between 2003 and 2013 that were listed in the Medicines Quality Database (MQDB) found that 56.4 percent of all failed samples (i.e., products considered substandard, counterfeit, expired, or those which failed the visual inspection) were antimalarials, which accounted for 6.5 percent of the failure rate, when calculated in proportion to the amount of antimalarials sampled. Antimalarials also represented 52.5 percent of all substandard medicines and 92.6 percent of all counterfeit medicines. (Hajjou et al., 2015).

Substandard, Falsified and Degraded Medicines

The debate around substandard and falsified medicines includes a wide-spectrum of fields, which is demonstrated by the range of terms used to describe them (e.g. adulterated, misbranded, deteriorated, unregistered, spurious, substandard, falsified, falsely-labeled, fraudulent, unregistered, counterfeit, fake, SSFFC, etc.). While there is no universal way to define medicines quality, quality medicine is generally defined as meeting the correct amount of active pharmaceutical ingredient (API) and passes other quality specifications (for example: visual inspection). Poor quality medicine tends to fall into three overlapping categories (Nayyar et al., 2015, Kaur et al., 2015):

- **Substandard:** Medicine that does not contain enough active ingredient due to unintentional errors caused in manufacturing
- **Falsified:** Medicine that does not contain enough or any active ingredient due to intentional fraudulent manufacturing, may carry false reputation of their source or identity.
- **Degraded:** Medicine that does not contain enough active ingredient due to poor conditions due to storage environments, handling, or transportation (light, heat, humidity, etc.). Stolen or diverted medicine at risk of becoming degraded.

For the purposes of this document, poor quality medicines will be referred to by the comprehensive term SSFFCs (Mackey and Liang, 2013; IOM, 2013). However, practitioners should take note of the differences between substandard, falsified, degraded and diverted medicines, as they each have different policy and programmatic recommendations.

SSFFCs as a Public Health Risk

SSFFC malaria medicines are comprised of a range of ingredients, ranging from ineffective doses of the right ingredient, inactive ingredients and toxic ingredients (Mackey and Liang, 2013). All threaten patients' health by leading to treatment failure, and in some cases, death (WHO, 2012; Kaur et al., 2016). While the full impact of SSFFC malaria medicine cannot be measured, it is estimated that "122,350 deaths in children under 5 years of age in 39 sub-Saharan African countries were associated with the consumption of poor quality antimalarials," accounting for approximately four percent of under-five deaths in sampled countries (Renschler et al., 2015).

Moreover, under dosing with SSFFCs can cause a low concentration of active drugs and result in parasite resistance to artemisinin (IOM, 2013 ; Kaur et al., 2016), which is particularly concerning as artemisinin-based combination therapy (ACTs) is the current first line treatment for malaria and no alternatives are expected to enter the market in upcoming years. As of February 2015, researchers have already detected parasite resistance to artemisinin in five countries around the Greater Mekong sub-region: Cambodia, Laos, Myanmar, Thailand and Vietnam. Increased instances of resistance, particularly multi-drug resistance, could lead to a spike in global malaria mortality rates (WHO, 2014a).

SSFFC malaria medicine is not only a wastes individual consumers' income, but also global and national funds (Bassat et al., 2016). With an estimated 10 to 25 percent of global spending lost to corruption (WHO, 2008), SSFFCs are an inefficient use of the limited money allocated to malaria. In some cases, countries waste money by paying for effective medicine, but substandard and falsified medicines from the start. In other instances, good quality medicine is made ineffective through the conditions medicine endures when it is diversion. While the global community is still learning the extent to which their medicines are diverted, U.S. investigate that "20 percent of donor-funded Coartem in Africa may be diverted each year – with a street value of about $60 million (USD)." Another 2010 study found that 6.5 percent of malaria medicines from informal markets in 10 African cities were stolen from other sources (Bate, 2013).

Finally, SSFFC malaria medicines should be considered a public health issue because increased morbidity and mortality even after "treating malaria," as well as artificial stock outs due to corruption or diversion, may negatively affect the public's perception of the quality of their health care and treatment options, as well as subsequently influence healthcare-seeking behaviors (WHO, 2011; Nayyar et al., 2012).

