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Review Article

Impact of Substandard and Falsified Medicines on Public Health: A Review

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Abstract

Substandard and falsified medicines, which are caused by low-quality drugs, pose a serious global health threat, resulting in over a million patient deaths each year, reducing the effectiveness of medical treatment, contributing to drug-resistant infections, depleting national health resources, and endangering public health in both resource-rich and resource-poor countries. Poor-quality medicines are harmful to people's health, especially when they're antimicrobials used to treat infectious diseases in high-burden communities. As multinational manufacturing and distribution systems become more complicated, the problem of inferior and fraudulent medical products continues to develop. Because of this complexity, there is a greater chance of manufacturing errors or medicines degrading between the plant and the consumer. Legislation, manufacturing procedures, supply chain management, as well as detection and reporting mechanisms are all being used to combat substandard and fraudulent pharmaceuticals. In addition to these initiatives, from a social standpoint, pharmacists' resourceful placement in all businesses, as well as public health education and involvement, should be optimized. This literature evaluation is being undertaken as a pilot study to determine the impact and insights for future research in order to better understand the impact of inferior and counterfeit medicines.

Keywords: Falsified Medicines; Substandard Medicines; Public Health

Abbreviation

WHO: World Health Organization; API: Active Pharmaceutical Ingredients; IMPACT: International Medical Products Anti-counterfeiting Task Force; HICs: High Income Countries; LMICs: Low-middle Countries; NABP: National Association of Boards of Pharmacy; SSFFC: Substandard/spurious/falsely-labeled/falsified/counterfeit'; TRIPs: Trade-Related Aspects of Intellectual Property Rights; VIPPS: Verified Internet Pharmacy Practice Sites

Introduction

Drug counterfeiting is a global issue with serious and well-documented effects for global health and patient safety, including drug resistance and patient fatalities. This multibillion-dollar enterprise has little regard for geopolitical boundaries, endangering public health in both resource-rich and resource-poor countries [1].

The prevalence of inferior and fraudulent medical items in countries, as well as patient use of these products, threatens to hinder progress toward the Sustainable Development Goals. Such items could be of poor quality, dangerous, or ineffective, putting people's health at risk. As multinational manufacturing and distribution systems become more complicated, the problem of inferior and fraudulent medical products continues to develop. Because of this complexity, there is a greater chance of manufacturing errors or medicines degrading between the plant and the consumer. In practically every country, rising demand for medicines, vaccines, and other medical products, combined with weak supply-chain management and the rise of e-commerce, creates chances for counterfeit pharmaceuticals to enter the supply chain [2].

There is rising, however delayed, concern that most of the developing world's medication supply, particularly its anti-infective drug supply, is of poor quality. This is a huge public health issue since poor-quality medications are widely available in underdeveloped nations, resulting in preventable morbidity, mortality, and drug resistance [3]. Having clear criteria is essential for determining the severity of any disease or public health concern. Such definitions have been absent in the arena of inferior and fraudulent medical items. Words like "fake" and "counterfeit" have been used interchangeably by the media, the general public, and even some academic researchers. Previously, the World Health Organization (WHO) used the umbrella phrase "substandard, spurious, fraudulently labeled, falsified, and counterfeit medical products," however different Member States understood the categories differently [4,5]. Considering the aforementioned issues; herein, the impact, prevalence, and the mechanism of combating of the Substandard and Falsified medicines were reviewed and documented.

Methodology

The review was compiled using a variety of academic literature databases, including PubMed, Google Scholar, JSTOR, and Research Gate. The databases were chosen to include literature published from 2001 to 2019 on substandard and falsified medicines, including keywords such as falsified medicines; substandard medicines; counterfeit; fake; public health, impact.

Literature Search Results

Public health impact

The goal of the study was to see what was known regarding the influence of poor and falsified/counterfeit medical items on public health. To achieve this purpose, it would be helpful to estimate the percentage of medical items that may be harmful to one's health. At the individual level, health impacts might include mortality, disability, and/or increased illness, as well as broader implications for health systems.

Mortality and morbidity

In the literature there is an international consensus that counterfeit/falsified medicines pose a serious threat to both individual health and public health in general. The nature of these fraudulent drugs ranges from those containing wrong dosage of ingredients, wrong ingredients, or ingredients of low quality [6], the consumption of which may, at best, fails to help improve patients' condition, and at worst, cause avoidable mortality and morbidity and also drug resistance [7-9]. There is also counterfeit medicines have a disastrous effect on global health and on individual patient safety, including patient injury, no treatment, and death. Importantly, contamination of the global drug supply chain can also lead to antimicrobial resistance for diseases with a high global disease burden and mortality, such as malaria, HIV, and tuberculosis (TB) [10].

Any product containing a dangerous contaminant (including dangerously high levels of the expected API) will pose an immediate hazard to the individual taking it. Patients may also die, or suffer a longer bout of disease, if their condition goes untreated because the "medicine" they take contains no API, or the API is at sub therapeutic concentrations. However, the thresholds at which sub therapeutic products become threatening to health are not well established, and are likely to differ across products. When prophylactics (for example vaccines) are either substandard or falsified, they may leave people unprotected against future disease [2,8,11].

Disease prevalence

When infectious diseases are not prevented because prophylactic products are substandard or falsified, or when infections are not cured or controlled, disease prevalence is likely

to rise. Some literature says, in case of infectious disease the patient condition may get worsen even though he is taking the fraudulent drug. Similarly, in chronic conditions like erectile dysfunction, it may be an indicator of some other conditions like diabetes or atherosclerosis which may lost an opportunity to get diagnosed by the use of these drugs from black market. Over hundred children died in Nigeria in 1993 due to the harmful substance in the counterfeit cough syrup. Similar cases were reported in China and India in 1990-2007 and in panama due to ethylene glycol in cough syrup instead of glycerol. In 2002 more than 190,000 deaths occurred due to poly ethylene glycol contamination in paracetamol syrup [6,9].

