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Reviewing strategies and systems-level measures to fight drug counterfeiting: an in-depth analysis of evidence extending beyond effectiveness

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Abstract
A recent systematic evaluation found that on-site medication registrations and quality inspections may reduce counterfeit and substandard drugs. Replicating successful therapy without making any changes is tough. A complete data analysis was also the aim, in addition to systematic actions to combat medicine counterfeiting. We searched fourteen databases electronically throughout our extensive examination. We analysed data on the treatments' effectiveness, viability, reliability, financial results, and difficulties and prospects. After choosing relevant papers, two reviewers abstracted the data individually and in duplicate. A narrative synthesis was done on the findings, which were classified by intervention. The outcome Nineteen of 10,220 citations were acceptable. The results include reducing pharmaceutical diversion, improving communication, providing drug quality feedback, and lobbying for strict licencing regulations to strengthen regulatory systems like registration. Onsite quality monitoring and inspection solutions may be practical and cost-effective for large drug samples undergoing preliminary testing. Implement counterfeit pharmaceutical laws, strict fines, tools to control internet medication sales, and legal and judicial education. Public awareness and education initiatives need several platforms and specialist material. Product authentication systems can detect counterfeit medications in the supply chain, but they require a sound information system design to work. To ensure pharmacovigilance systems work, underreporting must be addressed. The following paragraphs will explore the aspects that affect the design and execution of systemic medication counterfeiting prevention methods. These must be considered by policymakers to ensure their efforts are effective.

Keywords: Drug authentication technologies, Regulatory enforcement

Introduction

Public health issues like drug counterfeiting affect both developed and underdeveloped countries [1, 2]. Global drug sales may be 15% bogus [3]. This percentage may reach 50% in Asia and Africa [4].

The word "counterfeit drugs" is undefined [5]. A counterfeit drug is "one which is intentionally and fraudulently mislabelled with respect to identity and/or source," according to the WHO. Both branded and generic products may be counterfeited, including those with the wrong components, no active ingredients, insufficient active ingredients, or fake packaging [6]. To avoid intellectual property concerns, "falsified" is being replaced with "counterfeit" [7].

In countries with loose rules and enforcement and poor pharmaceutical manufacture, importation, distribution, supply, and sale controls, counterfeit drugs are common [1]. The fast surge in bogus pharmaceutical sales may be due to internet medicine purchasing [8, 9]. In a recent NABP study, most websites that marketed just prescription drugs did not follow industry standards or federal or state laws [10]. The World Health Organisation believes that over 50% of internet pharmaceuticals purchased from websites disguising their location are bogus [11]. Counterfeit drugs may increase drug resistance, treatment failures, morbidity, and death [12]. They may also reduce public health and medical trust. Pharmaceutical companies may be hesitant to report counterfeited pharmaceuticals since they potentially

counterfeited pharmaceuticals since they potentially damage their reputations [13].

Effective anti-counterfeiting techniques are a top policy issue in low- and middle-income countries, particularly the Eastern Mediterranean [14]. A recent effectiveness analysis found that drug registrations, WHO prequalification, onsite quality inspections, and monitoring systems—all essential components of multifaceted interventions—reduced substandard and counterfeit drug use [15]. The most effective medicines are difficult to replicate since they must be distributed without change, increasing the risk of failure [16]. Contextual evidence and a knowledge of systems-level treatments are needed to make health system decisions that improve intervention implementation and efficacy [17–19]. This research set out to explore the data beyond what systems-level changes might do to reduce drug counterfeiting. We focused on study on the therapies' efficacy, feasibility, consistency, and financial outcomes, as well as their barriers and facilitators.

Methods

Protocol and Registration

The protocol was filed under the CRD4201400 9269 designation in PROSPERO, an international prospective registry of systematic reviews [20].

Eligibility Criteria The inclusion and exclusion criteria were

Descriptive case studies, qualitative studies, economic studies, counterfeit pharmaceutical process assessment studies, prospective, retrospective, pre-post, cross-sectional, and non-randomized research were included. Unpublished and published studies were examined.

- We did not analyse abstract articles, editorials, comments, letters to the editor, reflections, proposals, or reviews. Unpublished French, Arabic, or English studies were also ignored.
- Problem: fake, contaminated, mislabelled, or manufactured drugs. The WHO classified counterfeit drugs [21]. These include drugs with the wrong active ingredient, no active ingredient, excessive impurities, insufficient active ingredient, or fake drug packaging. The evaluation focuses on counterfeit pharmaceuticals, but we included substandard medications where a study couldn't distinguish between the two or when a low-quality medication was suspect.

We did not analyse recommended therapies or procedures. Hospital-level measures to improve medicine distribution or reduce medication errors were also ignored. We also excluded studies on non-system-level analytical approaches like spectroscopy.

What outcome measures are used? The study found population coverage, regulatory visibility, efficiency, feasibility, reliability, economic outcomes (cost and cost-effectiveness), implementation-related factors (barriers, facilitators, gaps, and loopholes), and end user acceptability. We evaluated regardless of publication era or setting.

Selection Process

Two reviewers (RF and FA) independently assessed citation titles and abstracts for eligibility. Studies deemed eligible by one of the two reviewers were retrieved in full. The two reviewers individually and duplicate-screened the whole texts for eligibility. The screening form was pilot-tested and standardised. They settled differences via conversation or a third reviewer. We calibrated the selection procedure to assure authenticity.

Data Abstraction Process

Data from eligible trials were abstracted in duplicate and independently by two reviewers (FA and HA). To gather information on financing, research design, context (country and time period), intervention, and reported outcomes and findings, they used a standardised data abstraction form. Conflicts were settled via conversation or with the assistance of a third reviewer. There were neither many reports of the same research nor several reports combined into one.

Data Analysis and Synthesis

We synthesised the data and presented the findings narratively because of the qualitative character of the data. We divided up the data into groups according to the kinds of interventions under consideration. El-Jardali *et al.*'s conceptual framework for the various anti-counterfeit medicine techniques served as the basis for the classification (Fig. 1).