Risk Factors and Prevalence of SSFFCs

SSFFC malaria medicines are a truly global issue, demonstrated by a Pharmaceutical Security Institute (PSI) study from 2011, which identified 124 countries affected by illegal trade and manufacturing of medicines (IOM, 2013). While poor quality drugs can be found in developed and developing countries alike, their presence is most felt in parts of Africa and Asia where regulatory and enforcement systems for medicines are weak or in transition (WHO, 2012). A number of additional factors are associated with the production and sale of poor-quality antimalarials around the world, including "the inaccessibility and high price of quality ACTs, limited regulatory oversight, lack of penalties, self-prescribing practices, poor knowledge about product authenticity, demand for low-cost drugs, and a large unregulated private sector for purchasing pharmaceuticals," (Renschler et al., 2015). Similarly, some of the highest pharmaceutical producers are housed in countries with these risk factors – China, India, Pakistan, Vietnam, Ghana, Kenya, Nigeria, Togo, Uganda and the United Republic of Tanzania (WHO, 2010). According to Nayyar et al., "one of the biggest obstacles in the provision of quality-assured pharmaceuticals is the lack of effective manufacturing, regulator and quality processing in India and China," which are also two of the largest producers of good quality drugs and vaccines (Nayyar et al., 2015).

While estimates around the prevalence of poor quality antimalarials vary depending on sampling and analytical methods, a recent meta-analysis of quality medicine surveys from 21 countries in sub-Saharan Africa show that "35 percent of samples failed chemical analysis" (Bassat et al., 2016; Nayyar et al., 2012). In 2008, a WHO survey of ACT and SP samples from six countries in sub-Saharan Africa found that 28.5 percent of samples did not meet WHO quality requirements, and considered 11.6 percent of the samples as "extreme deviations…likely to be associated with negative health outcomes. Another 2011 study focused on six-countries in sub-Saharan Africa, 30 percent of antimalarial samples failed to comply with quality standards. Results ranged from Kenya and Tanzania, which were found to be reasonably under control, to Nigeria, which had the highest failure rate at 63.9 percent (WHO, 2011).

However, recent quality assurance results reveal that the prevalence may be closer to one in ten medicines, and that the problem is more substandard and degraded medicines than diverted. The ACT Consortium at the London School of Hygiene and Tropical Medicine tested samples selected from areas of Tanzania, Cambodia and Nigeria and found no falsified drugs, but a significant amount of substandard (31 percent in Cambodia, 12 percent in Tanzania and 9.3 percent in Nigeria) (ACT Consortium, 2015a, 2015b; Kaur et al., 2015; Yeung et al., 2015). Tabernero et al. (2015) also recently repeated a 2003 study conducted in Laos around the availability and quality of antimalarials, and found that "all samples contained the correct active pharmaceutical ingredients" (APIs) – a vast improvement compared to the 2003 results (where 84 percent of artesunate samples were falsified). Researchers did, however, find that 25.4 percent were substandard or degraded (Tabernero et al., 2015).

Malaria medicines are particularly at risk for quality issues and represent the medicine type with the highest quality failure rate in a recent U.S. Pharmacopeial Convention (USP) Medicines Quality Monitoring study in Africa, Asia and South America. An analysis of the medicine samples collected between 2003 and 2013 that were listed in the Medicines Quality Database (MQDB) found that 56.4 percent of all failed samples (i.e., products considered substandard, counterfeit, expired or those which failed the visual inspection) were antimalarials, which accounted for 6.5 percent of the failure rate, when calculated in proportion to the amount of antimalarials sampled. Antimalarials also represented 52.5 percent of all substandard medicines and 92.6 percent of all counterfeit medicines. (Hajjou et al., 2015).

Furthermore, researchers have determined that where a consumer buys their medicines affects their risk of buying SSFFC malaria medicines. A 2013 study found 51 percent of medicines sampled from unlicensed outlets were substandard or falsified – a significant difference from the 24 percent of medicines sampled from licensed outlets. This finding is based on five studies: four out of five studies concerned antimalarial medicines (medicines sampled from sub-Saharan Africa and Cambodia) and one concerned antibiotics (medicines sampled from Myanmar and Vietnam) (Almuzaini et al., 2013). Surveys and drug seizure reports also provide evidence of artesunate monotherapy circulation in sub-Saharan Africa and Southeast Asia. These medicines are of concern, not only because they are no longer the first-line treatment for malaria, but also due to the fact that they are primarily purchased by adults buying from the informal sector (patent and proprietary medicine vendors), where medicines are at higher risk of degrading (Bassat et al., 2016).