Almost all drugs are counterfeited, but the commonly counterfeited medicines in developed countries were new, expensive lifestyle medicines, such as hormones, steroids, pills for erectile dysfunction and antihistamines [12,13]. However, in developing countries the most commonly counterfeited medicines are those which are used to treat life threatening conditions such as malaria, cancer, tuberculosis, HIV/AIDS, various antibiotics [13]. There are also adverse societal effects arising from the use of substandard drugs. The inadvertent use of suboptimal doses of drugs is likely to be one of the key factors contributing to antimicrobial resistance and thereby leading to the wider spread of disease [8].

Antimicrobial resistance

Substandard antimicrobials often contain low and erratic drug doses, while falsified ones can be diluted. In either case, exposing pathogens to sub therapeutic doses of medicines selectively allows the growth of resistant organisms. Poor-quality drugs have contributed to the rise of drug-resistant tuberculosis. Drug-resistant staphylococcus infections are an emerging problem, especially in India, Latin America, and sub-Saharan Africa. Antimalarial resistance threatens to undo the good that artemisinin therapies have done, threatening global malarial control programs [14].

The literature argues that, Antimicrobial resistance is driven in part by pathogens being exposed to sub therapeutic doses of treatments, which may be due to administration of substandard and falsified antimicrobials. In many cases the levels of the API are so low or nonexistent that the treatment will be ineffective [2]. Efforts at quantifying the link between substandard and falsified medicines and antimicrobial resistance have been both anecdotal and statistical, although predominantly focused on research on antimalarial. Based on field surveys, for example, Dondorp and colleagues have shown that 53% of antimalarial sampled in south-east Asia contained incorrect levels of the API [15].

At best, these medicines are ineffective; at worst, they injure patients by causing drug-resistant infections or death. In Africa, for example, substandard antimalarial cause drug resistance by exposing parasites to sub-lethal doses of active components [16]. Also counterfeit, substandard and falsified medicines pose a considerable threat to health. Although detailed knowledge of their prevalence and impact on human well-being is limited, they can fail to cure, promote antimicrobial resistance and ultimately kill [9,17].

Companies are confronted and colleagues estimated the human and economic consequences of antimalarial resistance at more than 116 000 deaths per year in another study [18]. One major area of concern is the growing number of substandard and falsified antimicrobials. The WHO Global Surveillance and Monitoring System reported that 42%of the 1,500 cases of substandard and falsified medical products reported between 2013 and 2017 were from the Africa region. Antibiotics and antimalarial were most commonly reported, representing around 36% of all the products reported by member states [19]. Suleman and colleagues believed that high prevalence of poor quality Mebendazole, Albendazole, and tiniidazole in Ethiopia: up to 45% [20].

Loss of confidence

A further potential effect of substandard and falsified medical products is the loss of public confidence in medication and in health systems. Where doubts about the quality of medicines lead people to stay away from particular health facilities, refuse vaccination for their children or fail to take treatment as prescribed, their health may suffer [9]. Substandard medicines also have social and economic effects, as they may reduce patients' confidence in their doctors, pharmacists, and even in modern medicines as a whole [21].

Pharmaceutical companies can be very guarded about the issue. Publicizing particular cases can lead to diminished sales because patients or doctors lose confidence in the quality of the brand [17].

Substandard or falsified medical products can moreover contribute to an erosion of trust if patients and households develop a suspicion or mistrust of health professionals, the health system and even other public institutions. This can result, for example, in patients forgoing treatment altogether or even seeking alternative treatment from unregulated outlets and/or care providers. Various stakeholders, from academics to policy-makers, have highlighted this as a significant consequence for health systems [9,14,22].

Socioeconomic consequence

Substandard and falsified medicines effect health directly and pose a danger to individual patients and to public health. They also have economic and social consequences, including the direct costs of additional treatment and indirect social costs of lost confidence in the health system and the government [14]. The most direct cost of substandard and falsified medical products to patients and their families is the money they spend on medical products that cause harm, or that do not work. Products that are toxic, or that fail to cure or prevent further disease, will certainly represent a wasted financial outlay. Toxicity, treatment failure, or infection resulting from failed prophylaxis may also lead to extra spending on health services and new medical products [2].

All of the above clinical and humanistic factors contribute to an increased economic burden, both on a national scale and to individuals. In some developing countries, up to 90% of the population have to pay for their medicines, and these costs can account for a large proportion of household income [23]. Paying for replacement or additional drugs, or for repeated courses of inadequate ones, may impose a severe economic burden on a household, especially if combined with loss of income due to illness. At a national level, the costs associated with inadequate or contaminated drugs may include those for lost productivity, in addition to increased direct healthcare costs if these are at least in part met by the state. As noted by Wertheimer and Norris, development of resistance secondary to the use of commonly available (often generic) drugs will necessitate the development of new, probably more expensive alternatives, thus further aggravating the economic burden of treating infectious diseases [24].

In many high-income nations, health insurance and other systems for achieving universal health care are well-established, lowering health spending from household budgets (also known as "out-of-pocket" spending). Several middle-income countries, as well as a few low-income countries, are increasingly adopting such systems. As a result, the percentage of out-of-pocket spending has decreased slightly. Although the decline has been most pronounced in low-income countries, individuals and families continue to take the burden of health-care spending in LMICs, accounting for roughly 37% of total spending, compared to 14% in high-income nations [14].

Poor quality medicine- how defines it?

Establishing the magnitude of any disease or public health challenge depends on having clear definitions. In the field of substandard and falsified medical products, such definitions have been lacking. The media, the general public and even some academic researchers have used words such as "fake" and "counterfeit", often interchangeably with other terms. The World Health Organization (WHO) previously used the catch-all term "substandard, spurious, falsely-labelled, falsified and counterfeit medical products", although the various terms were interpreted differently by different Member States [25]. Most controversially, the term "counterfeit" was sometimes used in some jurisdictions to refer to medicines that infringed patents or other intellectual property rights [2].

