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Article

Counterfeit medicines: relevance, consequences and strategies to combat the global crisis

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Counterfeiting of medicines, also known as "falsification" or "adulteration", is the process in which the *identity*, *origin,* or *history* of genuine medicines are intentionally modified. Currently, counterfeit medicines are a global crisis that affects and is mostly caused by developing countries in Asia, Africa and Latin America. These countries lack strict law enforcement against this practice and have low-income populations with medicinal needs. Lately, the crisis has escalated, impacting developed countries as well, e.g., the US and the EU, mainly via the Internet. Despite this extension, some current laws aim to control and minimize the crisis' magnitude. Falsification of medicines maintains an illegitimate supply chain that is connected to the legitimate one, both of which are extremely complex, making such falsification difficult to control. Furthermore, political and economic causes are related to the crisis' hasty growth, causing serious consequences for individuals and public health, as well as for the economy of different countries. Recently, organizations, technologies and initiatives have been created to overcome the situation. Nevertheless, the development of more effective measures that could aggregate all the existing strategies into a large functioning network could help prevent the acquisition of counterfeit medicines and create awareness among the general population.

Keywords: Counterfeit medicines. Falsification. Legislation. Medicines supply chain. Brazil.

INTRODUCTION

The term "counterfeiting" refers to the idea of "falsifying" the content that an original product intends to transmit, causing a misunderstanding for the consumer regarding the identity of such product (Goyanes, 2008). Thus, adulterated, fake or counterfeit drugs are the those that deliberately/fraudulently has a false presentation of *identity* (packaging, labeling, name, composition of excipients and active ingredients or their quantities), *origin* (manufacturer, country of manufacture or marketing authorization holder), or *history* (records or distribution documents), excluding those with unintended defects (World Health Organization, 2018; The European Parliament and The Council of The European Union, 2011).

Most commonly, adulterations are related to the composition, since counterfeit drugs may not contain an active pharmaceutical ingredient (API), contain a wrong or different dosage of API, or may contain undesired substances, making them illegal and harmful to the population's health (United States Food and Drug Administration, 2019b). In 2013, a semi quantitative thin-layer chromatography analysis was performed on 713 samples of two first-line anti-tuberculosis medicines collected from low and middle-income countries in Africa, China, India and Brazil. 29 samples showed less than 80% rifampicin or isoniazid, and 36 samples demonstrated less than 10% of both APIs (Bate *et al*, 2013). In 2017, 13 confiscated tablets falsely labeled as "Viagra", circulating in the Brazilian market, were examined by infrared spectroscopy. 10 tablets demonstrated reduced dosages of sildenafil, and 8 tablets contained starch and 6 tablets contained calcium sulfate as undesired substances (Neto, Lisboa, 2017).

The counterfeiting of medicines is a huge and worldwide crisis that has escalated in the last two decades

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due to a rapid globalization, with 10% of all medicines sold worldwide estimated as counterfeits (Fantasia, Vooys, 2018). The main factors contributing to its spread are related to the high costs of medicines and treatments, failures in the legal supply chain, gaps in legislation, easy access to technologies, poverty, as well as lack of strict law enforcement

Developing countries in Asia, Africa and Latin America have been heavily affected by the counterfeit drug market, considering that they present many of the previously mentioned factors and have large low-income populations with medicinal needs. In those countries, counterfeit or poor-quality medicines are appraised to be more than 30% of all marketed medicines, with this rate higher than 50% in certain regions (Jackson *et al*., 2010; Yadav, Rawal, 2015). These countries, especially India and China, are also the sources of falsified medicines. The European Commission estimates that 75% of all globally distributed counterfeit medicines originate in India (Yadav, Rawal, 2015).

In Brazil, the sale of counterfeit medicine has grown in the last decade, marked by a significant increase in arrests by Brazilian Federal Police (BFP). Some of the data collected between 2007 and 2010 revealed that 610 medications were confirmed as falsified by forensic reports, coming mostly from the Southern and Southeastern states that have important seaports and border other Latin American territories. (Ames, Souza, 2012).

Despite the strong incidence in Asia, India and Latin America, developed countries in the European Union (EU) and the United States (US) frequently sell and purchase these counterfeit drugs. The World Health Organization (WHO) evaluates that in some of these countries, more than 20% of medicines sold are counterfeit (Liang, 2006). North America is where the highest number of incidents (1750) involving counterfeiting, illegal diversion and drug theft were reported in 2018 (Pharmaceutical Security Institute, 2019). In addition to the internet being the central source to access counterfeit medicines in developed countries, such medicines represent 50% of all those sold on the internet, which is projected to increase annually (Mackey, Liang, 2011; Fantasia, Vooys, 2018).

This literature review addresses the occurrence of counterfeiting / falsification of medicines in the world and in Brazil. In addition, the risks to patients' health, and social, economic and public health impacts, as well as the most current regulations, are analyzed and discussed. All data used herein was collected from organizations' official websites and indexed articles from Pubmed, and Google Scholar archives, between 2006 and 2020.

Current Legislation

Regarding the huge emergence and seriousness of this global problem, the law enforcement in developed countries (including Brazil) seeks to adopt measures that outlaw the practice of counterfeiting medicines, while at the same time try to control and minimize its extent, as illustrated in Figure 1. The *Trade-Related Aspects of Intellectual Property Rights* (TRIPS) agreement, signed in 1994 by the World Trade Organization (WTO) are currently formed by 164 member countries, including Brazil, European countries and the USA. It legally refers to the counterfeiting of medicines as an intellectual property (IP) violation held by the owners of copyrights, patents and trademarks, being characterized as "counterfeit of trademark products".

