

# HealthTech Report

## Prevalence of counterfeit or substandard antibiotics in developing countries

Literature review

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## Contents

Introduction .....	1
Objective .....	1
Search methodology .....	1
Results .....	2
Limitations .....	2
Systematic literature reviews of counterfeit/substandard drugs.....	2
Single-country and multi-country studies of counterfeit/substandard antibiotics .....	4
Summary of the findings for the antibiotics of interest.....	7
Gray literature and media reports .....	7
Other findings in published literature.....	9
Conclusion .....	9

## Introduction

Counterfeit medicines are defined by the World Health Organization (WHO)<sup>i</sup> as medicines which are deliberately and fraudulently mislabeled with respect to identity and/or source. This term can apply to both generic and branded products and may include the following: correct ingredients, wrong ingredients, no active pharmaceutical ingredients (APIs), insufficient ingredients, or fake packaging. Substandard medications are defined as genuine medicines produced by manufacturers authorized by the national medicine regulatory authority which do not meet quality specifications set for them by national standards.<sup>ii</sup>

Although the problem of counterfeit and substandard drugs is acknowledged, the extent of the issue is not well documented. Estimates of global prevalence of counterfeit drugs alone range from 1% to 50%. The extent of the health and economic consequences of substandard medicines is even less well documented.<sup>iii</sup> Current research shows that antibiotics are the most counterfeited medicines and account for 28% of global counterfeit medicines.<sup>iv</sup>

Counterfeit and substandard drugs are particularly prevalent in low-resource settings due to the lack of regulatory oversight. In an effort to further the work of the UN Commission on Life-Saving Commodities Technical Reference Team on injectable antibiotics, we undertook this literature review to describe existing evidence on this issue for the antimicrobials currently being considered by WHO for outpatient treatment of neonatal sepsis in low-resource settings. Because the work of the UN Commission on Life-Saving Commodities currently focuses on sub-Saharan Africa, we have concentrated this literature review on evidence of counterfeit and substandard antibiotics in Africa.

## Objective

To locate reports and evidence of counterfeit/substandard antimicrobials in African countries, with a focus on gentamicin, oral amoxicillin, and benzylpenicillin.

## Search methodology

**Terms:** “antibacterial agents” OR antibiotics OR gentamicin OR amoxicillin OR penicillin, combined with counterfeit OR fake OR substandard OR “substandard” OR “poor quality” OR “Quality assurance” OR “quality testing” OR “black market” Africa OR “sub-Saharan Africa.” The search took into account various spellings of drug names (gentamycin and amoxycillin).

**Years:** 1994 to 2014

**Sources:** PubMed, Google Scholar, World Health Organization website, Google search engine

## Results

The search resulted in numerous journal articles related to counterfeit or substandard anti-infective medications in Sub-Saharan Africa, as follows:

- Counterfeit/substandard antibiotics (any type): 16
- Counterfeit/substandard issues or policy recommendations (general): 19
- Testing procedures (any medicine): 52
- Counterfeit/substandard antimalarial, antiretroviral, antitubercular, or other: 30

We reviewed in detail 16 articles that explored counterfeit/substandard quality issues of the antibiotics of interest. We also reviewed 19 articles that addressed counterfeit/substandard quality issues in general, and included a brief summary of those. We excluded the articles from our review that examined only drugs that were not of interest (antimalarial, antiretroviral, etc.) or that focused on testing procedures.

## Limitations

The present document is a literature review that summarizes the information available on the topic of interest; therefore, the reader must be aware that the studies and reports that we identified and reviewed may have limitations. Potential key limitations include lack of pertinent information about the study design, incorrect interpretation of data, improper sampling protocols, and incorrect use of test procedures. Other limitations beyond these may also exist.

## Systematic literature reviews of counterfeit/substandard drugs

We identified and reviewed the following two systematic literature reviews related to issues of counterfeit and substandard drugs in the market.