Such clashes are often caused by a second fundamental problem: the absence of a clear, internationally agreed terminology to define different sorts of legitimate or illegitimate medicine [11]. Everyone agrees that there are two categories of legitimate medicine on the market: proprietary medicines, which are initially marketed under patent, and generic medicines, which are lawful copies of the proprietary medicines either because in a given country the patents have expired or were never granted or because the manufacturer has a licence to use the patent. Despite price differences, both proprietary and generic medicines are produced according to good manufacturing standards, are properly regulated for quality, and can bear brands or trademarks [26].

For the illegitimate medicines, however, the situation is rather complex. In the literature, there are different terms used to refer to poor-quality medicines, such as counterfeit, substandard, falsified, spurious, degraded, fake, and falsely-labeled. Among them, the term "counterfeit" appears to be especially controversial [27]. However,

placing all illegitimate medicines under the SSFFC umbrella gives the misleading, mistaken impression that they are all deficient in the same way, when actually there are many possible deficiencies, each requiring different solutions [28].

In response to the global threat posed by substandard and falsified medicines, the 70th World Health Assembly introduced new terminology and definitions for the category of 'substandard/spurious/falselylabelled/falsified/counterfeit' (SSFFC). The new terms 'substandard', 'falsified' and 'unregistered medicines' were proposed to exclude 'counterfeit medicines' (the infringement of intellectual property) from the category. The introduction of global standardized definitions can be considered a crucial step towards developing and advocating interventions to combat substandard and falsified medicines [19].

The World Health Organization (WHO) defines a substandard medicine as an authorized medical product that does not meet quality standards or specifications, produced by a known manufacturer with no intent to fool or defraud the patient [19,28]. Substandard medicines enter the legitimate supply chain and reach patients when the technical capacity to enforce good manufacturing practices (GMP) and good distribution practices (GDP) is limited [19].

The WHO defines a falsified medicine as a medical product that is deliberately and fraudulently mislabeled concerning identity and source. Falsified medicines are produced in unsanitary and unregulated conditions by an unknown manufacturer. They can contain incorrect quantities of the active pharmaceutical ingredient (API), inert ingredients and dangerous contaminants. The packaging of falsified medicines is nearly always identical to the original medicine, making it challenging to identify without running a series of detection tests on the contents of the medicine [19]. Counterfeiting is an intellectual property concept, and should not be confused with issues concerning the safety, quality and efficacy of medicines. Specifically, they support the definition of counterfeiting contained in the TRIPS Agreement, with no amendments [29].

WHO definitions of substandard, unregistered/unlicensed and falsified medical products

For many years, the response to this important threat to public health was embroiled in a discussion of complex definitions that meant different things to different people. Reflecting this complexity, until May 2017, WHO used the term "substandard/spurious/falsely-labelled/falsified/counterfeit medical products". The WHO Member State mechanism on substandard and falsified medical products was tasked with revising these definitions to ensure that they were based on a public-health perspective, with no account taken of intellectual property concerns. Based on these deliberations, the World Health Assembly, which governs WHO, adopted the following definitions: [2,28].

Substandard medical products

Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or their specifications, or both [11,17,19,28].

Unregistered/unlicensed medical products

Medical products that have not undergone evaluation and/or approval by the national or regional regulatory authority for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation [11,28].

Falsified medical products

Medical products that deliberately/fraudulently misrepresent their identity, composition or source [28].

The Prevalence of the Problem

Literature shows the problem is growing, but its size remains unclear. The lack of reliable data has been widely acknowledged among international organizations and academia. It is estimated in an International Medical Products Anti-Counterfeiting Taskforce (IMPACT) report (2008) that over 30% of medicines in many African countries and some part of Asia are falsified. In areas which are heavily affected by infective diseases such as malaria, tuberculosis and HIV/AIDS, this figure goes even beyond 50% [30].

The phenomenon of drug counterfeiting was first identified as an emerging problem by the WHO in 1985 [13]. But, since then this problem has grown to a much larger extent with more than 10% of drugs globally are counterfeit, and in some countries the situation is even worse with more than 50% of the drug supply is counterfeit [13]. The problem of spurious drugs in India is a very common problem [31]. The developing countries are not merely the victims

of the problem, but also serve as the sources of fake drugs with India and China being the biggest culprit's globally. One statistic by the European Commission described India as the source of 75% of fake drugs and according to one report; most of the fake drugs in Nigerian markets originate from India. From January 1999 to October 2000, 46 reports of counterfeit drugs were received from 20 countries; 60% from developing countries and 40% from developed nations [13] .

Counterfeit medicines are found more in the drug markets of developing countries (10-50%) than in developed countries (1%) due to various reasons like poor regulatory control on drug market and economy of the population. That is in developing countries expensive drugs are available at a cheaper rate through black market. So public awareness about the consequences of consuming counterfeit medicine is the main factor in controlling the spread of these medicines in the market [6]. Although most of the manufacturing and trade in counterfeit medicines occurs in Asia, counterfeit medicines are pervasive worldwide. This hazard was evidenced by the Interpol counterfeit seizures in 2009, including 20million pills in China and Southeast Asia, 34 million pills in Europe, and hundreds of millions of dollars in counterfeit drug seizures in Egypt [10].

The European Union (EU) is particularly threatened by an influx of counterfeit medicines, especially those sold on the Internet. With estimates depicting annual increases of counterfeit sales of 15% per annum and one in five Europeans admitting they have purchased a prescription drug without a prescription, counterfeits have become a serious public health problem in this region [1]. Also other literature done, in the European Union, medicines are now the leading illegitimate product seized at the border, increasing 700% from 2010 to 2011 [and the seizures would be even higher, if the EU enforced more than just intellectual property violations] [32].

Indeed, the literature on counterfeits in resource poor countries is deeply concerning. Surveys and studies have shown that an estimated 30% of drugs sold in Kenya are counterfeit, that between 38% and53% of vital antimalarial drugs in mainland Southeast Asia are counterfeit, and that in several other cases, patients have been left untreated and died as a result of counterfeit vaccines that comprised only water or saline [9,33].The World Health Organization has estimated that over 10% of all drugs in the supply chain worldwide are counterfeit. Tragically in some countries counterfeit drugs make up more than 30% of the drug supply. It is estimated that drugs purchased over the internet are counterfeited in about 50% of cases [2].