This international law says that any product, which is a copy/plagiarism of a validated and registered trademark, including packaging and unauthorized manufacturer, infringes on the owner's rights of the trademark and is under the jurisdiction of the importing country's law (Dégardin, Roggo, Margot, 2013; World Trade Organization, 1994). In this case, the agreement presumes that all member countries shall apply penalties to offenders that include imprisonment and/or monetary fines consistent to the level and severity of the offense. In cases where falsified medicines are available, the countries must also confiscate and destroy any material that has been used for their implementation (World Trade Organization, 1994).

In the USA, the *Prescription Drug Marketing Act* (PDM) of 1987, which is still enforced today, was signed by the President on April 22nd 1988. It aims to ensure that all drugs purchased by American consumers

are effective and safe, as well as to protect consumers from adulterated, low quality or expired medicines. Such legislation was necessary to increase security in the drug distribution system, preventing the insertion and sale of low-quality or falsified drugs (United States Food and Drug Administration, 2018a). In 2013, the *Drug Supply Chain Security Act* was established by Congress, defining a new electronic system that identifies and traces some prescription drugs as they are distributed around the whole country. This system is able to better protect consumers from potentially dangerous, counterfeited or poor-quality medicines, as it improves recognition and elimination of those drugs from the supply chain (United States Food and Drug Administration, 2019a).

Two main legislations against counterfeit medicines are enforced today in the EU. The first is the *Directive 2011/62/EU* created by the European Parliament and the Council and applied to all EU countries - also recognized as the *Counterfeiting Directive*. This *Directive* generated a code for medicines used for human purposes that prevents counterfeiting activities from occurring in the legitimate supply chain. This legislation establishes a control of medicine marketing in the EU jurisdiction from the manufacturer to the final consumer, including internet sales. Additionally, the *Directive* determines the penalties that are applied to counterfeiting agents and all those involved in the illegal distribution (The European Parliament and The Council of The European Union, 2011).

The second legislation was also created by the European Council, and is known as the *Medicrime* convention, signed in 2011, which condemns the counterfeiting of any medical product. It was the first restrictive judicial instrument in the criminal law system. The convention obliges all signatories to recognize as crimes: the production and distribution of counterfeit drugs, any involvement in the supply chain, as well as the falsification of documents, their unauthorized supply and any sale inconsistent with the requirements. In addition, it foresees the Internet as a aggravating factor for the sale counterfeit medicines (Council of Europe, 2015).

In the Brazilian national territory, the edition of *Law No 9.677* (of July 2nd, 1998) in the Brazilian Criminal Code (BCC), popularly known as the *Remedies Law*, was the first concrete and specific initiative against medicine counterfeiting, characterizing it as a heinous, second degree crime. In the same year, this law was reedited in *Law No. 9.695* (of August 20th, 1998), which includes the counterfeiting of drugs in Article 1, VII-B of *Law No 8.072 / 1990* (of heinous crimes) and other measures that were not previously provided by *Law No. 9.677.* Therefore, the crime of falsifying, corrupting or adulterating a product envisioned for therapeutics or medicinal purposes is punishable by imprisonment from 10 to 15 years, and a fine provided by *Law No 9.695* (Presidência da República, 1940, 1998a, 1998b).

Subsequently, with the emergence of the *Brazilian National Health Surveillance Agency* (ANVISA) in 1999 (Piovesan, Labra, 2007) it was possible not only to punish the counterfeiting of medicines, but also to optimize the prevention and fight against the crime. This upgrade was consolidated by the establishment of regulations created to control the production and distribution chains of medicines in the country (Hurtado, Lasmar, 2014). An example of ANVISA's actions is provided by *Law No. 11.903* (of January 14th, 2009) called the *Traceability Law*, which specifies production and consumption medicines tracking through detection and storage technologies and data electronic transmission, as well as the coordination of information through a database called the *National Medicines Control System* (Presidência da República, 2009).

