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Review Article

A Literature Review on the Global Burden and Impact of Substandard and Falsified Medicine

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Abstract

Substandard and falsified medicines are a global health concern negatively affecting individuals, the public, the pharmaceutical industry and governments all over the world. This review aims to examine the global prevalence of substandard and falsified medicines, its impact on health and the health system, including socio-economic impacts and strategies for curbing this menace. A literature review of published articles between January 2000 and May 2020 was done with keywords "substandard", "counterfeit", and "falsified medicines". Articles were sourced from PubMed, World Health Organization (WHO) databases and Google Scholar. There are reports of substandard and falsified medicines from all WHO Regions with noticeable prevalence in the African Region. These medicines have been reported to cause death, antimicrobial resistance, increase prevalence of diseases, and loss of confidence in the health system. Increased patients spending, loss of productivity, strain of limited health systems resources, and loss of government revenue are major socio-economic implications of substandard and falsified medicines. An increase in criminal sanctions, global harmonization of drug regulatory authorities, and appropriate education of healthcare professionals and patients on how to prevent, detect, and respond to reported cases of substandard and falsified medicines are strategies that can be implemented to curb the menace of these medicines. Registered pharmacists and pharmacy students play critical roles in addressing this global health issue.

Keywords Substandard, counterfeit, falsified medicines, strategies

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Background

Substandard and falsified medicines are a global menace negatively affecting individuals, health systems, economy and governance. Substandard medicines are authorized medical products that do not meet their required (national or international) standards or specifications or both while falsified medicines, on the other hand, are products that deliberately or fraudulently misrepresent their identity, composition or source medical products [1,2]. These medicines are everywhere in licensed markets, unlicensed markets, ungoverned websites, social media platforms or smartphone applications [3]. They can be detected through examination of packaging for spelling errors, checking for manufacture and expiry dates, checking medicine smell, color and visual inspection and verification services, like the European Union logo, for the online sale of medicines [4,5]. Substandard and falsified drugs are reported all over the world. About 10% of all medicines in the world are either substandard or falsified [2].

Substandard and falsified medicines may contain lethal contaminants, an overdose or a sub-therapeutic dose, could harm patients, cause adverse drug events, prolong disease and probable death. The use of these medicines as prophylactic drugs increases infectious disease prevalence through widespread transmission as well as antimicrobial resistance due to sub-therapeutic antibiotic doses [1,2]. Treatment failure caused by these medicines could make the public lose confidence in the healthcare system, medicines and vaccines [2]. This review aims to examine the global prevalence of substandard and falsified medicines, its impact on health and the health system including the socio-economic impacts. Also, it aims to review the strategies implemented by different countries to curb the menace of substandard and falsified medicines.

Methods

A literature review of published articles between January 2000 and May 2020 was done with keywords "substandard", "counterfeit", and "falsified medicines". Articles were sourced from PubMed, WHO databases, and Google scholar.

Articles that stated the prevalence, occurrence or impact of "substandard", "falsified" or "counterfeit" medicines published in peer-reviewed journals between January 2000 and May 2020 were reviewed. Only those relevant articles published in English were included in the review. WHO's publications that included the keywords were also

included in the review. Books, book chapters, and grey literature were not included in this review.

Substandard Counterfeit and Falsified Medicines - A Global View

There have been reports of substandard counterfeit and falsified medicines in all regions of the world [1].

In Africa, packets of the antimalarial artemether-lumefantrine and anithelmintic mebendazole tablets were detected with no artemether, lumefantrine, mebendazole or other active pharmaceutical ingredients [2,6]. In 2020, the WHO reported 9 different falsified chloroquine products from Niger, Cameroon and the Democratic Republic of Congo [4]. Additionally, some anti-tuberculosis medicines (isoniazid and rifampicin) failed basic quality testing from pharmacies in Angola, Brazil, China, Democratic Republic of Congo, Egypt, Ethiopia, Ghana, India, Kenya, Nigeria, Russia, Rwanda, Thailand, Turkey, Uganda, Tanzania and Zambia [7]. It is estimated that about 30% of drugs sold in some parts of Latin America, Asia and Africa are falsified [7]. In 2011, 64% of antimalarial medicines in Nigeria were found to be falsified [8].