Despite the numerous medicine quality studies that have and are being conducted, the variances in data sources and sampling make it difficult to compare results (Almuzaini et al., 2013). The lack of quality reports and limited access to adequate analysis methods also creates challenges for the global prevalence and impact of SSFFC medicines (Tabernero et al., 2014).

Public Awareness of SSFFC Malaria Medicines

Limited information is available on the extent to which residents of malaria-affected countries are aware of substandard and falsified medicines, but the evidence shows that awareness is suboptimal (Bassat et al., 2016). General knowledge seemed to be relatively low in the early 2000s, but awareness campaigns from groups like the International Medical Products Anti-Counterfeiting Task Force (IMPACT) has helped (IOM, 2013). A 2010 Gallup poll revealed that the majority of the public in 15 of the 17 sub-Saharan African countries surveyed were aware fake medicines were a problem – not only SSFFC malaria medicines. Results ranged from South Africa (25 percent) and Botswana (32 percent) to Nigeria (83 percent), Sierra Leone (83 percent) and Cameroon (91 percent) (Ogisi, 2011). Generally speaking, well-educated urban consumers are the most aware of SSFFC medicines, and take precautions to avoid them. Consumers living in remote areas without registered pharmacies or with less financial resources are the least aware. Even if they are aware, they are often not in the position to take precautions, because they have no choice but to buy from open markets or they do not have enough money to buy from a registered pharmacy (IOM, 2013). A 2010 IRIN Africa interview with a Togoloese vendor demonstrates the normalization of poor quality medicine, as well as the barriers to reducing risk of buying good quality

medicine: “This is what I and my family have always used, and we have never had a problem… I cannot afford medicines in the pharmacy. So the day the authorities eradicate the street market they will be signing our death warrant” (IRIN, 2010). Raising awareness about SSFFC malaria medicine is especially key given the high rates of self-prescription/treatment seeking without first consulting a health provider (Bassat et al., 2016).

Current Efforts to Combat SSFFCs

Quality Assurance

Quality Assurance Policies and Protocol

The WHO estimates “30 percent of countries lack any capacity to oversee medicine manufacture, importation or distribution” (Renschler et al., 2015). However, a number of activities are being conducted to improve these mechanisms, as well as the prevalence and impact of SSFFCs. Many of the major international health organizations, for example, have established quality assurance policies to ensure that they are purchasing their medicines from standardized and legitimate sources. In 2010, the WHO and Global Malaria Programme (GMP) supported programs by releasing the *Good Procurement Practices for Artemisinin-based Antimalarial Medicines* in 2010 (WHO GMP, 2010). The WHO promotes and utilizes two approval systems: **WHO Prequalification Programme** (WHO PQP) and **Stringent Regulatory Authorities** (SRAs). In the WHO PQP system, manufactures are invited to submit “expressions of interest’ for producing [medicines] that are considered priorities for evaluation by WHO.” WHO PQP personnel then conduct a standardized product assessment and publicize findings on its website (WHO GMP, 2010). According to the SRA protocol, regulatory authorities register a product for limited release and then reassess it. Should experts determine that the product is acceptable, they may authorize it for an unlimited period (WHO GMP, 2010). Theoretically, Global Fund to Fight AIDS, Malaria and Tuberculosis will only approve a product if it has passed the WHO PQP or SRA process; however, they sometimes rely on panels of experts in situations where neither option is available (WHO GMP, 2010). The United States Agency for International Development (USAID) requires from either the U.S. Food and Drug Administration (FDA) or SRA (IOM, 2013).

While the prequalification process is lengthy (a minimum of 2 months), the program is effective. A 2008 study found that pre-qualified medicines met quality standards more often than non-prequalified medicines (3.6 percent of prequalified samples failed standards, compared to 60.4 percent of non-prequalified samples) (WHO, 2011; Bassat, 2011).