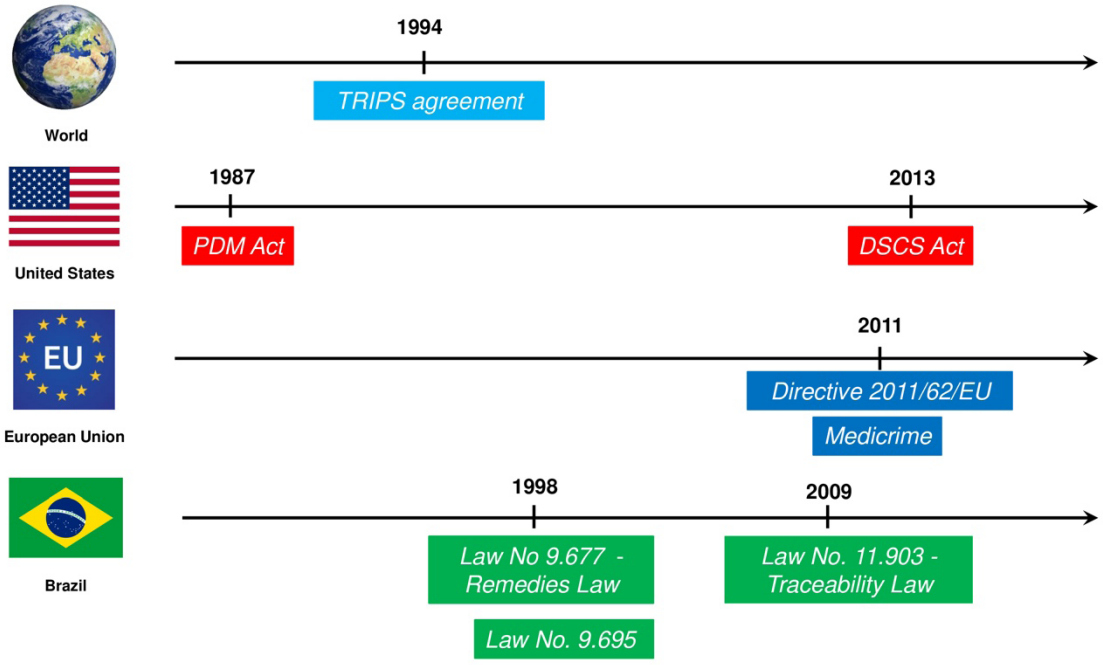

FIGURE 1 - Timeline of the current legislation in the world, specifically in the United States, European Union, and Brazil.

Medicine Supply Chains and The Causes of Counterfeiting

Legitimate or legal medicine supply chains are complex and difficult to track, even though raw materials and semi-finished products are not involved. The manufacturing industries usually sell medicines to distributors who deliver them directly to hospitals, pharmacies and drugstores, which finally dispense them to consumers (Silveira, 2012). However, medications can also go through anywhere from 20 to 30 intermediate parties between the manufacturer and the consumer, characterizing the *trade or parallel importation* (Liang, 2006). The core of this type of importation is the repackaging process, when new labels translated to the language of the importing country are set. This process must follow the necessary regulatory requirements of the country and labels must be approved by the specific Sanitary Authority (Silveira, 2012; Dégardin, Roggo, Margot, 2013).

On the other hand, the illegitimate or illegal supply chain has become a well-structured framework composed of manufacturers, distributors and local sellers, whose main objective is to "complicate" the legitimate chain, so the traffic of their counterfeit medicines is undetected (Dégardin, Roggo, Margot, 2013). Usually, packaging and medicines are produced in different countries and are then exported with other components to a final destination where they are prepared and distributed. For instance, counterfeit medicine originating in Asia can be packaged by a fake packaging process in Africa and vice versa. Final drugs are sometimes hidden and/or smuggled and declared as something different in their attached documentation. Mostly, they are exported by air or sea through complex or unusual routes and can easily access legitimate chains at any moment (Silveira, 2012; Pisani, 2017).

Therefore, it is clear that the legitimate supply chain is extremely vulnerable to the activities and flow of counterfeiting most of the time, which makes surveilling and controlling this type of trade difficult tasks (Liang, 2006). Consequently, even hospitals, pharmacies and drugstores are exposed to falsified medicines. Because of this, it is crucial that those establishments are able to work with efficient systems that can track the supplied batches and manage their quality to ensure that a genuine medicine reaches the consumer.

One of the reasons for the wide expansion of the illegal supply chain is not necessarily related to the population's purchasing power and/or quality of life, but rather to easy access and privacy. In this context, the internet is an important means for distributing falsified medicines, since it is directly linked to the consumer and takes advantage of an individual's need to obtain pharmacological treatment, especially elderly and disabled people (Dégardin, Roggo, Margot, 2013).

In addition to being a fast, free and easy way of communication between consumers and distributors, the internet is also a channel that is difficult for regulatory and surveillance authorities to control and track. In general, this happens because legislation does not foresee situations that involve the sale and purchase of fake or poor-quality medicines, which makes preventive measures more complex. Also, unlike the legal supply chain, the commercialized medicines in this illegal chain are those that are in high demand for treating diseases (such as anti-infectious agents, antibiotics, etc.). Furthermore, there are other factors that sometimes cause consumers to feel uncomfortable buying medicines through legal means (e.g., anabolic steroids, agents for erectile dysfunction treatment, etc.). Thus, consumers prefer to use the internet or other illegal channels which provide not only purchasing privacy, but more affordable prices as well (Silveira, 2012).

Following this idea, phosphodiesterase - 5 (PDE-5) inhibitors (sildenafil - Viagra®, tadalafil - (Cialis®) and vardenafil (Levitra®) are the most frequently commercialized medicines in the illegal supply chain worldwide. Due to the issue of privacy related to these drugs, the internet ends up being the main source of access for consumers. In the US, there is a hypothesis that most selective PDE-5 inhibitors reach consumers by the internet, via duplicitous websites (Jackson *et al*., 2010). Websites that claim to sell authentic Viagra, end up delivering a fake drug, containing only 30% to 50% of the API shown on the label, 77% of the time (Campbell *et al*., 2012). According to WHO, antimicrobials come in second place, representing nearly 50% of all counterfeit drugs worldwide, with 78% originating from developing countries (Kelesidis, Falagas, 2015; Pisani, 2017).

In Brazil, the situation is similar to developed countries, since erectile dysfunction medications are the main target for falsification, followed by anabolic steroids, prostaglandin inhibitors, cancer and AIDS treatment medicines. In the previously stated apprehension by BFP, around 69% of the 610 drugs presented as counterfeit were selective PDE-5 inhibitors (Viagra® and Cialis®), 26% were anabolic steroids (Durateston®, Hemogenin®, Deca-Durabolin®) and 3.5% were prostaglandin inhibitors (Cytotec®) However, it is assumed that sea, land and airports are the main routes for those medicines to enter the country in the illegal supply chain (Ames, Souza, 2012). Moreover, herbal medicines are also a common target of the counterfeit market in Brazil due to their popularity among the population, which holds cultural beliefs that the more natural a medicine is, the less harm it does. (Hurtado, Lasmar, 2014).