Results

Search Results

The research flowchart is shown in Figure 2. Nineteen of the 10,220 citations that were found via database and online searches were included in the analysis. After going through the reference lists of the included papers, no further studies were found. The following factors led us to remove 41 studies during full-text screening: Not a primary research study or country case study (n = 9), not about interventions to combat or prevent drug counterfeiting (n = 5), not a systems-level intervention (n = 7), not a study conducted in English, French, or Arabic (n = 3), not a prevalence study (n = 1), and not an assessment of the study's intended outcome (n = 9). Electronic Supplementary Material 3 displays the features of the 19 included studies. Country case studies (n = 9) accounted for the bulk of the research, with the remaining studies being either surveys (n = 4), mixed methods (n = 3), qualitative investigations (n = 1), prospective audits (n = 1), or the use of online algorithms (n = 1). Every research, with the exception of one conducted in French [22], was published in English. Three studies [10, 23, 24] included more than one country, one [25] concentrated on online platforms, while the remaining 15 covered the following countries: 1 each for Belgium and Greece, 1 each for Germany, 1 each for Mali and Mauritania, 1 each for South Africa, 1 each for Hong Kong, 1 each for China, 1 each for Tanzania, 1 each for Turkey, 1 each for Sweden, 1 each for the USA, 2 each for Burkina Faso, 1 each for the Philippines, 1 each for Nigeria, 1 each for Kenya, 1 each. In order to provide general suggestions, the multicountry studies combined and examined data from many nations. The studies that were included looked at different kinds of treatments. Among them were drug laws, legislation, and decrees (n = 6), product authentication technology (n = 3), pharmacovigilance systems (n = 5), public awareness and education (n = 2), onsite inspection and surveillance systems (n = 2), pharmacovigilance systems (n = 5), and recursive trust labelling for identifying fraudulent medical websites (n = 1). Efficiency, dependability, cost, cost-effectiveness, population coverage, regulatory visibility, end-user

acceptance, capacity to identify counterfeit medications, and implementation were among the sorts of outcomes evaluated.

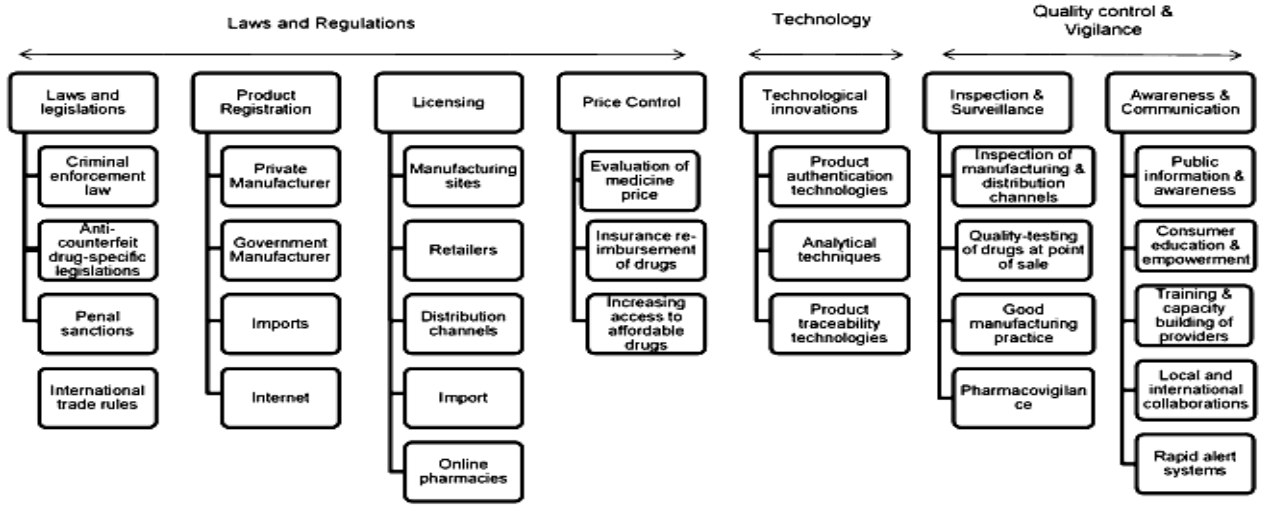

Fig 1: A framework for the different anti-counterfeit drug strategies This framework was adopted from the study by El-Jardali *et al*. [15]