Quality Assurance Strengthening

A number of technologies have been developed to protect consumers from products that may have slipped through the procurement process, or may have never been assessed in the first place. **Mobile verification technologies**, produced by companies like mPedigree, Sproxil and PharmaSecure, allow

consumers to confirm the quality of a particular medicine by texting a hidden serial number found under a scratch-off surface. Upon texting the company, consumers immediately receive a response via short message service (SMS), letting them know if the code is linked to a registered manufacturer (IOM, 2013). A number of recently developed technologies could also be used by drug regulation, quality assurance and law enforcement specialists inspecting medicine quality, including the Global Pharma Health Fund (GPHF) Minilab, TruScan™ RM Analyzer (Raman spectrometer), counterfeit detection device (CD-3), chemical color tests cards, counterfeit drug indicator (CoDI), track-and-trace packaging design and colormetric assays. However, further work must be done on many of these devices before they will be validated, affordable and scalable (GPHF, 2014; GPHF, 2015; USP Convention, 2015b; Bassat et al., 2016).

A number of global organizations are working to improve malaria medicines quality assurance and information dissemination. For example, the **WWARN Quality Assurance/Quality Control program** supports local laboratories to strengthen their assay quality. The **ACT Consortium** focus one of its four research themes on quality of medical products and has conducted a series of quality assurance studies in several countries (Bassat et al., 2016). **ACTwatch** also conducts nationally representative surveys to assess antimalarial quality and availability, using outlet surveys, supply chain studies and household surveys to determine trends within the public and private sector (ACTwatch, 2016)

Additionally, the Promoting the Quality of Medicines (PQM) program provides technical assistance to quality assurance testing sites to promote sustainable local surveillance capacity in USAID-supported countries (The Lancet, 2015; USPP Convention, 2015a). At the time this document is being developed, the PQM program has donated approximately 180 **Global Pharma Health Fund (GPHF) Minilabs™** (GPHF, 2014; GPHF, 2015; USP, 2015b). USP-Ghana also launched the Center for Pharmaceutical Advancement and Training (CePAT), which offers programs to educate and strengthen the capacity of medical regulatory officers on a variety of topics (e.g. dossier evaluation, medicine registration, good manufacturing practices and pharmaceutical control, etc.), and trained 125 participants from nine African countries in its first year. CePAT is currently conducting field tests for the aforementioned **CD-3** device (Nayyar et al., 2015; USP Convention, 2015b). CD-3+ field tests will evaluate its ability to detect SSFFC ACTs, along with two previously developed devices, the GPHF Minilab™ and TruScan™ RM Analyzer (USP Convention, 2015b).

The **Global Health Assurance Partnership (GHAP)** also provides technical assistance and capacity building to national government agencies mandated to respond to pharmaceutical crime. The GHAP was created to expand upon the success of the previous Joint Inter Agency Task force (JIATF). JIATF emerged as a Global Fund-established Special Initiative designed to proactively address the challenge of illicit medicines using a data-driven approach. GHAP offers three core services: Market Assurance Reviews (MARs) providing a detailed picture of the scope and scale of stolen and falsified medicines within a particular country; Supply Chain Assurance Reviews (SCARs) providing end-to-end assurance that subject supply chains are conforming without leakage; and Technical Assistance and Capacity Building to enable National Medical Regulatory Agencies (NMRAs) and other national specialist agencies (GHAP).

Surveillance and Monitoring Systems

Lack of effective surveillance creates major barriers to combatting SSFFC malaria medicines, as mandatory reporting and routine quality assessments make it difficult to know the scale of the problem, identify areas to strengthen the supply chain, and advocate for solutions (Bassat et al., 2016). Bassat and colleagues argue that this is especially the necessary given the current "globalized marketplace [where] medical products can be manufactured in one country, packaged in another, and supplied to others with limited international oversight of manufacturing, testing, or storage practices for legitimate medicines or the introduction of deliberately falsified products into the supply chain (Bassat et al., 2016).