The causes of the prevalence of substandard and falsified medicines

Reasons for the emergence and prevalence of falsified medicines differ from country to country and from region to region, due to a variety of political, economic, social and cultural factors. The most obvious difference is between rich countries and poor countries. In impoverished nations like Nigeria, the demand for affordable essential medicines is strong, but meanwhile we have to bear in mind that this is also a country where over 70% of medicines rely on importation and people have to live with chaotic distribution networks [34]. Nearly all kinds of medicines, Over-the-Counter (OCT) or prescription-only (POM), good-quality or poor-quality, are mixed together and can be found in open market, street vendors, public and private hospitals, and hawkers on motorcycles [34].

There are now more of these products, in part because the global demand for medicines, vaccines and diagnostic kits has grown so rapidly in recent years. The growing market has created new opportunities for unscrupulous traders, businesses, and criminals. By analyzing the database of cases reported to WHO as a whole it is possible to begin to identify patterns – clusters of factors and trends that allow the makers and sellers of substandard and falsified products to thrive [29]. Like any other commerce, the trade in substandard and falsified medical products depends on profit margins. It does best where demand is high, and where there is a shortage of supply; indeed, even very low-cost products are attractive as long as the potential sales volume is high enough. The trade is driven by an unpleasant combination of the ill-informed, the careless, the unprincipled and the criminal, so it thrives in places where the technical capacity is poor and the risk of detection is low [29].

Constrained access to affordable, safe and quality medical products

Medical products that are falsified or poorly made find their easiest access to the market when they fill a vacuum. That vacuum

often arises when people need or want medicines that they cannot obtain or afford. The price of a medical product is an important consideration for many patients and their families, especially if it is not sufficiently covered by insurance or by a national health system, and if people have to pay for it out of their own pockets. If a good quality medicine from a known supplier is too expensive, people may try a cheaper one, bought from an unlicensed supplier, in a street market or over the Internet [29]. Avastin, a trademarked brand of the cancer medicine bevacizumab was widely used in the United States to treat many types of cancer, including advanced breast cancer, at a cost of around US$ 2400 per injection. In November 2011, following a review of new clinical trials that showed no real benefit for breast cancer patients [35], the United States medicine regulator (US FDA) decided that the manufacturer should no longer sell it for that use. Several health insurance companies changed their policies to match, saying they would not cover the cost of the medicine for new users. But some women and their doctors still wanted to use it [14,36].

High prices are not the only reason that people have difficulty obtaining the medical products they need. This section provides examples of many cases in which necessary medicines are simply not available. The reasons for the shortages include poor infrastructure, war, disasters or geographical isolation, all of which disrupt distribution. Sometimes, stocks have run out because of bad planning, theft or mishaps higher up the supply chain. In other cases, medicines just cannot be manufactured fast enough. When a shortage of quality medicines, vaccines or diagnostic kits occurs, other, less reliable products often quickly flow in to fill the gap [29].

Lack of legislation and regulations enforcement

Being one mostly criticized topic in the literature, deficiencies in nationwide and worldwide legislation and enforcement are considered as a major hurdle in battling against the issue of falsified medicines [29,37]. Medicine falsification is financially rewarding, whose profit can compare with the manufacturing of narcotic drugs. Nevertheless, the penalty for this kind of pharmaceutical crime is light [38]. In some countries, producing falsified medicines does not even count as a crime, while in some countries like Norway, imprisonment of possessing falsified medicines without legal reasons is maximum 4 months [11,38]. In addition, as medicine falsification activity becomes more organized, even highly globalized, the lack of international law and inconsistent definitions of this crime among different nations unfortunately make it difficult to extradite and prosecute falsifiers [11].

A competitive generics market benefits consumers, as does a rigorous and unpredictable inspection regime [14]. In many developing countries, lack of confidence in the regulatory system breeds low enthusiasm for generic medicines [14,39]. An influx of generic medicines will only reduce the circulation in falsified and substandard drugs when there is a system to assure consumers of medicines quality. The drugs regulatory authority has the ultimate responsibility for the quality of medicines in the country. That includes registering medicines, issuing licenses and market authorization, post market surveillance, quality control testing, oversight of drug trials, and manufacturer and distributor inspections [14].

This range of responsibilities requires significant technical depth in staffing and political will to enforce regulations. Staffing shortages are often a problem in the public sector in low- and middle-income countries, where regulators are poorly paid and not well respected. Staffing shortages at the regulatory authority are a particularly serious problem in India and China, two main pharmaceutical producing nations with massive industries to oversee [14]. There are similar problems in less industrialized countries. A WHO survey of 26 drug regulatory authorities in sub-Saharan Africa found that only one country's regulator published guidelines on good distribution, while only 20 percent published internationally rigorous manufacturing practices [29].

Last but not least, the booming yet loosely regulated internet pharmacies pose a potential threat to consumers, in that the public with rather low awareness of the danger of falsified drugs are exposed to a large quantity of illicit online pharmacies. Even worse, when prescription-only medicines can be purchased without prescriptions, drug misuse may happen and drug quality cannot be ensured. To some extent, online pharmacies also accelerate the global movement of goods including falsified pharmaceutical product, yet regulations on this cyberspace are lacking [40]. When introducing legislation or guidance on a policy level, outcomes are often not applicable to LMICs and are challenging to implement in these countries. One example is the WHO Good Manufacturing Practices certification, which is primarily used in LMICs. These guidelines are often adjusted to fit local conditions and their

implementation is challenging because the strict enforcement of the guidance might lead to significant barriers to the growth of domestic companies [19].

Vulnerable supply chain

Although substandard and falsified medicines are a more significant problem in LMICs, their presence is not limited to countries with poor regulatory controls or weak pharmaceutical governance; these medicines have infiltrated medicine supply chains in countries of all economic levels. In April 2014, the European Medicines Agency published a warning for nine batches of trastuzumab vials stolen from Italian hospitals that later appeared in Finland, Germany and the UK. These vials had been intentionally compromised so that the API was absent or diluted and/or vial integrity was damaged causing a loss of sterility [19].