In Ghana, 348 antibiotic samples were analyzed and 66.38% of all the samples were substandard. The substandard samples contained less than 90% or more than 110% of the dose of the active ingredients than the label claimed [9]. A study conducted in the Democratic Republic of Congo illustrated that 27% of 239 tested samples representing artemether/lumefantrine, amoxicillin powders for suspension, and paracetamol tablets were of poor quality [10]. Also, 26.7% of 90 samples of cardiac medicines from the Democratic Republic of Congo were found to be substandard [11]. A study that tested 506 medicine samples from the Democratic Republic of Congo reported that 5.1% of medicines stated to be produced in Europe, 17.7% of medicines stated to be produced in Asia and 22.2% of medicines stated to be produced in Africa were substandard [12].

A study in Mongolia in the Western Pacific Region analyzed 1770 drug samples and estimated that 10.1% (179) samples were substandard. The prevalence of substandard products was observed to be three times higher for locally manufactured products (18.6%) than for imported counterparts (6.1%) [13]. An increasing number of substandard and falsified medicines have been reported in both Canada and the United Kingdom [14]. In the United Kingdom (Europe), the Medicines and Healthcare Products Regulatory Agency (MHRA) reported a 10-fold increase in the report of defective poor-quality medicines from 2001 to 2011 [3].

In 2012, contaminated prednisolone was responsible for fungal infection in about 700 individuals and caused at least 61 deaths in the United States of America [15]. The United States Food and Drug Administration (FDA) reported falsified botulinum toxin-A (Botox) in 2015 [16]. About 15 cases of falsified medicines were reported in the United Kingdom between 2005 and 2011 [16]. This existing evidence in literature shows that substandard and falsified medicines are a global health challenge.

Impact of Substandard and Falsified Medicines on Mortality

The total deaths documented due to counterfeit medicines are thought to be underestimated because this information is only reported when counterfeit drugs are seized and a causal relationship between the deaths and the counterfeit drug is established [17]. Additionally, in poorly resourced countries, deaths caused by substandard and falsified medicines are not reported in public health statistics. Thus, the overall death toll attributable to counterfeit medicines is unknown [17]. However, there are various incidents reported globally.

Substandard and falsified antimalarial medicines have contributed significantly to the malaria burden in Nigeria. A study in 2019 reported that 11.8% of ACTs (Artemisinin-based Combination Therapy) in Nigeria were either substandard or falsified and they are responsible for 12,300 deaths annually in Nigeria [18]. The WHO estimated that in Africa, about 169,000 children could die annually from pneumonia treated with substandard and falsified medicines [1].

Similarly, in South-east Asia, the death toll is much larger; in 2001, China reported 192,000 deaths attributed to counterfeit medicines [19]. A substandard cough medication was found to be the cause of death for 33 children in India, in 1998 [20]. The affected children were all treated with a substandard over-the-counter cough syrup just prior to their deterioration in health, leading to acute kidney failure. In 2008, 84 children died after consuming teething syrup contaminated with diethylene glycol [20]. Cough syrup adulterated with diethylene glycol became a global concern, resulting in 109 deaths in Nigeria, 236 deaths in Bangladesh, 26 deaths in Argentina and 85 deaths in Haiti [21]. Western countries are not exempted from this problematic issue. In the United States, adulterated heparin was found to be the cause of the death of 81 patients. Manufacturers were found guilty of using an over-sulfated structurally similar product, chondroitin sulphate, because it reduced production cost significantly [17].

Asia is the most significant contributor to the trade of counterfeit medicines [22]. Developing countries are the target market for counterfeit medicines because the cost of the authentic drug may be too expensive for the majority of the population to afford

and also due to weak legal control [22]. Counterfeit drug manufacturers use hazardous chemicals which are identical to active pharmaceutical ingredients [17]. These chemicals could be poisonous and fatal if administered to a patient [17]. With these advancements, mortality rates are only likely to increase as counterfeit drugs are becoming more difficult to combat.