While there is not one universal tracking and reporting system for cases of SSFFCs, a number of organizations run surveillance activities and can notify key players when necessary. For example, in 2010 WHO launched the **Rapid Alert System** (RAS), a web-based communication network that alerts focal persons of member countries and partner organizations. Once confirmed, a WHO moderator informs RAS members of the incident and also incorporates the information into a database (WHO, 2005). The **Rapid Alert Form** created a system to provide WHO with the information it needed to conduct an initial risk assessments about suspected products. For example, in March 2013, WHO was able to issue a drug alert about an antimalarial medicine circulating around Western and Central Africa, which contained no active ingredients and was branded as a WHO prequalified drug and a part of the Global Fund Affordable Medicines Facility-malaria (AMFm) program (Quality and Safety of Medicines, 2013). The **Medical Product Alert System** is a voluntary tool that helps disseminate information about incidents of SSFFC medicines. It has received over 1,000 reports since it began in 2013 (Bassat et al., 2016).

Additional databases include those created by PSI, WorldWide Antimalarial Resistance Network (WWARN) and USP. **PSI's database** allows all major drug companies to report any poor quality medicine cases detected by their surveillance operations (The Lancet, 2011; IOM, 2013). **WWARN's Antimalarial Quality Surveyor** is a visual systematic review of quality medicines reports, which uses Google Maps technology (Tabernero et al., 2014). Lastly, **USP's MQDB** is a public online tool that houses the results of quality testing conducted in Latin America, Southeast Asia and Africa. The database is a part of the USAID/USP PQM program, and is, in principle, updated biannually. This system is limited because it features USAID-priority countries; however, quality reports are based on standardized guidelines, which provide the benefit of allowing practitioners to compare data across study sites and countries. It also includes samples from public, private and informal sectors (i.e. unlicensed facilities), so findings are more representative of the local market (Krech et al., 2014).

Communication and Advocacy

Combatting SSFFC malaria medicines requires education and advocacy efforts that reach the general public, as well as key players. To this end, the WHO started IMPACT to build coordinated networks to combat the production, trade and selling of SSFFC medicines (WHO, 2015b). In partnership with IMPACT, the World Health Professions Alliance (WHPA) created the "BE AWARE Toolkit for Health Professionals: Helping to Fight Counterfeit Medicines, Keeping Patients Safer," to raise awareness of substandard and falsified medicines among health professionals. The kit includes recommendations to

help doctors talk to their patients about falsified medicines and the precautions they can take to protect themselves, a reporting form to report any suspected substandard medicine, an inspection checklist to help assess medicine quality, an information leaflet to share with other health professionals, and a leaflet/poster for patients (World Health Professions Alliance, n.d.).

Some global organizations have created and implemented communication activities to raise public awareness of SSFFCs. The International Criminal Police Organization (INTERPOL) "Proud to Be," campaign features a song by Yvonne Chaka Chaka and Youssou N'Dour that warns listeners about potential bad medicines circulating in their countries (IOM, 2013). Many of these campaigns put the ownership on the consumer by asking them to "come together against the fakes" or "not buy fakes." This may not be an appropriate ask, given how advanced SSFFC malaria medicines manufacturers can be and how difficult it can be to differentiate SSFFCs from quality medicine. The United Nations Office on Drugs and Crime (UNODC) also created a brochure for consumers called "Counterfeit: Don't Buy into Organized Crime," which promotes considering the price, checking for a guarantee or after-sales service, checking the quality of the packaging, considering the drug location and source, and looking at the official company's website to see if they list licensed retailers. However, these are for all counterfeit products, including automotive parts, electrical components and toiletries (UNODC, 2015). Fight the Fakes is an advocacy campaign against SSFFCs that provides resources for healthcare professionals, government and policymakers, media, and patients. The campaign lists a number of broad recommendations for consumers, which are not specific to antimalarials or a geographic area/ audience. These messages include: speaking with your doctor or pharmacist if you experience side-effects, paying attention to the taste and smell of medicines, contacting authorities if you notice suspicious cases or notice an anomaly on the packaging, only purchasing medicine from sources that require a prescription, and being wary of low prices (Fight the Fakes, 2015).