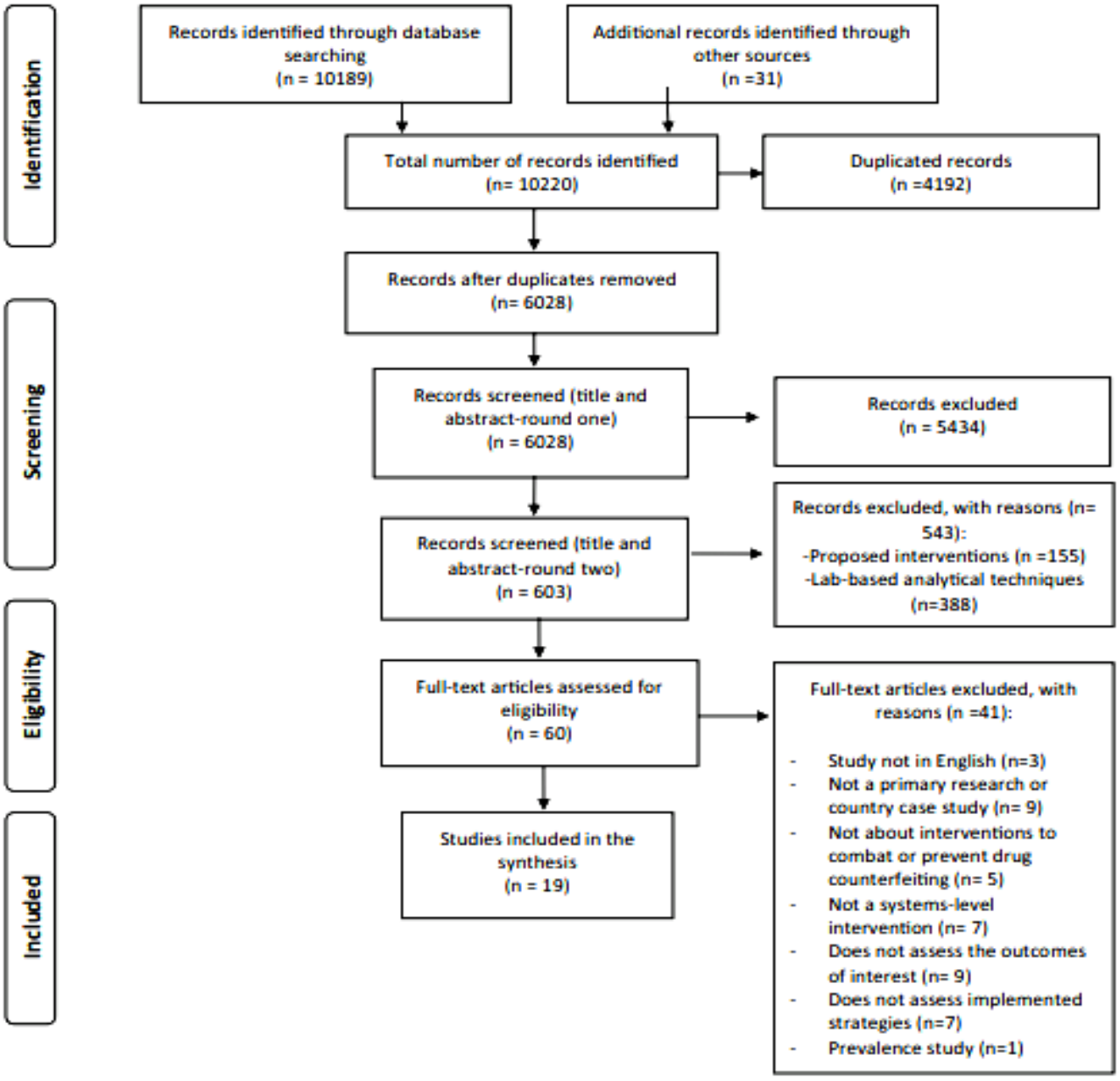

Fig 2: Flowchart for selection of the studies

Findings by Intervention

In Electronic Supplementary Material 3, we provide a synopsis of the results of every research that is included. A narrative summary of the results, categorised by kind of intervention, is also given below.

drug diversion; poor coordination, monitoring, and control; a lack of standardised regulatory tools and criteria; the existence of regulatory double standards with regard to the various drug regulatory functions; communication gaps; insufficiency of funds; shortages of qualified staff and equipment; and the lack of a central drug regulatory authority. None of the included studies described any steps done or how they worked to address the issues impeding the efficacy of regulations. The Medicines Control Council's quality assurance system includes important regulatory procedures such as medication and supplier registration, licencing, and auditing [26]. This research was carried out in South Africa. Key stakeholders in semi-structured interviews revealed a number of issues that might prevent the aforementioned system from being implemented correctly. These included the diversion of public medications into the private sector, which has an impact on the distribution of medications within the public sector; inadequate communication between regulators, manufacturers, and providers; a lack of response to complaints regarding the quality of drugs received; and vague licencing requirements, which lead to incompetent people working as wholesalers. When questioned about the most important tactics used to safeguard medicine quality, participants cited using standard operating procedures, audits between manufacturers and distributors and/or providers, and buying registered pharmaceuticals from licenced suppliers. The WHO's multicountry research looked at the experiences of ten chosen nations with drug regulatory agencies [10]. Various factors hindering the efficacy of regulations were noted in the various nations. These included: (1) fragmentation of drug regulatory responsibilities, which could result in lapses in implementation with increased risk of duplication of efforts and wastage of resources; (2) delegation of drug regulatory powers in the form of either delegation with full authority but without coordination, or delegation without authority and accountability; (3) assignment of multiple functions to drug regulatory authorities with potential for conflicts of interest arising in respect to mandates and resource allocation; (4) regulatory double standards in which exemptions are sometimes made, depending on where the drug comes from, who manufactured it, or where it is distributed; (5) the lack of availability of regulatory tools such as documented guidelines and checklists for inspection among all drug regulatory authorities; (6) shortages of qualified personnel; (7) the absence of adequate and sustainable financing mechanisms; and (8) the lack of balance of priorities whereby different drug regulatory functions receive varying degrees of emphasis (e.g., formal vs. informal sector inspection and pre-marketing vs. postmarketing product assessment). The task forces in Nigeria that deal with counterfeit drugs have been successful in seizing a small number of counterfeit medications; however, due to issues with corruption, communication breakdowns, insufficient funding, scarcity of both human and material resources, and poor training of task force members, the task forces were deemed ineffective. In addition, the task forces' monitoring, coordination, and supervision were seen as inadequate by the respondents [27]. The task forces should be under one agency's control, state and federal task forces should be centralised, pharmacists should be the only ones allowed to join, military officers should not be allowed to join, corrupt military officers should be identified and fired, seized goods should be destroyed rather than allowed to enter circulation, and sufficient funding, supplies, and trained personnel should be provided. Adequate security for non-military members should also be provided.