Moving forward, there are numerous causes that explain the rapid global expansion of counterfeit medicines, mainly those that are political and economic in nature. First, high profitability is the starting point, since medicines are expensive products with high added value (Burns, 2006). This makes them more valuable targets for business as production is much less expensive than that of the original ones, which involves spending money and time on research development, licenses or health registration. Even if a counterfeit medicine has the correct ingredients, their quality standards and workforce wages would be much lower (Reynolds, Mckee, 2010).

Second, existing legislation is vague and fragile, and only benefits the companies with reference medicines that can partially manage to defend themselves against the problem. However, the punishments established by the laws of many countries do not suit this type of felony, as they do not consider the crisis that is generated for the public health in their scope. Thus, from a legal point of view, the crime of counterfeiting and public health are dissociated, creating a huge disadvantage in the combat against counterfeiting medicines. Furthermore, companies that manufacture generic or similar drugs cannot use intellectual property laws as a defense strategy (Shepherd, 2010; Attaran, Bate, Kendal, 2011; Newton *et al.,* 2011). In many countries, court decisions and court cases, especially those in developing countries, are often bureaucratic and time-consuming. Additionally, enforcement is oftentimes weak and appears to facilitate

or collaborate in the crisis in some countries (Organization for Economic Cooperation and Development, 2008).

Third, genuine medicines are expensive and carry the burden of importation processes, taxes and responsibilities of patient safety. On the other hand, the search for cheaper and easier alternatives encourages the expansion of other reckless – sometimes dangerous - means, such as sales on the streets or internet distribution (Wertheimer, Norris, 2009; World Health Organization, 2018). In addition, unlike drug dealers, counterfeiters run a low risk of being caught. Fourth, there is corruption in many developing countries, where genuine medicines are often stolen at different levels of their legitimate supply chain. Bribes, drug cartels and even terrorism financing are regular incentives that keep the drug counterfeiting chain growing (Organization for Economic Cooperation and Development, 2008; Reynolds, Mckee, 2010; Dégardin, Roggo, Margot, 2013, 2015).

Fifth, countries are rarely able to supervise millions of medicines that are constantly arriving through many airports, land borders and seaports coming from thousands of different manufacturers. Therefore, it is common for these countries to fail to confiscate all of these drugs and to presume that these medicines are of acceptable quality (Pisani, 2017; Charles, 2020). When diligent and cooperative agreements between health authorities are presented, the importing country can carry out inspections in the manufacturing countries to approve the assumed quality. Although, even in better equipped and regulated countries as those in the EU - where the pan-European regulatory body is reinforced by country-specific regulatory agencies - counterfeit medicines can still enter the market, and are hardly detected. (Pisani, 2017).

Finally, some measures are currently being taken, however, are sporadic and very specific. There is still no well-structured system or properly implemented method to inspect, control or directly interfere in any stage of the illegitimate supply chain at a global level. Therefore, counterfeit medicines are wildly, openly and easily exported and imported around the entire world. Also, they contain packaging technologies that mask their true nature and generate a very similar product that can effortlessly deceive the consumer.

Consequences of Counterfeiting Medicines

Risks to Patient's Health and Impacts on Public Health

The use of counterfeit medicines causes several risks and harmful effects to the health of a patient, creating a "snowball" effect, which ends up causing a greater risk to the health of an entire population. The different scenarios involving these risks depend on the composition of each medicine. The first scenario is related to the fact that patients suffer from chronic diseases or are at risk of dying since the "medicine" used does not contain the correct API or has sub therapeutic concentrations of the API (World Health Organization, 2017).

In the case of counterfeit antimicrobial agents, for example, the lack of correct API levels can promote microbial resistance. Subsequently, the use of a higher potency antimicrobial is required, since the first one was adulterated and had no efficacy (Liang, 2006). Microbial resistance is a serious problem both individually and collectively because colonies of resistant pathogens are established and dissemination is facilitated. Patients who develop resistance to infections due to counterfeit drugs present complications in their own treatment and accumulate these dangerous pathogens. When such patients travel to other regions or countries, they can easily expose the local population to the mutant infection, without even being aware of the outcomes (World Health Organization, 2017). Additionally, the incorrect use of a more potent antimicrobial not only exposes the patient to worse adverse effects but can also compromise the medication's efficacy. Oftentimes, a more potent antimicrobial is the last option available for treating a possible microbial resistance, which can generate loss of effectiveness in therapies if used improperly (Nayyar, Breman, Herrington, 2015). Besides, counterfeit antimicrobials also reduce the patient's adherence to their use and leads to treatment failure, increasing a populations' morbidity and mortality (Kelesidis *et al.,* 2007).

A second scenario would be the counterfeit medicine containing a dangerous contaminant, such as bacteria-lactating water, anti-freezing agent or even extremely high levels of API. Such scenario can lead to an increase in toxicity, even if the medicine has a low therapeutic index.

In this case, the patient's conditions may worsen and lead to death (Kelesidis, Falagas, 2015). Another possible scenario could occur when counterfeit medicines are composed of different API's, unintentionally exposing patients to drug interactions. This circumstance may lead to toxicity, increase the probability of other infections, as well as lead to therapeutic failure (Blackstone, Fuhr, Pociask, 2014).