Impact of Substandard and Falsified Medicines on Antimicrobial Resistance (AMR)

Antimicrobial resistance (AMR) occurs when the sub-therapeutic concentration of antimicrobials kill only a portion of susceptible pathogens [1]. The pathogens that survive mutate and become resistant to the antimicrobial agent. These mutant variants then reproduce rapidly and transfer the mutations that confer the resistance [1]. This, in turn, results in the establishment of drug-resistant colonies, making infections difficult to treat [1].

Antimicrobial resistance (AMR) may be directly linked to the use of substandard and falsified medicines [1]. Around 90% of the antimalarial medicines in Africa were found to be falsified [23]. Concurrently, not less than 116,000 deaths occur annually in Africa due to antimalarial resistance [24]. The continuous use of substandard and falsified anti-tuberculosis drugs may result in an exponential rise of multidrug-resistant (MDR) and extensively drug-resistant tuberculosis (XDR-TB) infection [7].

Impact of Substandard and Falsified Medicines on Prevalence of Diseases

Vaccines save 2-3 million lives per year, by preventing diseases. Substandard and falsified vaccines can reverse this scenario by increasing mortality due to failure to prevent life-threatening diseases such as meningitis and rabies [23,25]. In 2015, falsified Neisseria meningitidis type C vaccines were linked to 8,580 cases of meningitis C in Niger and nearly 600 people died [2]. The widespread prevalence of falsified vaccines may lead to a rampant rise in cases of preventable infectious diseases, and this will also increase the demand for antimicrobial medicines. The increase in demand for antimicrobials could then be exploited by illegal drug traders to sell substandard and falsified medicines, which may have fatal consequences [2].

Medicines used to treat non-communicable diseases are also affected. WHO reported that 15.8% of total products reported to the Global Surveillance and Monitoring System as substandard and falsified medical products were used for non-communicable conditions such as diabetes, cancer, mental health and cardiovascular

conditions [2]. This may lead to an increase in mortality caused by non-communicable diseases.

Impact of Substandard and Falsified Medicines on the Healthcare System

The use of substandard and falsified medicines may lead to treatment failure and often results in prolonged illness and eventually death. The poor population in low and middle-income countries are more prone to be the target of counterfeit medicines, so they are highly affected by these consequences. Treatment failure, adverse drug events and prolonged illnesses caused by substandard and falsified medicines could result in the loss of public confidence in health professionals and health care facilities. This could further result in them refusing vaccination, not taking treatment as prescribed and seeking alternative treatment from unlicensed personnel [2,26].

If the sale and use of substandard and falsified medicines are not controlled, they could ultimately result in an increase in chronic disorders, and large outbreaks of preventable infectious diseases all at the same time.

Economic and Socio-economic effect of Substandard and Falsified Medicines

Substandard and falsified medicines have a direct economic and socio-economic impact on the individual patients, health systems, pharmaceutical industries and the government [1].

Increased Patient's Spending

Treatment failure, drug toxicity and adverse drug events caused by substandard and falsified medicines will increase the patient's out-of-pocket spending. This is due to further laboratory investigations, additional medical care, and prolonged stay in the hospital, increasing admission costs. Patients that have lost confidence in the healthcare system will incur additional travel expenses in search of quality healthcare [1].

Loss of Productivity

Prolonged illness caused by these medicines leads to loss of productivity as the affected patient is unable to work. This negatively impacts businesses and the wider economy and may further contribute to the vicious cycle of poverty. Falsified medicines account for the loss of more than 750,000 jobs in the United States [8].

Antimicrobial resistance caused by substandard and falsified antimicrobials may lead to prolonged recovery time and increase the loss of productivity. Adverse drug events and secondary infection(s) caused by the prophylactic failure may result in the premature death of the affected individual [1].

The Strain on Health Systems Resources

The use of substandard and falsified medicines may cause premature death leading to a waste of human effort and health care resources. This waste causes a strain on the health care system which is oftentimes overburdened due to limited resources, especially in low- and middle-income countries [1,27].

Health care systems resources are further strained as a result of repeated therapy, increased disease prevalence and transmission of drug-resistant infections associated with the use of substandard and falsified medicines [1]. Health care systems also bear the cost of increased outpatients visit resulting from drug toxicity and adverse drug events associated with these medicines [1].