Onsite Quality Surveillance and Inspection Systems

This factor was examined in two nation-level case studies [28, 29]. Both studies demonstrated that onsite quality monitoring and inspection equipment may be cost-effective for large medication samples undergoing first-field testing. The first case study focused on a 1.5-year Tanzanian pilot project using Minilab kits, thin-layer chromatography (TLC) drug quality testing methods [29]. The plan improved inspectors at major ports of entry's capacity to assess imported pharmaceutical quality and three non-ports-of-entry locations' post-marketing monitoring drug screening capabilities. Minilab was cheap, had a high sample throughput, required just minimal training, and required little resources for quality screening. Kits originally cost US$5000, which was affordable. No recurring costs were associated with sample processing, which cost US$1.5 per sample. Since the programme began, 1257 medicine samples have been assessed outside the central quality control laboratory, roughly triple the number normally checked. Minilab's large sample size made it cost-effective and increased regulatory awareness and reach nationwide. Only five counterfeit goods were detected in the many samples examined. 46 batches (3.7%) failed USP dissolving. Since it can only reliably detect "grossly" inferior or "wrong" pharmaceutical samples, the Minilab kit should only be used with full-service quality control, the authors explain these poor numbers. Increasing inspectors' testing competency and sample screening reliability may lessen the operator's visual perception's impact on detection reliability. The second study examined the Chinese National Institute for the Control of Pharmaceutical and Biological Products' mobile laboratory quality inspection system for on-site quality testing and rural drug monitoring [28]. Mobile labs enhanced the drug surveillance programme, expanded the monitoring zone, collected real-time data, and helped regulatory authorities respond rapidly to adverse drug product reaction evidence. Near-infrared spectra (NIR) provided reliable quick screening, eliminating all 329 bogus batches. After a diethylene glycol poisoning incident that killed 11 people, mobile labs checked suspected drugs on the market. All mobile lab-positive diethylene glycol prescriptions were confirmed by gas chromatography. Mobile labs saved money by transferring only suspect batches to a district laboratory for examination. Comparing the average analysis cost per batch of medicines using the focused mobile lab to the normal district lab, the authors found that the technique reduced district lab analysis costs by over 90%. Implementation challenges included the mobile laboratory's requirement for software to retrieve information and automate NIR analysis. These concerns may challenge undeveloped countries without sufficient assistance.

Drug Laws, Legislation, and Decrees

Six studies [10, 27, 30–32] sought to evaluate the merits and demerits of regulations and legislation pertaining to the issue

of fake and falsified medications in various nations. One of the research focused particularly on the rules and regulations governing internet pharmacies and medicine purchases [24]. The lack of laws and regulations specifically targeting counterfeit drugs, the absence of regulations pertaining to the online sale of drugs, the lack of a sufficient administrative and legal framework to make the fraudulent falsification of pharmaceuticals a crime, and the inadequate enforcement capacity to properly implement and enforce laws were some of the major weaknesses that were highlighted by various studies. None of the included studies described any steps done or how they worked to address the issues impeding the efficacy of the law. The regulations of Nigeria pertaining to the production, trade, delivery, importation, and exportation of narcotics were insufficient to kerb the illicit production and selling of drugs. Furthermore, it was noted that there were shortcomings in the way the different drug laws were implemented and enforced [27].

The amount of counterfeit drugs seized at the retail level in Hong Kong has increased in recent years due to the existing legislative system, totalling US$98,625.45 in 2008 [30]. However, a number of weaknesses were noted by important stakeholders, including the lack of legislation specifically addressing counterfeit drugs, the existence of penalties that do not address the underlying public health impact of drug counterfeiting, the light penalties (the highest penalty was a fine of US$1290), and the lack of public health awareness and education among judges, attorneys, and prosecutors who may feel bound by the current commercial legislation. The anti-counterfeit legislation in Kenya was ultimately suspended because it concentrated on intellectual property rather than drawing a clear difference between quality-assured generic pharmaceuticals and counterfeit drugs [32].

Without necessarily concentrating on laws that specifically address anti-counterfeit pharmaceuticals, the WHO multicountry research offered an overview of drug-related legislation in general [10]. It was discovered that drug laws in many nations did not cover all goods with therapeutic claims or all actions pertaining to the production, importation, distribution, dispensing, and advertising of medications in the public and private domains. Furthermore, they did not define the regulatory instruments, operational standards, and sanctions for subpar performance, nor did they make clear the roles, duties, and connections amongst the many organisations engaged in drug regulation. The efficacy of drug laws might thus be compromised by the aforementioned deficiencies. Since it required extensive credentialing requirements and the use of pedigree papers for all prescription drugs subject to wholesaling or dispensing in Florida, the Prescription Drug Protection Act of 2003 has been billed as the strongest anti-counterfeit drug wholesale law in the nation [31].

Nonetheless, several loopholes were identified, including the fact that wholesalers with ‘‘suspicious’’ backgrounds could still obtain a permit by listing another person on an application; administrative oversight that placed more emphasis on meeting timelines for processing applications and issuing permits than on closely scrutinising the responses in the application forms; the restriction of pedigree paper use to only 34 selected drugs; and failure to verify or authenticate pedigree papers, or in some cases, circulation of inaccurate pedigree papers by wholesalers. The full effect of Florida's drug pedigree regulations has been further undermined by the subsequent passage of House Bill HB 371 in 2006, which eliminated the pedigree paper trail in many drug transactions. The WHO Global Observatory for e-Health conducted a survey of 114 nations to look at member states' progress and issues with regard to online safety and security [24]. More specifically, 66% of the nations said in their response that they did not have any laws governing the activities of internet pharmacies. When such laws did exist, they were more common in industrialised nations and more frequently than not forbade the establishment of Internet pharmacies (19 vs. 7%, respectively). Furthermore, the vast majority of nations (86%) said that they did not control, certify, or accredit websites offering online pharmacies. Seventy-five percent of the nations said they had no laws allowing or outlawing the practice of buying pharmaceuticals online from outside. Nearly 80% of respondents said they "do not have, do not know, or did not respond" when asked whether breaking laws prohibiting the internet sale of narcotics has repercussions. The results made clear that more robust governance structures are required to encourage the development of legislative and regulatory frameworks pertaining to the online distribution of medications.