Falsified medicines do not only circulate in unauthorized pharmacies and street markets, as traditionally described in developing nations, but have also penetrated into the legitimate supply chain and flowed directly to hospitals, doctors and authorized pharmacists, or even go straight to the end users – patients – through internet sales. The latter is particularly identified in the literature from developed countries. For example, in 2011 fake Avastin®, a drug for cancer treatment, was found to have entered the legitimate supply chain in the US. Shockingly enough, the supplier was a licensed wholesale company and they sold directly to doctors. According to data from Austria, using internet pharmacies poses a major risk for patients to purchase falsified medicines. The Austria health authority found that 95% of prescription drugs purchased via the internet were falsified [41].

Illegal online medicinal product sellers, sometimes called rogue online or internet pharmacies, threaten the health, lives, privacy and security of internet consumers globally. According to multiple source, which is generally consistent with the finding of the World Health Organization (WHO) and the National Association Boards of Pharmacy, at any one time there are approximately 40,000-50,000 active online medical product sellers worldwide, and 93%-96% of them are operating illegally. These sellers do not operate in compliance with the laws of the jurisdiction in which they are located, or to where they are selling the products. It has been estimated that these criminals could generate up to US$35m in one year from a single website [42]. The problem is compounded in low- and middle income countries that have weak or under-resourced infrastructures for regulating medicines—opening the door for the distribution of substandard and counterfeit medicines—including attenuation of drugs through weak supply chains (for example, degradation of a heat-sensitive product by the time it reaches the patient) [43].

Excessive fragmentation is an important difference between developed and developing countries' drug distribution systems. In developed countries, comparatively few large firms control the market and regulatory authorities require some chain of custody documentation. In low- and middle-income countries, the system is vastly more complicated. Sometimes multiple parallel distribution systems of varying efficiency run in the same country.

Factor	Developed Countries	Developing Countries
Payer or reimbursement	Strong presence of public or private insurance companies and limited out-of-pocket expenditure.	Mostly payments are made out of pocket. Social health insurance systems are expanding in many emerging markets. Private insurance plans are also growing in some emerging market countries.
Regulatory structure	Strong, well-defined laws and overall good ability to enforce regulations	Weak fragmented regulatory structures, ill-defined laws in some instances, and poor ability to enforce regulations.
Patented, generic vs. branded generic	The market for prescription drugs consists of patented drugs and generics.	Poor regulatory structure creates a strong market for branded generics (brand is used as a signal of quality by the patient).
Prescription adherence	Prescription drugs can only be dispensed with a formal prescription.	Retail drug shops often dispense medicines and also Act as the first point of health care contact for many patients.

Balance of power in the system	Buyer (insurance companies or national health system) monopoly creates good balance of power between the manufacturer and the patients. In the United States, pharmacy benefit managers and drug formularies are commonly used as a means to ensure further balance of power.	Balance of power is tilted toward the manufacturer and the distribution channel. The large fraction of patients purchases with out of pocket Funds and have little bargaining power.

Table 1: Differences in Overall Structure of the Pharmaceutical Market in Developed and Developing Countries.

Lack of awareness of the problem

Without a clear picture of the extent of the problem, which products are compromised, and where the products surface, it is difficult to develop an appropriate prevention strategy and monitor progress. An insufficient understanding of the scope of the problem also contributes to a lack of awareness about substandard and falsified drugs among health workers and the general population. Increasing public awareness will not in and of itself decreases falsified and substandard medicines, because consumers cannot distinguish safe and unsafe medicine in the marketplace. However, public awareness is useful way to drive political will for correcting the problem and to educate people on warning signs of compromised medicines [14].

The WHO and studies recommend the need for public awareness on the growing trade in counterfeit drugs and the public health risks associated with it [15]. However, information on public awareness on counterfeit drugs and the ability to identify or suspect counterfeited drugs is scanty [44]. Literature conduct in Tanzania 55.6% were able to distinguish between a genuine and a counterfeit drug while 130 (44.4%) failed and health profession (84%) were able to distinguish a genuine drug from a counterfeit antimalarial drug [44]. These innocent buyers are unaware of the whereabouts of the manufacturer or the quality of the product, and many times they are not even aware of the expired, degraded or substandard products which ultimately results in failure of the treatment and with antibiotics this lead to escalation of antimicrobial resistance [9,13].

As with medicine sellers, many consumers are unaware of the prevalence of poor quality in medicines. The Laos study concluded that 73 percent of consumers were unconcerned about the quality of the drugs they purchased. Additionally, 80 percent of urban consumers and 96 percent of rural customers were unaware that some medicines could contain less than the labeled amount of active ingredients. Consumers in urban areas were generally more aware of important criteria used to determine drug quality [14]. Other research suggests gaps in awareness, especially among the poorest people in society. A qualitative study of Sudanese policy makers and pharmacists suggested that awareness of counterfeit products is lowest among the poor and people living in remote areas. Participants at overseas site visits for this study mentioned similar patterns in many developing countries. Often, well-educated urban consumers understand the threat of fake drugs and take precautions to avoid them. The poorest patients, and those living in areas with few to no reliable pharmacies, are often the least aware [14].

Combatting the problem of substandard and falsified medicines

Key elements include awareness; better data; compliance with quality standards; strengthening regulatory and quality systems; increasing resources for regulatory agencies responsible for oversight and enforcement; and enhancing the ability to approve, bring to market, and maintain the availability of quality drug therapies, through appropriate incentives and investment.

Increase awareness of the problem of substandard and falsified medicines

Elevating the issue for practitioners, patients, and policymakers through outreach campaigns about risks and possible responses. Educating the public (public awareness) on the problems of falsified and substandard medicines is important, but only insomuch as education empowers people to act. The increasing awareness of falsified and substandard medicines could drive improved pharmacovigilance in developing countries. Awareness

campaigns and investigative reporting reach health workers as well as they reach the rest of the public. There is also a need for targeted health worker education on falsified and substandard medicines, emphasizing the correct reporting channels health workers can use to confirm suspected cases of falsified and substandard drugs [13,14,19,21,29,41].