**Almuzaini and colleagues** (2013)<sup>y</sup> conducted a systematic literature review to explore the evidence of poor-quality medicines (the term “poor-quality” is defined by the authors as either counterfeit or substandard). The authors searched medical databases for articles appearing between 1948 to January 2013. The search identified 2,363 studies that met initial criteria, to which the authors applied a set of 12 quality assessment criteria. The result was 15 studies which met the pre-specified criteria (6 of 12 quality criteria). Through this review, the authors found that the prevalence of poor-quality antimicrobial medicines is widespread throughout Africa and Asia, and the main problem identified was inadequate amounts of APIs. They note that only two of the studies in their review considered pediatric formulations (i.e., syrup and suspension) in their sampling. The 15 studies included 866 samples collected in 16 countries in Africa and Asia. While the bulk of the included studies were of antimalarial drugs, amoxicillin was included in four studies and benzylpenicillin was included in one study. The location where patients purchase their medicines significantly impacts the prevalence of receiving a poor-quality medicine. The percentage of failed samples from unlicensed outlets was 51% but only 24% in licensed outlets (see Table 1 below). Of the 15 studies identified, 93% found inadequate amounts of APIs, 47% found an absence of APIs, and 33% found dissolution failure. Further, purchaser perception of quality was also found to be an issue. The authors identified a study from Benin

which determined that 86% of individuals interviewed thought that drugs purchased from unauthorized markets were of good quality. The authors conclude that while the most extensively studied antimicrobials have been those in solid formulations, further research is needed to study other therapeutic classes of antimicrobials as well as pediatric formulations.

**Table 1: Percentage failure of samples collected at different sectors** (table from Almuzaini T, et al)

Country	Licensed outlets (public and private sectors)			Unlicensed outlets (informal market)		
	Total number of samples	Number of failed samples	Percentage of failed samples	Total number of samples	Number of failed samples	Percentage of failed samples
Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania	240	64	26.6%	27	12	44.4%
Madagascar, Senegal, Uganda	144	41	28.4%	53	23	43.4%
Cambodia	38	22	58%	133	100	75%
Myanmar	215	34	16%	23	20	87%
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	229	52	23%	136	37	27%
<b>TOTAL</b>	<b>866</b>	<b>213</b>	<b>24%</b>	<b>372</b>	<b>192</b>	<b>51%</b>

Kelesidis and colleagues (2007)<sup>vi</sup> conducted a review of available scientific evidence on counterfeit and/or substandard antimicrobial drugs, explored the causes and prevalence of the problem, and summarized the categories of antimicrobials that have been reported to be counterfeit or substandard. The authors found that a country's capacity to restrict dangerous pharmaceuticals depended heavily on the country's wealth, and almost one-third of WHO-member countries have poor means to control counterfeit medications. Lack of good manufacturing practices is common in the local pharmaceutical industries of the developing world due to hurdles such as frequent power cuts and water shortages. Further, tropical climates can pose challenging storage conditions for medicines that are sensitive to temperature and humidity. The authors noted that there have been limited medical studies of counterfeit and substandard drugs and that much of the information exists in the gray literature and newspapers. The authors note that Southeast Asia and Africa are particularly plagued by counterfeit antibacterial drugs such as penicillin and tetracycline. The authors conclude that the problem of counterfeit /substandard antimicrobial drugs is a significant problem which can result in adverse clinical outcomes (i.e., lack of effect and treatment failure), risk of developing bacterial resistance, toxicity, side effects, and death. Furthermore, physicians and patients lose confidence in the effectiveness of antimicrobials. It is recommended that international coordination is required to fight the problem of counterfeit and substandard antimicrobials. In their review, the authors found the studies described in Table 2 (results limited to antibiotics included in the scope of the technical reference team on injectable antibiotics).

**Table 2: Major studies regarding counterfeit/substandard antibiotics (drugs of interest only)** (excerpt from Kelesidis T, et al)

Drug	Country	Characteristics of counterfeit/substandard antimicrobials
Benzylpenicillin	Northern Myanmar	Inappropriate labeling, expired drug, reduced APIs.
Amoxicillin syrup	<b>Nigeria</b>	Low quantities of APIs.
Injectable benzylpenicillin, amoxicillin	<b>Zimbabwe</b>	Reduced level of APIs.
Amoxicillin	<b>Nigeria, Thailand</b>	Zero or very low quantities of APIs.
Amoxicillin suspension	<b>Nigeria</b>	Low levels of APIs.