Product Authentication Systems

Three studies examined the cost-effectiveness, usefulness, efficiency, and reliability of product authentication systems to prevent medicine counterfeiting [33–35]. Simoens examined the efficacy, affordability, and reliability of a mass serialisation technology-based patient safety communication service at the dispensing level in Greece and Belgium [33]. Mass serialisation gives each medication packet a unique number. A prospective mystery shopping audit of fictional test codes at 116 Belgian community pharmacies showed 100% reliability, with service replies matching authentication database answers. The service found that 212,205 of the 220,751 scans tested in Belgium between June and August 2008 were genuine, 1635 were recalled, 6630 were potentially recalled, and 281 were expired. None of the scans related to suspicious goods. Electronic Supplementary Material 3 shows comparable results for Greece. Based on five pharmaceutical software vendors covering 10,000 pharmacies that deliver 400 million packets yearly, the authors modelled a hypothetical country. Despite startup and annual operational costs, product recalls, expirations, and dubious product detection were beneficial.

An authentication service would become financially neutral if 0.47% of things are recalled or expire yearly, according to the modelling experiment. The cost-neutral scenario predicted US$6,753,608, Greece US$4,896,476 and Belgium US$8,535,749 in yearly authentication service benefits. An information system needed by pharmacies to deliver the service and serialised codes on reimbursable drugs are necessary. Different Swedish pilot experiments tested the reliability and usefulness of a 2-D matrix product verification system at the dispensing level [34]. Over 90% of pharmacists polled believed the system was easy to use. About 85% of respondents stated the system replied "generally fast" or "consistently fast."

Multiple codes on an item hindered user acceptability and caused confusion. The device could identify an illicit product before it was administered to the patient, but not when a questionable chemical entered the legal supply chain. Durability of the data carrier and quality of the present information system also influenced reliability. Altunkan *et al.*'s Turkish case study examined the pharmaceutical

industry's track-and-trace system [35]. The method ensures patients' drug supplies are reliable and prevents barcode fraud and phoney medication sales, reports said. No data were provided to support this claim. The technology was also said to detect harmful drugs in seconds and make stakeholder contact easier than before. The authors stressed the need of the Data Matrix, a data carrier, to track every supply chain unit's operation via web services. This permitted single identification and provided great accuracy and security at a lesser cost than RFID tags.

Pharmacovigilance Systems

5 case studies described pharmacovigilance systems as reporting systems that retroactively evaluate ADRs caused by counterfeit medications or prescription mistakes [23, 32, 36–38]. Drug concerns include missing active components, clinical consequences, adulteration, and contamination, according to the systems. However, implementation problems and facilitators exist. Kabore *et al*. observed that the Ministry of Health's official pharmacovigilance system increased ADR reporting and accounted for most 2010 National Drug Authority complaints [37]. While statistics have not shown local pharmaceutical issues, external drug safety alerts have been considered and acted upon. Seven drugs were stopped and removed from the national market in 2010, while 31 marketing authorisations were amended to reflect new safety information.

The study also acknowledged its ease of use, low cost, high coverage, medication lifecycle follow-up, non-interference with prescription habits, and ability to facilitate follow-up studies. Pharmacovigilance systems in 55 low- and middle-income countries were studied by Olsson *et al* [23]. The technology found counterfeiting, quality issues, antibiotic resistance, irrational pharmaceutical use, and poor patient care in 40 countries [23]. Seven countries used sentinel stations to track HIV/AIDS patients and others. Pharmacovigilance programmes received less than 1000 case reports in 72% of countries in 2007, but over 10,000 in Mexico, Singapore, and Thailand. Pharmacovigilance data helped regulatory tasks (88%, n = 42 countries) and led to product information updates (21 countries), safety warnings (24 countries), and market withdrawals (20 countries). The Philippine pharmacovigilance system may find counterfeit and substandard drugs that passed regulatory inspections and other concerns [38].

These included toxic Chinese "DeWitts" Kidney and Bladder Pills for renal illness patients, health supplements purporting to be natural, unlawful weight-loss goods, and steroid substance and phenylbutazone adulterating Chinese herbal medicines. The system notifies and warns health professionals and the public. In Kenya, Cohn *et al*. reported manipulated antiretroviral drugs in Medecins Sans Frontié™res (MSF) supplies [32]. An MSF-supported HIV/AIDS treatment programme nurse found two discoloured and moulding Zidolam-N batches. We immediately isolated and returned damaged batches to the distributor.

Kenya's drug regulatory agency, the Kenya Pharmacy and Poisons Board (KPPB) pharmacovigilance branch, and the WHO Pre-Qualification Programme investigated the quality problem. After detecting the phoney drugs in the MSF supply chain, 95% of patients who took them returned to an MSF clinic for medical evaluation and prescription replacement within three months. The KPPB and government did not publicly report the occurrence until many weeks later, which may have hampered response and enquiry. Beyond the WHO advice, KPPB provided no information or product recall. In 2008, the US "forensic" pharmacovigilance system reported ADRs from contaminated heparin [36]. The manufacturer and National Regulatory Authority detected a significant heparin allergic reaction in hemodialysis patients at a single paediatric hospital

Fast testing revealed contamination in heparin basic materials, active pharmaceutical components, and therapeutic products. This generated widespread notices and product recall requests in the US. USA contained the problem after 4 months. The exposure caused 785 adverse responses and 81 deaths. Pharmacovigilance has several challenges. All studies indicated underreporting as a concern. Low patient and healthcare provider awareness and recognition of counterfeit drugs and adverse drug events, adverse events being misinterpreted as part of the healing process, ignorance of reporting requirements, availability and accessibility of reporting forms, and fear of litigation and being held accountable for the ADR prevented underreporting [23, 37].

Lack of national guidelines and standardised operating procedures, insufficient stakeholder coordination and networking, no specific legislation, a lack of trained staff, and insufficient funding to sustain newly developed systems also hampered pharmacovigilance development in low- and middle-income countries [23, 37]. The system scored 70% in Burkina Faso, but absence of pharmacovigilance regulations, national standards, and SOPs and insufficient stakeholder coordination were its key flaws. The national drug authority reports ADRs and prescription errors, but not treatment failure or pharmaceutical product quality [37]. Many ideas have been made to implement such systems.