Impact on Pharmaceutical Industries

Pharmaceutical Industries lose about $10 billion to $200 billion annually to the sales of substandard and falsified medicines [1,18,27-29]. In 2010, the pharmaceutical industry in the United States lost an estimated $75 billion in revenue to falsified medicines [8,28]. The revenue lost to the sale of substandard and falsified antimalarial medicines in Nigeria is estimated at $892 million annually [18].

Pharmaceutical industries also must bear the cost of substandard drugs being recalled from the market [2]. The increased cost of production due to the incorporation of anti-counterfeiting technologies into products and packaging are borne by pharmaceutical companies [30].

Poor health outcomes associated with falsified medicines can make patients lose trust in the genuine pharmaceutical product that was falsified [27,31]. The brand and reputation of a pharmaceutical company may also suffer from unquantifiable damage due to counterfeiting [30].

Pharmaceutical industries invest about 15% to 17% of their revenue on research and development, to discover and develop novel pharmaceutical products. When these products are falsified, the incentives on innovation and creativity are lost [8]. This theft of intellectual property may limit investment in pharmaceutical research and development [8,30].

Loss of Government Revenue

National governments also lose hundreds of millions of tax revenue to the trafficking and smuggling of substandard and falsified medicines. East African countries reported an estimated $500 million-dollar unremitted taxes associated with substandard and falsified medicines [31].

Also, resources that should be focused on developing the health sector and other aspects of the economy are redirected towards curbing the menace of substandard and falsified medicines. Profit from the sales of falsified medicines are sometimes used to fund criminal and terrorist organizations, further increasing the threat to good health and well [32].

Factors causing Persistence of Substandard and Falsified Medicines

Limited access to safe and efficient medicines, bad governance, weak technical capacity, internet gateway, complex supply chain, poor detection and reporting culture are some reasons substandard and falsified medicines have thrived. This could either be due to quality medicines being unaffordable, unavailable or due to patients preference [2].

The affordability of high-quality medical products could be another reason for the persistence of these substances and falsified medicines. High-quality medicines have a higher cost of production than the substandard and falsified ones. The high cost of safe and effective medicines compels people who cannot afford them to go for the cheap and easily affordable substandard products sold by unlicensed distributors and on the internet [33]. Some medical practitioners purchase and dispense poor quality drugs all to maximize profit [2].

Also, safe and effective medicines are sometimes unavailable in the market. This could be due to poor health infrastructure, poor drug inventory management, poor regulation of medicines, porous drug supply chain and unpredictable surges in medicine demand due to wars, natural disasters and pandemics [2,34]. Slow manufacturing process, theft and mishaps in the supply chain disrupt the distribution of quality medical products. This creates loopholes in the supply chain which is swiftly filled by the suppliers of substandard and falsified medicines. Poor communication between health regulators and law enforcement agencies also permits the availability of these illegal products into the markets [2].

In other instances, the patient's preferences also come in. It was reported that some women use misoprostol (a drug used to treat peptic ulcers) to terminate pregnancy in its early stage because they could not afford or access safe and effective contraceptives. This has led to an increase in the manufacturing of falsified

contraceptives, as well as misoprostol [2]. Bad governance also contributes to the prevalence of substandard and falsified medicines. Some governments have failed to strengthen their medicines regulatory authorities leading to poor inspection and regulation of manufacturing procedures and storage warehouses. Cases of poor ethical and corrupt practices between the regulatory officials, unscrupulous manufactures and suppliers have also been reported. The sales of falsified medicines are encouraged when poor legislation fails to ensure appropriate criminal penalties and punishments of offenders [8,35].

There are so many unlicensed online traders with fake accounts who have managed to avail falsified and substandard medicines to consumers at cheaper prices. Most government regulatory bodies have failed to recognize these online dealers. This may be attributed to lack of proper insight into how these dealers optimize Information and communication technology in their operation. Some have also managed to succeed with their deeds after corrupting the regulatory agencies [2].