Education and communication are feasible in rich and poor countries alike. Representatives of 200 WHO member states stressed the importance of educational initiatives for consumers and health workers at the first meeting of the WHO global mechanism against falsified and substandard drugs [14]. The most wide-reaching communication strategies make use of many Channels, including print media, television, radio, the internet, mobile devices, and social media. Governments and NGOs have made good progress using these channels to promote understanding of the problem [29].

Health workers are the first line of pharmacovigilance and will be point persons in any consumer education campaign. Their training should include information on falsified and substandard drugs. Providers should be made more aware of their role in the postmarket surveillance of medicines, a new responsibility in many developing countries [13]. A health worker checklist might remind providers to ask patients for information about lack of response to treatment, slow response, and appearance of unusual symptoms. The list would also remind health workers about the proper channels for reporting an adverse event. In February 2005, the Nigerian drugs regulatory agency launched a national awareness campaign about fake medicines in Nigeria [13].

A counterfeit drug may look like the genuine version of the drug. Unfortunately, the only way to confirm whether it is counterfeit is by performing a chemical analysis in a laboratory. However, signs such as different doses of medicine inside the packs from those stated on the outside, the pack containing capsules when the box states tablets, expiry dates and batch numbers on the box not matching those of the drugs inside, and patient's information leaflets being in the wrong language or out of date may indicate whether a drug/product is counterfeited. Awareness of respondents on these signs is important towards suspicion of counterfeit drugs and avoidance of buying such drugs consequently reducing the market and profit of these illicit drugs [14].

USP is a longstanding proponent of raising awareness and taking action to improve medicine quality. Recognizing the key role that quality standards play in improving public health outcomes, USP is steadfast in its commitment to be a leading advocate for the use of quality standards throughout the world [43].

Strengthen legislation and regulation

Legislation should effectively manage the risks to patients, while simultaneously promoting access to affordable medicines, and stimulating innovation in new and better products relative to each country [19]. Most HICs have strict laws in place concerning the manufacturing, supply, distribution and dispensing of medicines, making it less likely that substandard medicines are produced or that falsified medicines penetrate the supply chain. Unfortunately, when looking at LMICs, a sufficient healthcare system is not in place; instead, they have weak regulatory bodies that cannot cope with the burden of poor-quality medicines. Illegal organizations will gravitate towards countries where these systems are the weakest [14].

Current regulatory and legislative leniency in LMICs is likely to be a function of outdated laws; these require updating with more stringent prosecution methods and stricter penalties [14]. To be able to introduce new laws and enforce penalties, more robust medicine regulations, surveillance and law enforcement need to be implemented. Countries with a higher incidence of substandard and falsified medicines generally lack appropriate product registration; good laboratories that can test product quality; a mechanism for surveillance and monitoring; and appropriate oversight, compliance and enforcement to remove compromised products from the market. It is critical to invest in and build strong, sustainable quality assurance systems and robust post market quality surveillance as part of an overall prevention, detection, and response framework for medicines [14,29]. Building local capacity and introducing innovative safeguards (i.e., surveillance technologies) helps to eliminate substandard and falsified products. Publicly available test specifications supported by acceptable procedures and reference materials are key to the implementation of surveillance programs, serving as an important adjunct to other methods, such as visual inspection [43].

Medicines and medical products by strengthening regulatory systems and building manufacturing capacity in low-and middle-

income countries, including building product quality surveillance systems and helping to detect substandard and falsified products. Other Initiatives exist through the WHO, the World Bank, and other organizations [43]. Framing the counterfeit and substandard medicines issues in the context of 'medicine crime' overlooks the best approach to counter the supply of illegal and dangerous medicines: ensuring the availability of affordable, quality assured essential medicines. Also, An international agreement, patent restriction, and maintain high quality standards in the generic industry: ensure that all proven effective and necessary medicines are affordable, available, and of assured quality will do a great deal more to combat falsified and substandard medicines [45].

The remedy to this global problem lies in appropriate regulatory processes and rules and strict implementation of these, along with coordination between the players at every level from the policy maker to the regulator to the consumer [31]. The problem is very big and requires radical steps to be taken. The law enforcement is very important and anybody involved in such corrupt practices should be arrested and along with the punishment they should be penalized [46].

Good manufacturing practice and good distribution practice

GMP is defined as the minimum standard that a medicines manufacturer must meet in their production processes. GDP highlights that medicines are to be obtained from the license supply chain and are consistently stored, transported and handled under suitable conditions [14,19]. A strong chain of custody through the drug distribution system can reduce the risks introduced with product diversion and porous supply chains. Track-and-trace systems allow all interested parties to know where the product is at any time and see a record of where it has been previously [14]. These systems allow manufacturers and others to track their products, meaning to follow drugs forward in the distribution chain. They also allow patients or pharmacists to trace the drug, or to verify its past locations.

Medicines and ingredients are part of a complex global supply chain: before a product even reaches the patient, multiple ingredient manufacturers, suppliers, and distributors from different parts of the world have participated in making, storing, and handling the product [43]. Standards for the identity, strength, quality, and purity of medicines are important constituents of a comprehensive prevention, detection, and response framework. Medicine quality can be defined as "a balanced, risk-based set of characteristics, systems, and requirements that consistently ensure a medicine's delivery of stated and implied clinical outcomes for patients [43].

Solutions to address online pharmacies

In the United States, the National Association of Boards of Pharmacy (NABP) runs the Verified Internet Pharmacy Practice Sites (VIPPS) accreditation program to recognize safe online drug stores. Accredited online pharmacies comply with state licensing requirements for both the state that the pharmacy is in and all the states in which it sells, including authentication of prescriptions, observance of quality-assurance standards, and submission to regular state inspection [43].