These included raising healthcare provider knowledge, incorporating pharmacovigilance into undergraduate, postgraduate, and health professional curricula, formalising hospital and public health programme pharmacovigilance structures and activities, and fostering a "reporting culture" [37]. To promote reporting, medical practitioners get continuing medical education credits, reporting forms are sent to all possible reporters' institutions, and reporters receive personalised recognition letters [23]. Combining adverse event data from countries into VigiBase increased detection sensitivity and specificity and supported analytical methods [36]. Expanding regulatory authorities' communication, developing newsletters and websites, and updating public safety information with media are crucial [23]. Pharmacovigilance should be led by governments to assure medicine safety via policy, regulation, and funding [23].

Public Awareness and Education on Counterfeit Drugs

Two credible research enhanced awareness of medication counterfeits. Cuchet-Chosseler *et al*. examined a poster campaign against counterfeit street drugs in Mali and Mauritania [22]. A survey examined schoolchildren's poster exposure and the campaign's efficacy. Street drug dangers were heard by 84% of youngsters. Only 41% recalled the posters' content, while 61% saw them in pharmacies. After watching ads and knowing about the risks, more respondents demanded stricter regulation over illicit drug outlets. The intervention enhanced participants' knowledge of illicit drug shops' hazards, although attitudes and actions differed.

Better use of broader media channels (e.g., TV), distribution of posters in more public places, better elaboration on drug

prices as key messages (to contest the common belief that street drugs are cheaper, thus more appealing), and school curriculum integration of this topic were some areas for improvement. Trainers might generate and monitor key messaging for future campaigns to ensure they reach the target audience without distortion. Thomson *et al*. evaluated whether online counterfeit medicines knowledge and education might reach the target audience and effect sales [39]. The authors constructed a fake internet pharmacy to inform consumers about fake drugs. The online pharmacy was promoted for 9 months. Within this period, 360,532 online pharmacy searches (85%) visited the website. These included 182,602 unique visits to the landing page warning about illegal online pharmacies, 142,676 to the principal warning page, and 16,378 to further information. The German Institute of Medical Documentation and Information (DIMDI) list of credible online/high street pharmacies was also clicked by 12,227 unique visitors. Primary messages reached the target audience and changed consumer behaviour once safe purchasing knowledge was raised.

Recursive Trust Labeling

Recursive trust labelling (RTL), an adaptive learning technique that detects bogus medical websites using graph-based and content classifiers, was tested [25]. Using 100 million connections from 930,000 websites, 1000 of which were bogus and real medical websites, the strategy was tested. RTL had above 90% accuracy on all three test bed subsets in a performance study. Research shows RTL can spot fraudulent medical websites. Robustness study suggested 30-website samples. 4 Talk 4.1 Results and Analysis Nineteen studies reveal medication counterfeiting beyond systemic changes. The study highlighted numerous essential criteria required to create and deploy systematic medication counterfeiting measures.

The last effectiveness evaluation advised medication registration, WHO prequalification, and on-site quality checks to prevent counterfeit and substandard pharmaceuticals [15]. This investigation found three regulatory and two onsite quality monitoring publications. The findings recommend reducing medication diversion, improving communication between suppliers, producers, and regulatory agencies, addressing drug quality concerns after registration, and clarifying and stronger wholesaler licencing in addition to enforcing legislation. One regulator is needed for drug regulation to work. The regulatory authority should balance official and informal drug regulation since drug counterfeiting is rampant in the latter sector. Additionally, integrity-driven individuals with the necessary skills and competence should be hired, regulatory standards and norms should be created and enforced, and appropriate and sustainable financing should be supplied. Monitoring the regulatory process reveals new issues and ensures actual activities meet goals.

We showed that onsite quality monitoring and inspection technologies might help regulators test large samples for preliminary drug testing at cheap cost and increase regulatory visibility statewide in low-resource situations. The mobile lab screens using near-infrared spectroscopy, TLC, visible microscopy, and chemical reaction test kits [28], whereas the Minilab kit employs TLC [29]. TLC is cheaper (a fully equipped kit costs US$5000–10,000) [29], but it can only identify drastically altered pharmaceuticals, therefore it may overlook marginally poor drugs. Mobile laboratories and Minilab kits should be used with a full-service quality control laboratory to verify bad or fraudulent findings. One research found that pharmaceutical regulations may have increased retail counterfeit medicine sales [30].

Laws and legislation specific to counterfeit drugs, a strong administrative and legal framework that criminalises fraudulent falsification, an emphasis on public health rather than intellectual property, attention to the entire ecosystem of illicit online pharmacies, and strong enforcement and public education for judges, attorneys, and the public are needed to succeed. RFID and track-and-trace are advertised as drug counterfeiting prevention tools, however they have limited proof. Our research found that 2D Data Matrix-based product authentication systems during dispensing may detect fake drugs across the supply chain. Low- and middle-income nations struggle to create a complete infrastructure that connects every pharmacy to an information system due to cost and time. Despite its hefty startup costs, one modelling research found such a system may be cost-effective.

All product authentication system research was trial studies, hence long-term performance was unknown. To enhance pharmaceutical safety and national post-marketing monitoring, low- and middle-income nations are quickly expanding pharmacovigilance initiatives. These devices have found several fake medications countrywide. Underreporting must be addressed to increase performance. Continuous training, observation, and feedback are essential. The national pharmacovigilance system must develop its legislative framework and procedures and increase stakeholder cooperation to collect data, produce indicators, evaluate drug-related hazards, and act as a meaningful public health tool [37]. Raising awareness and educating the public about counterfeit pharmaceuticals from illegal drug businesses improved their potential to change buying behaviours and reach target audiences. However, employing additional media venues, such as efficient social media interactions, and providing thorough and focused subject information may have improved outcomes.