The existence of weak technical deficit coupled with poor oversight of regulatory authorities has contributed to the persistence of substandard and falsified medicines. Lack of adherence to good manufacturing practice in industries, poorly equipped laboratories, lack of well-trained staff, lack of standard transportation facilities and proper tracking procedures also contribute to the availability of these medicines [2,35].

Neglect of Good Manufacturing Practice (GMP)

The neglect of Good Manufacturing Practice (GMP) can be either accidental or deliberate. Companies may not train their staff due to the fear of incurring extra cost. Small companies which are suppliers of domestic markets in India have been reported to produce substandard medicines because of their inability to afford standard equipment and the use of bad water for manufacturing [35]. The high cost of quality ingredients and chemical standards have also limited the implementation of GMP [36].

Complex Supply Chain

The total process of manufacturing, packaging and distribution of medical products to the desired consumers may be complicated. A country which supplies the excipient may be different from the one manufacturing the products. A company may repackage and brand a product for clients and customers in another different country. This complexity involves a higher turnover of products passing through many hands and international borders creating several loopholes for the illegal and unethical practice to come in [2,34].

Low Detection Levels, Lack of Knowledge and poor Reporting Culture
Most of the licensed manufacturers have failed to act in cases where their reputations have been damaged by the falsification of their products [37]. Some medical personnel lack awareness: of substandard and falsified medical products; and on how to detect them, and how to report them [38]. Lack of appropriate testing equipment, chemical standards, trained personnel and adequate funding has limited testing, detection and reporting of substandard and falsified medicines especially in low- and middle-income countries [2].

Strategies Implemented to Solve Substandard and Falsified Medicines

The WHO's Global Surveillance and Monitoring System (GSMS) reports that the prevalence of Falsified and Substandard medicines is likely to increase unless serious, well-resourced efforts are made to tackle the issue [2]. Coordinated participation between national and regional governments, global organizations, the private and non-profit sectors, and civil society is needed to tackle the problem of substandard and falsified medicines. Pharmacovigilance, collaboration between different disciplines, and collaborations between health authorities and law enforcement agencies are also very necessary [2].

The Safety and Vigilance Unit of the WHO's Essential Medicines and Health Products Department aims to strengthen national and global responses in three areas:

1. Improving affordable access to quality, safe and effective medical products.
2. Strengthening governance and regulatory capacities
3. Improving technical capability.

The WHO's GSMS aims to support WHO member States in minimizing the public health risks posed by substandard and falsified medical products. In achieving this goal, it supports countries with appropriate public-health focused investigation and response to incidents involving substandard and falsified medical products. WHO tackles substandard and falsified medicines using a three-pronged strategy of prevention, detection and response [2].

Prevention
Prevention has to do with hindering the production and distribution of substandard and falsified medicines. To do this, there must be proper education and awareness

about these products, there must be ready access to safe and effective medicines and quality manufacturing and distribution standards must be adhered to.
Education and awareness of patients, health professionals and other stakeholders is the first and crucial step in prevention. It aims at providing accurate and balanced information on the risks of substandard and falsified medical products, providing measures to avoid them, how to spot them and how to report them.

Access to safe and effective medicines must also be guaranteed. Limited access to affordable, quality medical products contribute to the prevalence of substandard and falsified medicines. WHO combats this by improving access to quality medical products through its WHO's Essential Medicines Programme, and active partnerships with others in the field of global health such as United Nations Children's Fund (UNICEF), Global Alliance for Vaccines and Immunization (GAVI) and other partners [2].

Manufacturers, distributors, health care professionals and other stakeholders must ensure appropriate technical and professional standards. The WHO's Department of Essential Medicines and Health Products works with countries and expert committees to create, develop and implement standards that will ensure only quality products are delivered across the global supply chain [2].

Detection

The detection of substandard and falsified medicines in the global supply chain requires a high level of awareness by all stakeholders, prompt sharing of information across countries and organizations, and appropriate technology (such as barcode authentication technology, track and trace technology and mobile applications) to detect such products. Trained personnel and equipped laboratories are essential to carry out appropriate testing and inspection of medicines. The WHO has established systems to help in the detection of such products. WHO developed smartphone applications for health professionals to take pictures of suspicious products and send them to regulatory authorities for authentication [2].