Criminal Investigation

Several organizations have conducted work on the criminal investigation and law enforcement issues surrounding SSFFC malaria medicines, including UNODC, World Customs Organization (WCO) and INTERPOL. For example, INTERPOL's Pharmaceutical Crime Programme has several operations to identify and disrupt transnational and criminal networks involved in pharmaceutical crime, including Operation Pangea (online illegal medicines), Mamba (Eastern Africa), Storm (Southeast Asia), Cobra (Western Africa), Giboia (Southern Africa) and Porcupine (specific sales in West Africa). Operation activities (primarily raids) have resulted in improved seizures, arrests and convictions. More specifically, Operation Cobra contributed to over 100 arrests (unlicensed street vendors and suppliers) and the closure of a number of outlets unauthorized to sell pharmaceutical products (INTERPOL, 2015a.) INTERPOL also offers e-learning courses for staff and partners to improve skills and knowledge (INTERPOL, 2015b).

The USAID Office of Inspector General (OIG) has also launched the "Make a Difference" (MAD) Malaria campaign in Benin, Nigeria and Malawi to solicit the involvement of local communities in the fight against SSFFC malaria medicines. The MAD Malaria campaign's main objective is to obtain actionable information concerning the theft, transshipment, resale or falsification of antimalarial medicines and

commodities within the USAID President's Malaria Initiative (PMI) funded countries. A central feature of the campaign is the toll-free MAD malaria hotline that allows community members to report information on distributors, sellers and manufacturers of stolen or counterfeit malaria commodities. Relevant and actionable information from individuals merits cash rewards. The overall aim of the MAD Malaria campaign is to enhance the integrity of PMI programs and incentivize citizens to participate in strengthening and protecting malaria programs within their countries.

Case Studies

While this document primarily features global activities to reduce the impact of SSFFC medicines, there are a number of notable country-specific programs that have been shown to improve medicine quality.

AMFm	In 2010, the Global Fund launched the **Affordable Medicines Facility-malaria** (AMFm) program, a multi-country pilot to expand access to and use of effective and afforable ACTs. AMFm's strategy worked on three levels: price reductions through manufacturer negotiations, buyer subsidy through co-payments and support for country-level interventions to promote appropriate use of ACTs. Evaluations found that all of the pilot countries (Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda and Tanzania) except Niger and Madagascar experienced substantial increases in the availability (25.8 to 51.9 percentage points) and market share (15.9 to 40.3 percentage points) of quality-assured ACTs (Tougher et al., 2012).
NAFDAC	In 2001, it was estimated that 40 percent of medicines circulating around Nigeria were substandard or fake (Bate et al., 2009; Ogundipe, 2011). Driven by this stark situation, the **National Agency for Food and Drug Administration and Control** (NAFDAC) took a hard stance against SSFFCs – retraining NAFDAC staff, establishing more NAFDAC state offices, refurbishing drug analysis laboratories, enforcing stricter drug regulations and conducting activities to raise public awareness. These activities were associated with a signifiant reduction in the presence of SSFFCs, which had sustainable effects. A 2015 study found that only 10.1 percent of ACTs sampled in Nigeria to be SSFFCs (Lettenmaier, HC3 Trip Report 2015).
ADDO	In 2001, Tanzania faced a nation-wide problem in drug availability, price and quality (primarily in the private sector). To this end, the Ministry of Health and Social Welfare and the Tanzania Food and Drug Authority began “duka la dawamuhimu,” an **accredited drug dispensing outlet (ADDO) program** to improve access to quality drugs and increase shopkeeper health education. The program, which helped increase ACT sales from three percent of all antimalarials to 26 percent in less than a year, provided trainings, incentives and regulation efforts for shopkeepers. Program evaluators attributed the program's success to its emphasis on community engagement and outreach from the beginning (Rutta et al., 2009 and 2011).
Rwanda Minitry of Health	Research repeatedly finds Rwanda has either an absence or lower presence of SSFFCs. Experts credit **Rwanda's strong public health supply chain and regulation system**s for this success – especially the mandate that only manufacturers with current WHO-approved certificates can receive contracts with the Ministry of Health (MOH). The country also created "Guidelines for Pharmacovigilance and Medicine Information System in Rwanda," formed pharmacovilance sub-committees at all health centers and trained health workers on reporting guidelines. Quality control tests are also conducted on every imported drug shipment and ACTs are systematically tested at every health sector level on a quarterly and annual basis (Binagwaho et al., 2013).

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