Studies show that there has been an increase in public awareness of the existence of substandard and falsified medicines and this proves to be an effective prevention method in HICs. A survey conducted by the EU Alliance for Safe Online Pharmacy explored consumers' perceptions of online pharmacies and showed promising results. It was found that a 70% change in consumers' attitudes towards online pharmacies when associated with falsified medicines, deterring them from purchasing medicines online [19,43]. Patients should be advised to avoid self-prescribing, and the importance of seeing a pharmacist or GP should be emphasized to promote the regulated and safe administration of medicines [19]. Mobile Product Authentication (MPA) is a technology developed by Sproxil which is a preventive measure for consumers to identify whether the drug is counterfeit or not. By this technology, using a cell phone, customers can text message an item-unique code and gets an instant response confirming the brand's genuineness. We can then send highly relevant targeted offers to the consumer's right at the point of sale. This is the world-first innovation by Sproxil. The scratch-off technology is proven its trend in the emerging markets. The mobile operator market chose scratch offs instead of holograms for popular pay-as-you-go subscription schemes [6,14,29].

An elegant system for assigning unique product numbers, mobile verification empowers consumers to act for their own safety. A reliable system for tracking and tracing drugs through the distribution chain would greatly reduce the likelihood of falsified and substandard medicines reaching patients. Recent technological

advances, such as the use of radio frequency identification and the expansion of mobile phones in developing countries, hold promise for supply chain security[14,29].

Discussion

The impact of substandard and falsified medicines to public health is serious threat. Due to these there is adverse effects, toxicity, lack of efficacy from incorrect active ingredients. According to some literature, any product containing a dangerous contaminant (including dangerously high levels of the expected API) will pose an immediate hazard to the individual taking it [2,8,11]. Because of the burden of substandard and falsified medicine across the world especially in low income country the disease was failure to cure or prevent future disease, increasing mortality, morbidity and the prevalence of disease. The literature also believed that the consumption of which may, at best, fails to help improve patients' condition, and at worst, cause avoidable mortality and morbidity and also drug resistance [7-9]. The disease prevalence is high country's like Nigeria, China, India and Panama due to harmful drug substance [6,9].

There is also progression of antimicrobial resistance and drug-resistant infections. The study done these believed that Poor-quality drugs have contributed to the rise of drug-resistant loss of confidence of medicines by consumer in health care professionals, health programmers and health systems. Furthermore, poor quality drugs induce; economic loss for patients, their families, health systems and manufacturers and other actors in the supply chain of quality medical products and increased burden for health care professionals, national medicine regulatory authorities, law enforcement and criminal justice systems [2,14,22,24].

The prevalence of the problem of substandard and falsified medicine high in developed and developing country, but the burden is more in developing country due to lack of awareness, weak regulation and legislation, weak supply chain, difficult to afford medicine like emergency medicines. According to literature also believed that since then this problem has grown to a much larger extent with more than 10% of drugs globally are counterfeit, and in some countries the situation is even worse with more than 50% of the drug supply is counterfeit [13].

To solve this issue, raise public awareness, and strengthen legislation and regulation, public and private sector global health players must collaborate and work together to identify, detect, warn, and confront the criminal element threatening the drug supply and patients. To address this serious challenge, the world must move forward

Conclusion

There are undesirable effects, toxicity, and a lack of efficacy from improper active components in poor and fraudulent medicines. Failure to treat or prevent future disease, resulting in increased mortality, morbidity, and disease prevalence. Antimicrobial resistance and drug-resistant diseases are on the rise. Consumers of medicines a lack of trust in health-care personnel, health-care programs, and health-care systems. Patients, their families, health systems, manufacturers, and other actors in the supply chain of high-quality medical products will suffer financial losses, while health care professionals, national medicine regulatory agencies, law enforcement, and criminal justice systems will face increased burdens. The prevalence of the problem of substandard and falsified medicine high in developed and developing country. To address this issue, global health stakeholders from the public and private sectors must cooperate and together work to understand, detect, warn, and address the criminal element threatening the drug supply and patients. their gratitude to Jimma University's ICT employer who worked in the Postgraduate Library.

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Bibliography

1. Tim K., *et al*. "The Global Counterfeit Drug Trade: Patient Safety and Public Health Risks". *Journal of Pharmaceutical Sciences* 100.11 (2011): 4571-4579.

2. WHO. "A study on the public health and socioeconomic impact of substandard and falsified medical products". Geneva: World Heal Organization (2017).

3. Newton PN., *et al*. "Impact of poor-quality medicines in the ' developing ' world". T*rends in Pharmacology Science* 31.3 (2010): 99-101.

4. Kaur H., *et al*. "Quality of Artemisinin-Based Combination Formulations for Malaria Treatment : Prevalence and Risk Factors for Poor Quality Medicines in Public Facilities and Quality of Artemisinin-Based Combination Formulations for Malaria Treatment : Prevalence and Risk". *PLoS One* 10.5 (2015): 1-13.

5. Dégardin K., *et al*. "Understanding and fighting the medicine counterfeit market". *Journal of Pharmaceutical and Biomedical Analysis* 87 (2014): 167-175.

6. M Sonal Sekhar., *et al*. "Counterfeit medicines: a real threat to the society". *IJPSR* 2.7 (2011): 1645-1650.

7. Newton PN., *et al*. "The primacy of public health considerations in defining poor quality medicines". *PLoS Medicine* 8.12 (2011): 6-10.

8. Johnston A and Holt DW. "Substandard drugs: A potential crisis for public health". *British Journal of Clinical Pharmacology* 78.2 (2014): 218-243.

9. Newton PN., *et al*. "Counterfeit anti-infective drugs". *Lancet Infectious Disease* 6 (2006): 602-613.

10. WHO. "Growing threat from counterfeit medicines". *Bulletin of the World Health Organization* 88 (2010): 247-248.

11. Attaran A., *et al*. "How to achieve international action on falsified and substandard medicines". *BMJ* 345.7884 (2012): 1-6.

12. Chika A., *et al*. "The Menace of Fake Drugs: Consequences, Causes and Possible Solutions". *Research Journal of Medical Sciences* 55 (2011): 257-261.