Given the belief that illicit drugs are cheaper and more appealing, one author suggested paying trainers to create and sometimes analyse messages to reduce distortion [22]. Another proposal was to explain drug prices in critical messaging. The previous systematic study did not address this issue, however unlicensed internet drug stores have sold counterfeit medications worldwide [8, 24]. Previous research solely examined online medication quality, website features, supply difficulties, customer profiles, and clandestine online pharmacies [24]. Three relevant research in the present systematic review demonstrated weaknesses in laws and regulations controlling online pharmacies and drug transactions, as well as the potential of online educational platforms to reach vulnerable groups and educate them about online drug hazards.

Few remedies exist for worldwide Internet and illegal online pharmacy issues despite rising awareness [5, 24]. After an 18-year-old overdosed on internet narcotics, the US established the Ryan Haight internet Pharmacy Consumer Protection Act in 2008. Internet purchases of forbidden drugs need legal prescriptions. However, many doubt its efficacy [24]. Online pharmacy certificates, seals, and verification may increase

patient safety, according to certain research.

Strengths and Limitations

Our systematic review improves efficacy evaluation and gives context for interpretation. Synthesis that integrates application context would explain systems-level interventions and associated problems. Strengths include pre-publication of a protocol, database searches, and include published and unpublished research for completeness. Our comprehensive assessment achieves policymaker and stakeholder priorities. Our systematic review's primary flaw was not assessing bias in each research. The research focused on descriptive country case studies. Pharmaceutical companies funded [33] and planned [18] product authentication technology research, therefore reporting bias was possible. We discovered one trial for a few therapies, making conclusions difficult. We only examined English, Arabic, and French research, thus we may have overlooked important papers in other languages.

Implications for Policy

To execute and be effective, health system policymakers must consider contextual considerations when making choices to avoid or combat prescription counterfeiting. To detect counterfeit pharmaceuticals and protect drug quality, policymakers and stakeholders may seek to tighten drug registration and add stringent post-marketing monitoring utilising "standard pharmacovigilance methods of registration, analysis, and investigation" [36 Legislation targeting counterfeit pharmaceuticals from a public health standpoint, high fines and punishments, and public, judge, and attorney education regarding pharmacists' involvement in drug quality might reinforce such regulatory efforts. For maximum efficacy, legal and regulatory actions should include the whole illegal internet pharmacy ecosystem.

In liberal regulatory jurisdictions, "rogue" internet pharmacies may operate without uniform legislation and cooperation agreements [24]. Site-specific quality inspections at several supply chain stages may provide regulators with cost-effective early testing of large pharmaceutical samples and regulatory visibility in low-resource environments. Only suspicious samples are submitted to the lab for examination, which may aid nations with few national laboratories.

Consider national labs long-term. Product authentication technologies have the potential for long-term efficiency, dependability, and cost-effectiveness, but their high infrastructure and IT start-up costs may prevent their implementation, especially in low- and middle-income countries with limited resources. Finally, decision-makers and interested parties should sponsor countrywide public awareness and education campaigns utilising different media and provide detailed and specialised information regarding the hazards of obtaining drugs from unauthorised sources and warning indicators.

Implications for Research

Despite the serious health dangers of drug counterfeiting, few methodologically sound research have examined therapies. Future research should address the methodological faults in prior ones by thoroughly describing recruitment and sampling processes and using reliable and adequate data collection equipment. Additionally, more detailed and unbiased cost-effectiveness research on system-level interventions is needed. International organisations are promoting product identification systems to stop counterfeit drug sales. Given the growth of online drug sales, it's important to review efforts to regulate or prevent online medication counterfeiting. Finally, standardising the concept of counterfeit medications is crucial to ensure consistency when implementing interventions and comparing outcomes across studies and situations.

Conclusion

Effective design and implementation of systematic actions to kerb medicine counterfeiting relies on many factors. We found data on numerous system-level therapies' effectiveness, reliability, price, regulatory visibility, acceptability, ability to recognise fake drugs, and implementation challenges. Policymakers must consider these to ensure good implementation and intervention success. The findings suggest that strong regulatory measures, on-site drug quality control and monitoring, national pharmacovigilance systems, and educational and awareness campaigns regarding illicit drug shops' hazards are beneficial. Minimising drug diversion, strong post-marketing monitoring, and equal weight for drug regulatory obligations strengthen regulatory systems. Legal and legislative deficiencies include the lack of counterfeit medication regulations, online medicine sales laws, administrative and legal frameworks to make drug falsification illegal, and weak enforcement. Previous studies' design and data collection weaknesses should be addressed in future research. System-level initiatives like online pharmaceutical counterfeiting prevention and product authentication systems need additional study to determine their cost-effectiveness.

References

1. Buowari OV. Fake and counterfeit drug: a review. Afrimedic J. 2013; 3(2):1-4.
2. Chika A, Bello SO, Jimoh AO, Umar MT. The menace of fake drugs: consequences, causes and possible solutions. Res J Med Sci. 2011; 1(5):257-61.
3. Fighting fake drugs: the role of WHO and pharma. Lancet. 2011; 377(9778):1626.
4. Newton PN, Green MD, Fernandez FM, Day NP, White NJ. Counterfeit anti-infective drugs. Lancet Infect Dis. 2006; 6(9):602-13.
5. Mackey TK, Liang BA. Improving global health governance to combat counterfeit medicines: a proposal for a UNODC-WHO-Interpol trilateral mechanism. BMC Med. 2013; 11:233.
6. World Health Organization. Report of the situation of counterfeit medicines based on data collection tool: WHO Regions for Africa and Eastern Mediterranean. 2010. Available from: http://www.who.int/medicines/services/expertcommittees/pharmprep/WHO.ACM3IMPACTSurveyDataCollectionToolReport.pdf. Accessed 7 July 2016.
7. Newton PN, Amin AA, Bird C, Passmore P, Dukes G, Tomson G, *et al*. The primacy of public health considerations in defining poor quality medicines. PLoS Med. 2011; 8(12)
8. Clark F. Rise in online pharmacies sees counterfeit drugs go global. Lancet. 2015; 386(10001):1327-8.
9. MacKey TK, Liang BA. Promoting online drug safety: using public-private partnerships to deter illicit online drug sales. J Commer Biotechnol. 2011; 17(3):266-71.
10. Ratanawijitrasin S, Wondemagegnehu E. Effective drug