Countries and antibiotics of interest bolded

**Table 3: Countries and characteristics of reported counterfeit/substandard antibiotics (drugs of interest only)** (excerpt from Kelesidis T, et al)

Antibiotic	Country where reported	Characteristics of counterfeit/substandard antibiotics			
		No APIs	Reduced APIs	Wrong APIs	Inappropriate labeling
Penicillin	Cambodia, <b>Madagascar</b> , Brazil, Northern Myanmar	<b>Madagascar</b> , Brazil	Brazil, Northern Myanmar		Cambodia, Northern Myanmar
Amoxicillin	China, Nepal, India, Thailand, <b>Sierra Leone, Nigeria, Cameroon, Guinea</b>	Nepal, <b>Sierra Leone, Cameroon, Nigeria, Thailand</b>	<b>Nigeria</b> , Thailand		<b>Guinea</b>

Countries and antibiotics of interest bolded

## Single-country and multi-country studies of counterfeit/substandard antibiotics

The published single-country and multi-country studies on counterfeit and substandard antibiotics which were reviewed are summarized in Table 4 below.

**Table 4: Summary of single-country and multi-country studies**

Author(s) and year	Results	Drugs	Countries where reported
Mbinze JK, Dispas A, Lebrun P, et al. (2013) <sup>vii</sup>	Authors developed generic methods to trace and screen drugs using liquid chromatography. Two-thirds of the products screened did not comply with specifications.	16 antibiotics and 3 beta-lactamase inhibitors	<b>Democratic Republic of the Congo</b>
Bate R, Mooney L, Hess K, Milligan J, Attaran A. (2012) <sup>viii</sup>	Authors investigated the quality of anti-infective medicines by analysis of basic product quality and country of manufacture. Over a four-year period, covert shoppers procured 2,652 essential drugs to treat malaria, tuberculosis, and bacterial infection. Authors concluded that approval by a stringent regulatory authority (SRA) or the WHO prequalification program is correlated with higher quality at a statistically significant level than those that have not been approved by either an SRA or WHO. However, the authors found that the quality of WHO-approved products is inconsistent with notable differences between the WHO-prequalified manufacturers in India and China (failure rate of drugs manufactured at WHO-prequalified sites in India was 2.39%, whereas the failure rate of drugs manufactured at WHO-prequalified facilities in China was 17.65%). Possible reasons for this included poor storage during transportation, poor manufacturing, or potentially high-quality counterfeiting of the Chinese-made products	Antibiotics, antimalarials, and antitubercular drugs	<b>Africa</b> (11 cities), India (3 cities), and 5 mid-income cities (São Paulo, Moscow, Bangkok, Istanbul, and Beijing)