In general, all of the situations described above lead to indiscriminate growth in population morbidity and mortality, which has the greatest impact on a countries' public health. Another extremely relevant impact on public health is a patients' loss of confidence in pharmacological treatments, health systems, including public institutions, and even in health care professionals. In this context, the tiniest of doubts or suspicions regarding the efficacy or necessity of a treatment and/or quality of a medication lead the population to avoid specific health facilities, reject vaccination and neglect prescribed treatments. The aftermath includes patients withholding full treatment or obtaining alternative treatments at unregulated and even illegal establishments, contributing to the spread of this unauthorized service (Newton *et al*., 2006; World Health Organization, 2017). Regarding patients with infectious diseases, the lack of correct treatment, due to distrust in their effectiveness, leaves patients in infectious states, making them potential vectors of diseases, which presents enormous risks to global public health (Kelesidis, Falagas, 2015).

Furthermore, the increased consumption of counterfeit medicines impacts national and international statistics of drugs' adverse effects, which are essential for controlling safety and effectiveness in post-marketing surveillance. PDE-5 inhibitors are an excellent example of this since counterfeit ones, are difficult to identify and monitor for defects and adverse drug reactions that make drug recall necessary because they are produced outside the specifications of any regulatory authority, (Jackson *et al.,* 2010). Another example of such impact is antimalarial agents, which are visually identical to the original ones but are adulterated with starch. At first, they may not trigger toxicity, but they will not have the desired effectiveness either. Consequently, health systems with gaps in regulatory capacity, including post-marketing surveillance and pharmacovigilance, may experience delays or failures in collecting data about the lack of efficacy, unexpected or abnormal efficacies and/or toxicity of counterfeit medicines (World Health Organization, 2017).

Exploring further, since the beginning of 2020, the world has been suffering from a pandemic event triggered by the new coronavirus (Sars-Cov-2), which unexpectedly impacted global health care systems (World Health Organization, 2020a). As with any pandemic event, the disease affects a huge number of people from a wide geographic area, and can sometimes happen in a short period of time. Depending on the level of symptoms, immediate hospitalization and care is required, generating thousands of emergencies at the same time. Consequently, hospitals become overloaded, the demand for medicines and medical supplies increases absurdly and these supplies are used up, leading to the possible collapse of health care systems (Madhav *et al.,* 2018). Currently, this scenario represents Brazil, US, Italy and many other countries, where hospital beds and Individual Protective Equipment are constantly being required (Armocida *et al*., 2020; Lemos *et al*., 2020).

In this case, a pandemic event can prompt people to seek miraculous treatments and medicines (for example, chloroquine as prophylactic and severe Sars-Cov-2 infection treatments) lacking safety protocols and proof of efficacy (Borba *et al.,* 2020; Biguetti, Marrelli, Brotto, 2020; Guastalegname, Vallone, 2020). This induces false marketing and incorrect use of medicines that are supposed to treat other comorbidities, leading to adverse effects and unavailability of those medicines for whom need it the most. Therefore, in the coming months, this pandemic event could provide a huge opportunity and profitability for the counterfeit marketing. When counterfeit medicines that lack efficacy and safety are introduced to desperate populations, it can broaden damage and lead to unpredictable outcomes. Because of that, it is essential for all States to be aware of this possible development and reinforce surveillance.

Economic and Social Impacts

All previously discussed health risks, such as treatment failures, exposure to diseases and increased

mortality and morbidity, are costly for patients and families and place even more tensions on healthcare systems. In addition to the impact on public health, counterfeit medicines have important socioeconomic effects (World Health Organization, 2017).

Medicines not funded by family budgets are often paid for by the government, health systems and even health insurance providers. Thus, everyone ends up bearing the costs of counterfeit medicines that cause therapeutic failure or toxicity. Exams, treatments and additional care consume money, skilled labor and infrastructure throughout the healthcare system, reducing resources that are frequently overburdened. Moreover, when incidents of counterfeit medicines cause public distress, programs such as vaccinations, which generate public and government spending, are weakened and denial effects are multiplied (Newton *et al.,* 2011).

Adverse effects (including efficacy absence) caused by therapies using counterfeit medicines can have additional expenses due to extended treatments associated with the correct and quality-assured medicine. Also, additional health care costs may incur from adverse reactions or resistant infections that would not have occurred if the previous medication was original, safe and effective. In cases where antimicrobial resistance is suspected to be the cause of treatment failure, there are additional costs to conduct susceptibility tests and acquire higher order antimicrobials that are more expensive (Wertheimer, Norris, 2009; Newton *et al.,* 2011).

Therefore, the effects of consuming falsified medicines also extend to the productive economy. Since a patient's productive status lowers with their health state or physical condition, they are eventually forced to stop working for the duration of the necessary treatment, while still receiving their rights and benefits. As a result, there is a decrease in the quality of life for a country's productive capacity, as well as an unbalanced increase in spending by the private and public sectors on the population. Subsequently, this circumstance leads to an impoverished population and long-term economic and social losses in a country (Wertheimer, Norris, 2009; World Health Organization, 2017).

Strategies to combat Counterfeiting Medicines

The preeminent solution to this crisis is associated with a large regulatory process and strong implementation, together with coordinated actions at all levels and by all members of the legitimate supply chain: from the government's political action to the consumer. Counterfeiting medicine is a solemn matter that requires radical measures to be taken (Yadav, Rawal, 2015). At the political level, some organizations and actions already exist, however many others could be generated to join movements between national and international organizations, governments and specific legislation. At the supply chain level, few technologies have been implemented to monitor, detect or protect genuine products. Other sustainable initiatives could be executed by authorities, as well as consumers.