regulation. A multicountry study. Geneva: World Health Organization; 2002.
11. World Health Organization. International Medical Products Anti-Counterfeiting Taskforce. Counterfeit drugs kill! 2008. Available from: http://www.who.int/impact/FinalBrochureWHA2008a.pdf. Accessed 8 July 2016.
12. Kelesidis T, Kelesidis I, Rafailidis PI, Falagas ME. Counterfeit or substandard antimicrobial drugs: a review of the scientific evidence. J Antimicrob Chemother. 2007; 60(2):214-36.
13. Swaminath G. Faking it-I The menace of counterfeit drugs. Indian J Psychiatry. 2008; 50(4):238-40.
14. Bigdeli M, Javadi D, Hoebert J, Laing R, Ranson K, Alliance for Health Policy and Systems Research Network of Researchers on Access to Medicines. Health policy and systems research in access to medicines: a prioritized agenda for low- and middle-income countries. Health Res Policy Syst. 2013; 11:37.
15. El-Jardali F, Akl EA, Fadlallah R, Oliver S, Saleh N, El-Bawab L, *et al*. Interventions to combat or prevent drug counterfeiting: a systematic review. BMJ Open. 2015; 5(3)
16. Edwards N, Barker PM. The importance of context in implementation research. J Acquir Immune Defic Syndr. 2014; 67(Suppl 2)
17. Lavis JN, Rottingen JA, Bosch-Capblanch X, Atun R, El-Jardali F, Gilson L, *et al*. Guidance for evidence-informed policies about health systems: linking guidance development to policy development. PLoS Med. 2012; 9(3)
18. Lewin S, Bosch-Capblanch X, Oliver S, Akl EA, Vist GE, Lavis JN, *et al*. Guidance for evidence-informed policies about health systems: assessing how much confidence to place in the research evidence. PLoS Med. 2012; 9(3)
19. Wells S, Bullen C. A near miss: the importance of context in a public health informatics project in a New Zealand case study. J Am Med Inform Assoc. 2008; 15(5):701-4.
20. Supreme Court won't review invasion-of-privacy case. AIDS Policy Law. 1996; 11(21):10.
21. World Health Organization. Medicines: spurious/falsely-labelled/falsified/counterfeit (SFFC) medicines. Fact sheet N 275. 2012. Available from: http://www.who.int/mediacentre/factsheets/fs275/en/. Accessed 7 Apr 2014.
22. Cuchet-Chosseler M, Bocoum O, Camara M, Abad B, Yamani E, Ordre des Pharmaciens du Mali. Results of a survey to evaluate the efficacy of a regional awareness campaign on counterfeit street medicines in Bamako, Mali and Nouakchott, Mauritania. Med Trop. 2011; 71(2):152-6.
23. Olsson S, Pal SN, Stergachis A, Couper M. Pharmacovigilance activities in 55 low- and middle-income countries: a questionnaire-based analysis. Drug Saf. 2010; 33(8):689-703.
24. World Health Organization. Safety and security on the internet: challenges and advances in member states: based on the findings of the second global survey on eHealth. Geneva: World Health Organization; 2011.
25. Abbasi A, Zahedi FM, Kaza S. Detecting fake medical web sites using recursive trust labeling. ACM Trans Inf Syst. 2012; 30(4):22-36.
26. Patel A, Norris P, Gauld R, Rades T. Drug quality in South Africa: perceptions of key players involved in medicines distribution. Int J Health Care Qual Assur. 2009; 22(5):547-60.
27. Erhun WO, Babalola OO, Erhun MO. Drug regulation and control in Nigeria: the challenge of counterfeit drugs. J Health Popul Dev Ctries. 2001; 4(2):23-4.
28. Jin S. The mobile laboratory: a new concept in medicines surveillance. WHO Drug Inf. 2009; 23(1):16-20.
29. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T. The use of minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. Health Policy. 2008; 87(2):217-22.
30. Lai CW, Chan WK. Legislations combating counterfeit drugs in Hong Kong. Hong Kong Med J. 2013; 19(4):286-93.
31. Laven DL. Prescription drug wholesalers: drug distribution and the inspection process (a Florida perspective). J Pharm Pract. 2006; 19(4):196-214.
32. Cohn J, von Schoen-Angerer T, Jambert E, Arreghini G, Childs M. When falsified medicines enter the supply chain: description of an incident in Kenya and lessons learned for rapid response. J Public Health Policy. 2013; 34(1):22-30.
33. Simoens S. Analysis of drug authentication at the point of dispensing in Belgian and Greek community pharmacies. Ann Pharmacother. 2009; 43(10):1701-6.
34. AstraZeneca. EFPIA product verification project-joint final report. European Federation of Pharmaceutical Industries and Associations; 2010. p. 1-32.
35. Altunkan SM, Aykac IT, Akpinar E. Turkish pharmaceuticals track and trace system. Health Inform Bioinform (HIBIT). 2012:24-30.
36. Labadie J. Forensic pharmacovigilance and substandard or counterfeit drugs. Int J Risk Saf Med. 2012; 24(1):37-9.
37. Kabore L, Millet P, Fofana S, Berdai D, Adam C, Haramburu F. Pharmacovigilance systems in developing countries: an evaluative case study in Burkina Faso. Drug Saf. 2013; 36(5):349-58.
38. Hartigan-Go K. Developing a pharmacovigilance system in the Philippines, a country of diverse culture and strong traditional medicine background. Toxicology. 2002; 181-182:103-7.
39. Thomson J, Reid WS, Pullen H. Evaluation of counterfeit medicines available via the internet in Germany; implications for patient safety across the globe. J Sex Med. 2013; 10:254-5.
40. Bate R, Tren R, Hess K, Mooney L, Porter K. Pilot study comparing technologies to test for substandard drugs in field settings. Afr J Pharm Pharmacol. 2009; 3(4):165-70.