Author(s) and year	Results	Drugs	Countries where reported
	<p>(however, the failed drugs contained a high level of the API[s], which is unusual for counterfeit medicines). The authors recommend that nations importing WHO-approved products, particularly those from China, must invest in post-marketing surveillance to identify reasons for failure and strengthen their monitoring process.</p> <p>[NOTE: When collection began in six of the eleven African cities, the primary aim of the study was antimalarial drugs, so the samples from African cities are biased toward antimalarials. Further, only a limited number of antibiotics are included in the WHO prequalification program. Those are: Amoxicillin + clavulanic acid, scored tablet 250 mg + 62.5 mg; Amoxicillin + clavulanic acid, tablet 500 mg + 125 mg; Azithromycin, tablet 250 mg and 500 mg; Ceftriaxone, injecting vial 1 g; Ciprofloxacin, tablet 250 mg and 500 mg; Sulfadiazine, tablet 500 mg].</p>		
Onanuga A, Eboh D. (2012) <sup>ix</sup>	<p>Authors sampled 10 brands of ciprofloxacin and 7 brands of injectable gentamicin sold at pharmacies and markets in southern Nigeria. None of the samples collected had exceeded the expiration date indicated on the label. The gentamicin brands sampled were manufactured in China and India. Analysis found that 71% of the gentamicin brands sampled had low antibacterial activity. Although the cause was not pinpointed, authors conclude that a variety of factors from quality of APIs to poor storage conditions may have caused degradation of the APIs.</p>	Ciprofloxacin, <b>gentamicin</b>	<b>Nigeria</b>
Patil DD, Pandit VS, Pore SM, Chavan CS. (2012) <sup>x</sup>	<p>Authors collected 65 samples of 23 commonly used drugs from India's Central Drug Store and retail pharmacies. Testing found that 50% of the drug samples (including amoxicillin and gentamicin) from government stores failed visual inspection. Authors recommend that basic quality control tests (visual inspection, disintegration, and color reaction) are easy tests that should be performed by tertiary-care government hospitals that serve large populations.</p>	23 drugs including: <b>amoxicillin (capsules), gentamicin, and benzylpenicillin</b>	India
Nair A, Strauch S, Lauwo J, Jahnke RW, Dressman J. (2011) <sup>xi</sup>	<p>Evaluation of 14 samples of amoxicillin and amodiaquine formulations collected from 5 registered pharmacies in Port Moresby, Papua New Guinea (PNG). Authors confirmed that counterfeit and substandard amoxicillin products are entering the distribution chain in Port Moresby, PNG.</p>	<b>Amoxicillin</b> and amodiaquine	Papua New Guinea
Seear M, Gandhi D, Carr R, Dayal A, Raghavan D, Sharma N. (2011) <sup>xii</sup>	<p>Authors collected 300 samples of artesunate, ciprofloxacin, and rifampicin from 100 outlets in Chennai, India. While the group mean for ciprofloxacin was close to normal manufacturing limits, the artesunate and rifampicin were below the widely accepted manufacturing range. In total, 43% of samples fell below normal pharmaceutical standards, but no tablet contained less than 50% of stated dose. Minimal evidence exists to support claims about the prevalence of drug counterfeiting. Authors found that while the quality of some anti-infective drugs was below standards (likely due to decomposition during storage or poor manufacturing), there was no evidence of criminal counterfeiting.</p>	Artesunate, ciprofloxacin, rifampicin	India

Author(s) and year	Results	Drugs	Countries where reported
Okumura J, Taga M, Tey S, Kataoka Y, Nam N, Kimura K. (2010) <sup>xiii</sup>	In 2007, authors collected 254 samples of amoxicillin, ampicillin, cephalexin, and acetaminophen from pharmaceutical outlets in Cambodia. Of the 254 samples, 66 were amoxicillin. Results show that more than 90% of 500-mg amoxicillin capsules failed the United States Pharmacopeial Convention (USP) 30 TEST 1 dissolution test. Many of these passed the USP 28 test and USP 30 TEST 2. The authors conclude that many users would select the most stringent method when multiple methods existed in the USP, which may lead to a high failure rate. They recommend that USP take developing countries into consideration and develop a more detailed user-friendly manual for selection of appropriate testing methods.	<b>Amoxicillin</b> , ampicillin, cephalexin, and acetaminophen	Cambodia
Muazul J, Adamul A, Egwim O, Duru C. (2010) <sup>xiv</sup>	Due to reuse of single-dose ampoules in low-resource settings, authors conducted a small study of the microbiological quality of remnants of sodium bicarbonate (NaHCO <sub>3</sub> ), potassium chloride (KCl), and gentamicin single-dose ampoules used in the emergency pediatric unit of a teaching hospital in Nigeria. Samples included three 10-ml ampoules of NaHCO <sub>3</sub> , three ampoules of KCl, and nine 2-ml ampoules of gentamicin. Ampoules were stored uncovered or covered in cotton/wool or plaster. At 0, 8, 16, 24, and 48 hours, 1 ml was withdrawn from each sample and incubated. After 8 hours of storage, contamination had begun to manifest in the NaHCO <sub>3</sub> and KCl, and after 16 hours contamination had begun to manifest in the gentamicin as well. The vulnerability to microbial contamination was found to be NaHCO <sub>3</sub> > KCl > gentamicin. The contaminating organisms included yeast and <i>Staphylococcus aureus</i> . Authors conclude that single-dose ampoules should be used only once.	Sodium bicarbonate, potassium chloride, <b>gentamicin</b>	<b>Nigeria</b>
Kyriacos S, Mroueh M, Chahine RP, Khouzam O. (2008) <sup>xv</sup>	Investigated quality of locally produced and imported amoxicillin capsules and suspensions in Arab countries. Authors collected 111 samples of amoxicillin from retail pharmacies. They found that 56% of capsules and 8% of suspensions did not meet USP requirements. After 7 to 14 days, 38% of the total samples were outside the pharmacopeial limits. All European brands except one met pharmacopeial limits.	<b>Amoxicillin</b> capsules and suspension	Lebanon, Jordan, <b>Egypt</b> , Saudi Arabia
Prazuck T, Falconi I, Morineau G, Bricard-Pacaud V, Lecomte A, Ballereau F. (2002) <sup>xvi</sup>	Testing of antibiotic quality in advance of a sexually transmitted disease study in Northern Myanmar, authors collected 21 samples of 9 different antibiotics from 5 drug sellers and 5 general practitioners in Myitkyina. The authors found that 33% did not contain the stated dose, 14% were expired, 29% did not have an expiration date, and 5% did not contain any API. Authors recommend that public health policies based on national treatment guidelines should include rigorous monitoring of quality control.	9 antibiotics, including <b>benzylpenicillin</b>	Northern Myanmar
Okeke IN, Lamikanra A. (2001) <sup>xvii</sup>	A small study of 5 samples of ampicillin purchased from different dispensing points in a small town in Nigeria. These samples were evaluated in an in vitro bioavailability study. Results showed that ampicillin capsules of low quality are being dispensed from both authorized and unauthorized sources.	Ampicillin capsules	<b>Nigeria</b>