Organizations

Recently, other international groups have been complementing the institutional capacity that WHO could not fully provide. The main organization involved is the *United Nations Office on Drugs and Crime* (UNODC), an organ specialized in creating policies and directing actions to fight all forms of transnational organized crime. Its scope includes preventing and fighting all types of crimes, from illicit drug trafficking to terrorism, and seeks criminal justice worldwide (United Nations Office on Drugs and Crime 2013). All of these elements have direct links to counterfeit medicine markets, which the emerging UNODC involvement has already brought the necessary attention to. However, UNODC might be able to contribute even more to the cause, since it already administers some international treaties against other types of crimes, such as the *United Nations Convention Against Transnational Organized Crime* (UNTOC). This convention has wide international action, applicability and viable mechanisms that could be extended in the future to include crimes of medicine falsification (Mackey, 2013).

Working together with UNODC, the *International Police* (Interpol) has been a key player in the international fight against counterfeit medicines because it can mobilize local and specific borders, police, as well as

recruit public and private sectors' scientific and financial resources (ex: scientific experts, financial institutions, laboratory facilities, etc.). All those resources are crucial for developing intervention plans that provide support for land-based operations aimed at directly intervening in the legitimate and illegitimate supply chains of counterfeit medicines (Interpol, 2011). In fact, Interpol has been primarily responsible for the world's major counterfeit drug seizures, which started in 2013 with the creation of the *Interpol Pharmaceutical Crime Program* (IPCP). The program is a comprehensive pharmaceutical initiative against crime that partners with 29 of the world's largest pharmaceutical companies (Interpol, 2013).

The *International Medical Products Anti-Counterfeiting Taskforce* (IMPACT) was created in 2006 by WHO, and includes partnerships with all the main organizations involved in preventing the counterfeiting of medicines and medical products. It brings together international organizations, associations, regulatory authorities and groups of healthcare professionals and patients (World Health Organization, 2010). IMPACT's main objectives are to prevent the production and market of counterfeit medicines, as well as enable all partners to communicate and collaborate with one another, so they can manage monitoring actions to eliminate the adulteration crime.

Five IMPACT's departments were created for prevention purposes. One prepares strategic documents that help member countries to apply or update their laws. A second is currently responsible for influencing countries' regulations by advising national authorities on which improvements should be made to deal with counterfeit medicines more efficiently. A third front is dedicated to training individuals in charge of confiscations and to implement collaboration amongst the different countries' authorities. The fourth is in charge of disseminating helpful information to select technologies that can be used to screen and detect medicines. Finally, the last front is responsible for communication, creating models that provide support and alert the public (Burns, 2006; Virella, 2008; Delepierre, Gayot, Carpentier, 2012).

Composed of 69 non-profit organizations, *The Partnership for SafeMedicines* (PSM) is a public health association dedicated to propagating the importance of prescription drug safety, as well as to protect consumers from counterfeit or substandard medicines and other unsafe products. The group helps consumers, industries and governments recognize and implement significant resolutions that can combat the global counterfeiting crisis. PSM regularly publishes news archives, posts about current topics written by experts, presents drug safety bibliographies, holds press releases and provides an encyclopedia of key counterfeit medicine incidents worldwide (The Partnership for SafeMedicines, 2020a).

In the Brazilian territory, ANVISA is the main national entity that aims to maintain high standards of production, distribution and consumption of quality medicines around the whole country. Every day, ANVISA publishes resolutions regarding all falsified/ irregular medicines that have been identified and are circulating around the country in the *Brazilian Official Diary of the Union,* reporting on features regarding labelling and batch number. The resolutions basically aim to alert all legal supply chain parties, especially hospitals, pharmacies and consumers, to provide appropriate recall. (Agência Nacional de Vigilância Sanitária – Produtos Irregulares, 2020). Besides ANVISA, the *National Institute for Quality Control in Health* (INCQS) is a federal level unit of the Oswaldo Cruz Foundation (Fiocruz), which was created in 1981 and acts as a national reference for scientific and technological issues related to the quality control of products at all levels. (Instituto Nacional de Controle de Qualidade em Saúde, 2020).

Additionally, the BFP is an important agency analogous to Interpol, that possesses crucial information about seizures of counterfeit medicines and forensic reports, all of which are saved in a *Criminal System* database. Through this system and intervention of regional and local policies, it is possible to evaluate the extension of falsification of medicines throughout the country's territory in order to plan prevention measures and punishment actions that are executed by BFP and ANVISA (Ames, Souza, 2012; Hurtado, Lasmar, 2014).

Regionally, there are *Health Surveillances,* bodies of the Public Health subarea with "police power" - authority to intervene in private freedoms to ensure collective interests. Their goal is to control and assure quality of medicines and pharmaceutical supplies, by inspecting establishments that

manufacture, handle, transport or commercialize these products to verify the entire production process, methods and techniques used. Additionally, the *Public Health Central Laboratories* (LACENs) work directly with their respective regional Health Surveillance, evaluating the quality of medicines of public health interest (Laboratório Central de Saúde Pública de Santa Catarina, 2020). All together, the BFP, Regional and local law enforcement (States and police stations), ANVISA, INCQS, Health Surveillances and LACENs represent the entire Brazilian law enforcement responsible for regulating all medicine markets and inspecting all counterfeits that circulate throughout Brazil.

In addition, the *Regional Council of Pharmacy of Sao Paulo* (CRF-SP) - a professional body that regulates the role of all registered pharmacists in the State of Sao Paulo – has provided guidelines to assist all pharmaceutical professionals, as well as the general population, with counterfeit medicines. The guidelines contain easy-to-understand content about how to identify falsified medicines, which is responsibility of the pharmaceutical professional, and how to proceed when facing such issue. Presently, the CRF-SP has a functional email and phone number in which anyone can report any information regarding falsified medicines or pharmacists or establishments selling them. (Conselho Regional de Farmácia de São Paulo, 2012).