Response

Good governance and the swift action on national and international drug regulation agencies are important. Once poor-quality medicines are detected, appropriate investigations to detect the source of the medicines should be done. Reports should be communicated with the appropriate bodies. Pharmaceutical companies should also be alerted, and product recalls should be initiated when necessary. Appropriate criminal sanctions should also be applied and published by national or regional drug regulatory authority [2,39].

Strategies put in Place by Different Countries

In Germany, the Official Medicines Control Laboratory (OMCL) controls the quality of medicines in the supply chain by engaging in chemical, and laboratory analysis of product samples. They create awareness on substandard and falsified medicines and new trends used by illicit suppliers and distributors [39].

Italy, Belgium, Poland, and other countries in Europe, have adopted the Falsified Medicines Directive (FMD) to detect falsified medicines. The FMD requires medicines packaging to carry a unique identifier (barcode) and tamper-proof seals which will be used to verify their authenticity. The information contained in the barcodes are uploaded to secure databases like the European Medicine Verification System (EMVS). The barcodes are scanned to verify the authenticity of each medicine [40].

The United States Food and Drugs Authority helps to ensure, prevention, detection and reporting of poor-quality medicines [41]. The United States Agency for International Development (USAID) works with medicines regulatory bodies of different countries to ensure development of local capacity that will ensure the distribution of safe and effective medicines. The United States Pharmacopeia (USP) works with pharmaceutical manufacturers to ensure compliance with acceptable standards [41].

Other Strategies that can be Put in Place

Criminal sanctions on the trade, manufacture and distribution of substandard and falsified medicines should be increased to make the punishment for such act commensurate with the crime committed [30].

Implementation of global harmonization of drug regulatory authorities needs to be done to enhance transparency, detection and reporting of cases of substandard and falsified medicines. This will make the complex global supply chain more secure [42].

Health professionals should be educated on how to examine medicines for particulate contamination, spelling and packaging errors. They should also be aware of how to report suspicious cases for investigation. The public should also be educated on the health implications and possible fatality associated with the use of substandard and falsified medicines [3].

Substandard and Falsified Medicines and COVID-19

The COVID-19 pandemic has disrupted the global supply chain and may lead to a surge in substandard and falsified medicines. Initiatives must be implemented to ensure easy access to safe and effective medicines. Following the approval of COVID-

19 treatments and vaccines, a global coordinated production, secure distribution chains, and post-market surveillance will be needed to ensure that these treatments and vaccines are not substandard or falsified [43].

Limitations of the Study

One limitation to this study is the number of databases considered; some databases like 'Web of Science' and 'Scopus' were not included in the literature search due to lack of access to these databases. We were limited by the lack of comprehensive data and global reports on substandard and falsified medicines, especially from developing countries. Limited data is available on the estimated economic and socioeconomic impact of substandard and falsified medicines as well. There are also limited reports from national drug regulatory agencies on substandard and falsified medicines.

Conclusion and Recommendations

This review identifies that substandard and falsified medicines are a global threat to health, economics and good governance. Over the years, strategies have been implemented at the international level by the WHO and at the national level by national regulatory authorities of individual countries. However, these strategies must be strengthened, and appropriate actions must be carried out. Further awareness should be created on the menace and potential harm caused by substandard and falsified medicines. Health care professionals and patients should be educated on how to identify these medicines and how to report them. Manufacturing companies should be highly regulated to conform to national and international standards. Adequate laws and commensurate punishments should be enforced to ensure justice is served to the illicit traders and distributors of substandard and falsified medicines.

Pharmacists play a critical role in the curbing of this menace from the production point to the patient level, hence pharmacists should be adequately empowered at all settings for this. Pharmacists can educate patients about what to look out for in packaging of falsified medicines, they can also report adverse drug reactions which can raise awareness to substandard or falsified medicines in circulation.

Also, pharmacy students can increase public awareness on substandard and falsified medicines, highlighting the potential dangers and possible mortality associated with these medicines. They can also provide information on appropriate online and offline pharmacies that can supply safe and effective medicines.

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