Author(s) and year	Results	Drugs	Countries where reported
Taylor RB, Shakoor O, Behrens RH, et al. (2001) <sup>xviii</sup>	<p>Authors collected 581 total samples of 27 antimalarial, antibacterial, and antitubercular drugs purchased from 35 pharmacies in Lagos and Abuja. 279 (48%) of the samples did not comply with pharmacopeial limits. The antibiotics of interest resulted as follows:</p> <ul style="list-style-type: none"> <li>• Amoxicillin dry syrup: 5 samples of which 40% were outside of the British Pharmacopoeia (BP) limits.</li> <li>• Amoxicillin capsules: 32 samples of which 25% were outside of BP limits.</li> <li>• Benzylpenicillin (injectable): 20 samples of which 55% were outside of BP limits.</li> </ul>	27 antimalarials, antituberculars, and antibacterials. There were 9 antibacterial drugs including <b>amoxicillin and benzylpenicillin</b>	<b>Nigeria</b>
Shakoor O, Taylor RB, Behrens RH. (1997) <sup>xix</sup>	<p>Authors collected 96 samples (81 in Nigeria and 15 in Thailand) of chloroquine and selected antibacterials from Nigeria and Thailand. Drugs were collected from pharmacies and other drug retailers. The results indicate that 36.5% (36% Nigeria and 40% in Thailand) of the samples were substandard with respect to pharmacopeial limits. The majority of these poor-quality samples were collected from non-pharmacy retailers. Poor quality assurance during manufacture rather than fraudulent manufacture appeared to be at fault. Treatment failure and drug resistance are possible consequences of the use of substandard drugs.</p>	Chloroquine, <b>amoxicillin</b> (capsules and oral suspension), tetracycline, cotrimoxazole, ampiclox	<b>Nigeria, Thailand</b>