Technologies

The WHO's current surveillance system was developed due to breaches in the intrinsic processes of the medicines legal supply chain, which has created global production frameworks and increased interconnectedness of different drug markets (Pisani, 2017). No single country or region has been able to easily collect all the information needed to quickly respond to threats generated by the entry of poor quality and counterfeit medicines. Based on that, an initiative called the *Global Surveillance and Monitoring System* (GSMS), developed by WHO in the Western Pacific Region, was instituted. It is funded by the FDA with the support of the Bill and Melinda Gates Foundation and promotes training events supported by the European Commission, Asian Development Bank and the US Pharmacopoeia Convention. Also, it works with WHO member states to improve the quality of substandard and counterfeit medicine reports.

The GSMS system works through reports of suspected or validated falsified/substandard medical products made by member states. The reports are uploaded into a protected WHO database for instant comparison against other existing reports and for full data analysis. WHO contacts the reporting member states within a few days for further information/ details in the case of any matches in the database, as well as to provide technical support if necessary. When emergencies, such as adverse drug reaction incidents, are reported, the WHO contacts member states in 24 hours to provide any assistance needed, urgent laboratory analyses, and in more complex cases, field experts (World Health Organization, 2020).

Additionally, the system aims to ensure that all data collected is analyzed and used to influence policy, generate procedures for prevention and protect the public health at global, national and regional levels. The GSMS was piloted in 10 countries between 2012 and 2013, and was launched in Africa in July 2013. Today, the GSMS has the support of 194 countries working on voluntary committees to expand the system and its effectiveness around the world (Pisani, 2017; World Health Organization, 2020b).

Another emerging technology is the *Rapid Alert System* (RAS). This is a communication network created by WHO and partners that provides intersectional detection and notification of counterfeit medicine occurrences. The system seeks to promptly alert WHO member states and specific authorities to take action (World Health Organization Regional Office for Europe, 2014). However, RAS could be better exploited if consumers could make anonymous reports/complaints about illicit websites and counterfeit products. In this case, the results would be organized and communicated to all members in the system (from manufacturers to the public) to alert them about the risks of those websites and products (Mackey, Liang, 2011). This hypothetical function would be similar to *Medwatch* and the *SafeMeds Email Alert System*, both of which are the FDA's official notification systems (United States Food and Drug Administration, 2020; The Partnership for SafeMedicines, 2020b).

In 2014, WHO held a workshop about RAS implementation and training for *Substandard/Spurious/Falsely labeled/Falsified/Counterfeit* (SSFFC) medicines. 48 experts from 19 countries in the WHO European Region attended the workshop, including pharmaceutical inspectors, pharmacovigilance departments, quality control laboratories and other correlated departments. Thereafter, RAS was expected to be improved and covered by other stakeholders for refined reporting capacity. For this to happen, it is essential to obtain more assets such as a higher number of specialized laboratories that offer a full range of emergency forensic tests with quality assured, more accurate incident reports containing scale, extent and damage caused by SSFFC medicines, along with better analysis of those reports. In addition, to optimize RAS, it is important to develop other systems that can examine existing adverse reaction and medication ineffectiveness reports, which could identify any hidden signs of SSFFC medicines at the patient level in global supply chains (World Health Organization Regional Office for Europe, 2014).

Since 2001, the FDA has suggested that pharmaceutical companies use tracking and product authentication technologies as a higher level of safety for their own genuine medicines. In this context, the *Radio Frequency Identification* (RFID) technology has been directed to the pharmaceutical area to meet their security needs. The technology uses a small radio frequency chip as a very discrete electronic product code, containing essential product information. The implementation of RFID allows stakeholders in the supply chain to track the course of each batch of medicines uniquely and more efficiently. Some states in the US already require that all medicines be identifiable to patients through RFID chips (Gautam, Utreja, Singal, 2009; Coustasse, Arvidson, Rutsohn, 2010).

Moreover, some countries like Ghana and Nigeria have taken the lead in introducing technology built on mobile devices (cell phones, tablets, etc.) called *Message Alert System*, which basically gives consumers direct contact with producers, and vice-versa (The Partnership for SafeMedicines news, 2010; Yadav, Rawal, 2015). All products are given a unique code, then consumers are able to check the product's legitimacy by sending a free SMS containing the code to a specific number, which instantly sends them confirmation as to whether the product is genuine or not (Gautam, Utreja, Singal, 2009; The Partnership for SafeMedicines news, 2010).

Other Initiatives

Product protection means increasing the price/cost of the final product, which could cause logistical and financial problems. However, pharmaceutical industries are responsible for generating initiatives alongside governments to implement such technologies and guarantee that genuine and quality assured medicines actually reach the general population. A real example of this intervention is the GPHF-Minilab™, a mobile mini-laboratory used in developing countries, which was created by *The Global Pharma Health Fund* (GPHF) under the supervision and funding from MERCK Germany. This tool quickly analyzes the chemical and physical quality of the medication and is able to detect counterfeit ones (The Global Pharma Health Fund, 2020).

Some other initiatives to combat falsified medicines have been introduced in particular countries and some can be explored as means to mitigate the problem. For instance, the Nigerian *National Agency for Food and Drug Administration and Control* has successfully implemented security strategies to fight counterfeit medicines. Such strategies mainly consisted of reforming their own Agency and gathering support from the Port Inspection and Inspection Department to solve interruptions in inspection activities. Thereafter, studies reported a more than 80% reduction in the presence of falsified medicines in Nigeria from 2001 to 2004 (Chinwendu, 2008).