13. P Gupta KS and AP. "Countrfeit (fake) Druds & New Technologies To Identify It in India". *IJPSR* 3.11 (2012): 4057-4064.

14. Buckley GJ and Gostin LO. "Countering the Problem of Falsified and Substandard Drug"s. IOM (Institute Med Natl Acad Press Copyr. (2013): 624-6242.

15. Dondorp AM., *et al*. "Fake antimalarials in Southeast Asia are a major impediment to malaria control : multinational cross-sectional survey on the prevalence of fake antimalarials". *Tropical Medicine and International Health* 9.12 (2004): 1241-1246.

16. Christian L., *et al*. "The Problem of Substandard Medicines in Developing Countries". *Work International Public Affair* 81 (2012).

17. Clift C. "Counterfeit medicines : Health And Harm". *World Today Royal Inst Int Aff.* 66.12 (2012): 11-13.

18. Lubell Y., *et al*. "Artemisinin resistance - modelling the potential human and economic costs Artemisinin resistance - modelling the potential human and economic costs". *Malaria Journal* (2014): 1-9.

19. Ghanem N. "Substandard and falsified medicines : global and local efforts to address a growing problem Key points". *Pharma Journal* (2019): 1-12.

20. Suleman S., *et al*. "Quality of Medicines Commonly Used in the Treatment of Soil Transmitted Helminths and Giardia in Ethiopia : A Nationwide Survey". *PLOS Neglected Tropical Diseases* 8.12 (2014): 1-16.

21. Nsimba SED. "Problems Associated With Substandard and Counterfeit Drugs In Developing Countries: A Review Article on Global Implications of Counterfeit Drugs in the Era of Anti-Retroviral (ARVS) Drugs In free Market Economy". *East African Journal of Public Health* 5.3 (2008): 205-210.

22. Bloom G., *et al*. "Markets, information asymmetry and health care : Towards new social contracts". *Social Science and Medicine* 66 (2011): 2076-2087.

23. Kanavos P., *et al*. "Options for nancing and optimizing medicines in resource-poor countries". *World Health Report Background* (2010).

24. Wertheimer AI., *et al*. "Safeguarding against substandard/ counterfeit drugs: Mitigating a macroeconomic pandemic". *Research in Social and Administrative Pharmacy* 5.1 (2009): 4-16.

25. WHO. Substandard/Spurious/Falsely-Labelled/Falsified/ Counterfeit Medical Products Report by the Director-General 63 (2011).

26. Oxfam. "Eye on the Ball: Medicine regulation - not IP enforcement - can best deliver quality medicine" (2011).

27. WHO. "WHO's role in the prevention and control of medical products of compromised quality, safety and efficacy such as substandard/spurious/falsely- labelled/falsified/counterfeit medical products". 63 (2011): 1-7.

28. WHO member state mechanism on substandard/spurious/ falsely- labelled/falsified/counterfeit (ssffc) medical products working definitions (2015): 33-36.

29. WHO. "WHO Global Surveillance and Monitoring System for substandard and falsified medical products". Geneva: Geneva World Heal Organ (2017).

30. Cockburn R., *et al*. "The Global Threat of Counterfeit Drugs : Why Industry and Governments Must Communicate the Dangers". *PLoS Medicine* 2.4 (2005): 302-308.

31. Swaminath G. "Faking it - II : Countering and preventing counterfeiting of drugs". *Indian Journal of Psychiatry* 51.1 (2020): 9-11.

32. Commission E. "Report on the EU Customs Enforcement of Intellectual Property Rights: Result EU Bord". (2011).

33. Reynolds L and Mckee M. "Organised crime and the efforts to combat it : a concern for public health". *Global Health* 6.21 (2010): 15-17.

34. Erhun WO., *et al*. "Drug Regulation and Control in Nigeria : The Challenge of Counterfeit Drugs". *Journal of Health and Population in Developing Countries* 4.2 (2001): 23-34.

35. Pollack A. "Medicare coverage for breast cancer drug ends in some states". *New York Times Prescr Blog* 2.1 (2011): 1-23.

36. Dusetzina BSB., *et al*. "How Do Payers Respond to Regulatory Actions ? The Case of Bevacizumab". *Journal of Oncology Practice* 11.4 (2015): 313-318.

37. Lamy M and Liverani M. "Tackling Substandard and Falsified Medicines in the Mekong : National Responses and Regional Prospects". *Asia Pacific Policy Studies* 2.2 (2015): 245-254.

38. Liang BA. "Fade to black:Importation and counterfeit drugs". *American Journal of Law and Medicine* (2006).

39. Kaplan WA., *et al*. "Policies to promote use of generic medicines in low and middle income countries : A review of published literature, 2000 – 2010". *Health Policy (New York)* 106.3 (2012): 211-224.

40. Mackey TK and Liang BA. "Pharmaceutical digital marketing and governance: Illicit actors and challenges to global patient safety and public health". *Global Health* (2013).

41. Frontini R. "Falsified Medicines Directive: are we heading in the". *Journal of Medicine Access* 1.1 (2017): 55-57.

42. Isles M. "What's in a word? Falsified/counterfeit/fake medicines - the definitions debate". *Journal of Medicine Access* 1.1 (2017): 40-48.

43. USP. "Combatting Substandard and Falsified Medicines". *USP Global Public Policy Position* (2020): 1-6.

44. Mhando L., *et al*. "Public Awareness and Identification of Counterfeit Drugs in Tanzania : A View on Antimalarial Drugs". *Advances in Public Health* 2016 (2016): 18-23.

45. Hoen E and Pascual F. "Counterfeit medicines and substandard medicines : Different problems requiring different solutions". Author (s): Ellen ' t Hoen and Fernando Pascual Source : Journal of Public Health Policy 36.4 (2015): 384-389.

46. Sankalp Yadav GR. "Counterfeit drugs: Problem of developing and developed countries [6]". *International Journal of Pharmaceutical Chemistry and Analysis* 5.1 (2015): 46-50.