Regarding the production and distribution of medicines, one action that could be taken is restricting the sales of high-speed compression machines (essential for the production of tablets) to manufacturers registered by the respective Ministry of Health in the manufacturing country, excluding any other unauthentic buyers. Another possible idea would be to establish a prequalification list for health authorities of the importing countries, where manufacturers are invited to send samples of their products for analysis in reliable and authenticated laboratories. Manufacturers who pass the tests and agree to provide an Export Certificate and funds for any applicable penalties would be allowed to be registered

on the country's official approval list for importation (Wertheimer, Norris, 2009).

Lastly, understanding medicine counterfeiting phenomenon must be global, especially for consumers/patients, who need to be aware of all outcomes and uses in order to avoid consuming those medicines. To this end, governments, authorities and organizations worldwide, along with the media, must create countless campaigns and provide trainings to the entire global population, especially the underprivileged portion. The main focus should be the real threats that selling and acquiring counterfeit medicines can cause to human health and to the lives of all individuals (Fantasia, Vooys, 2018). These actions must be simple and easy to comprehend in order to give the population the necessary support, particularly about purchasing medicines on the internet (Blackstone, Fuhr, Pociask, 2014). Figure 2 reflects the possible strategies discussed in this paper, creating a network that connects both legal and illegal supply chains to reduce the crisis globally.

Consumers/patients should be attentive and meticulous when buying or using medicines and should always consult a pharmacist they trust in case of any queries. The FDA currently provides a practical online guide containing tips on how to purchase more safely over the internet. Basically, those tips advise all consumers to first check whether the intended website is safe and provides a legitimate address, then, check if the site provides customer service and if a prescription is required for prescription-controlled medicines (United States Food and Drug Administration, 2018b). Additionally, before taking the medicine, consumers should also check whether the package is properly sealed and has an appropriate expiration date, as well as examine if the contents correspond to the packaging, always preferring brands with recognized names and packages (Virella, 2008).

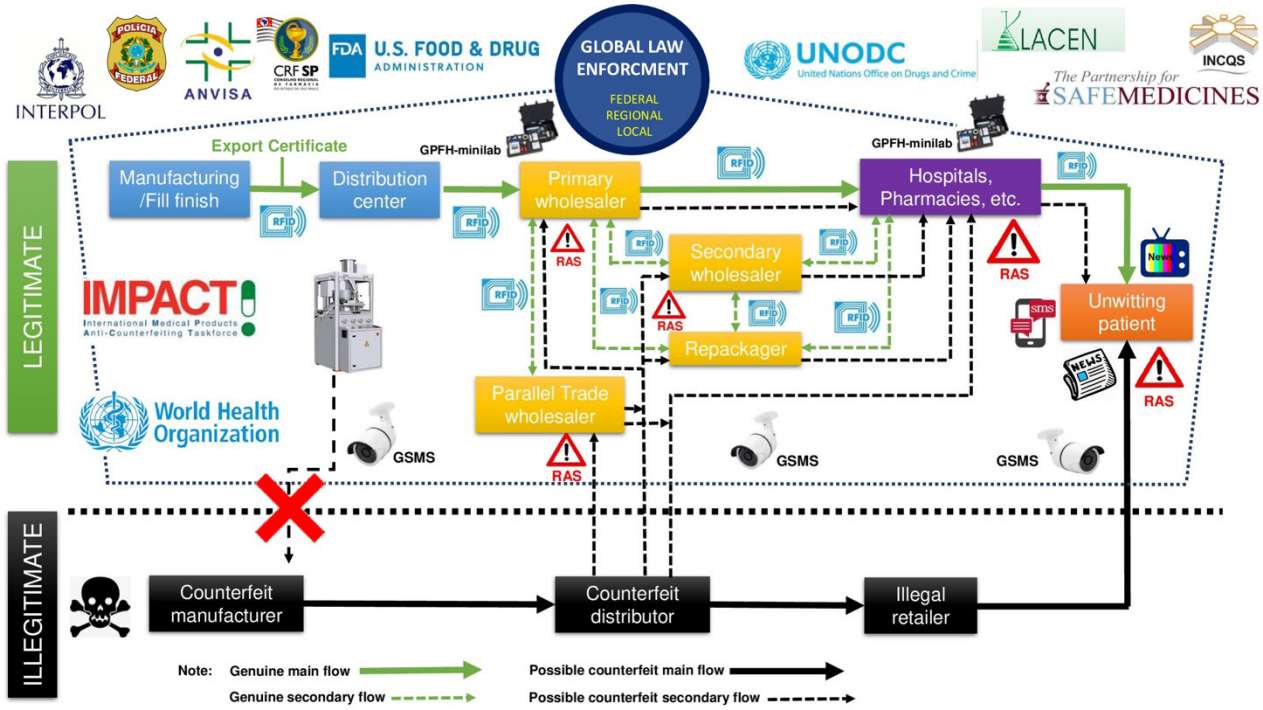

FIGURE 2 - Map of possible strategies to combat counterfeit medicines in the legitimate and illegitimate supply chains.

CONCLUSION

In view of the global impacts of counterfeit medicines, organizational, technological and political measures have been developed in recent years as strategies to combat the crisis at a global level. However, these strategies are crude and would be better explored if all measures were connected through a large network that could cover, control and inspect each stage of the legal supply chain. Moreover, pharmaceutical industries should be entrusted with project methods and mobilizing resources to protect the distribution of their genuine medicines, as well as to prevent the sale of their illegal copies, financially supporting the fight against counterfeiting worldwide.

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