Countries and antibiotics of interest bolded

## Summary of the findings for the antibiotics of interest

Although greater attention has been given to antimalarial and antiretroviral drugs, antibiotics still account for a large portion of counterfeit and substandard medications in Africa and Asia. Beta-lactams, which include penicillin and amoxicillin, account for 50% of counterfeit antibiotics. The most common counterfeit formulations are for oral administration (77%), but injected drugs do account for 17% of counterfeit formulations.<sup>iv</sup> However, it is clear that the three antibiotics of interest are not studied equally by researchers. Amoxicillin capsules and syrup have been studied more than either injectable benzylpenicillin or gentamicin. The concerns identified with all three medications were largely issues of substandard quality, meaning that they were expired or the active pharmaceutical ingredient was outside of pharmacopeial limits. However, authors were generally unable to pinpoint whether low quality manufacturing or poor storage conditions were responsible for the substandard quality of the medications. Several authors found that location of purchase was an important indicator of quality as the failure rate for medications purchased from an unlicensed outlet was much higher than for those purchased from a licensed outlet. One study looked at the reuse of single-dose ampoules of gentamicin in pediatric settings due to the unavailability of pediatric formulations. There is a need to ensure that pediatric formulations are more widely available in order to avoid both the serious health consequences from contamination and the waste that may occur when adult formulations are used in pediatric treatment.

## Gray literature and media reports

As many of the authors of the above journal articles have noted, further studies need to be conducted because much of the information on counterfeit and substandard antibiotics exists in

the gray literature and media reports. We include below a brief overview of gray literature and media reports pertaining to the antibiotics of interest.

In December 2010, the Partnership for Safe Medicines reported that 1.2 million vials of gentamicin were impounded by the Tanzanian Food and Drug Authority due to erasable labels, one of the primary conditions and guidelines used to distinguish between counterfeit and genuine products. The vials were impounded but not before about 37,000 vials reached the public market.<sup>xx</sup> The Promoting the Quality of Medicines program implemented by the USP compiles an ongoing list of media reports of substandard and counterfeit medications reported in countries assisted by the US Agency for International Development. The list notes the previously mentioned gentamicin event in Tanzania, as well as reports of counterfeit/substandard amoxicillin in Kenya, Nigeria, Sierra Leone, Cambodia, India, and PNG, and counterfeit/substandard penicillin in Cameroon, Kenya, and Cambodia.<sup>xxi</sup> A 2009 report on West Africa from the United Nations Office on Drugs and Crime reports on the finding of relabeled expired injectable gentamicin in Nigeria as well as substandard amoxicillin (capsules and/or oral suspension) found in Guinea, Nigeria, and Sierra Leone.<sup>xxii</sup> A 2013 news report from a Nigerian newspaper on the subject of illegal manufacture and substandard drugs and food products notes the death of a girl in April 2012 and a similar death in January 2013 from the administration of a 280-mg dose of gentamicin. This event occurred in spite of the fact that the 280-mg/2-ml dose of gentamicin was banned in Nigeria in 2010.<sup>xxiii</sup>

The quality of medications being distributed is not only a concern to developing countries. India, which supplies 40% of over-the-counter and generic prescription drugs to the United States, is under increased scrutiny by the US Food and Drug Administration (FDA). A 2014 article in the New York Times described recent lapses at a handful of Indian manufacturers and details poor conditions at one of the largest pharmaceutical manufacturers in India.<sup>xxiv</sup> The FDA has issued export bans on Indian-manufactured generic versions of several well-known drugs, including the antibiotic Cipro. WHO has estimated that one in five drugs manufactured in India are fake.<sup>xxv</sup> Spurious drugs have been linked to serious issues within India itself. As of 2013, nearly 8,000 deaths over five years in the Indian state of Jammu and Kashmir were linked to a medicine that contained 0 mg of amoxicillin, instead of the stated 500 mg. A separate investigation of ceftriaxone sodium, also in the state of Jammu and Kashmir, showed very dangerous particulate matter.<sup>xxvi</sup>

Counterfeit or substandard gentamicin has also caused harm in the United States. Between 1989 and 1994, gentamicin was connected to the deaths of 49 people and the severe illness of several hundred more across the United States.<sup>xxvii,xxviii</sup> A broker selling API to US manufacturers bought low-cost materials from non-FDA-approved facilities in China, which it then relabeled to indicate that it had come from an FDA-approved facility. The Centers for Disease Control and Prevention reported that harm was likely due to an endotoxin in the gentamicin. A 2003 investigation of bulk gentamicin from German and US markets found drug substances listed from individual producers with different impurity profiles. The results of this study suggest that these individual producers may have incorporated material from undisclosed sources.<sup>xxix</sup>

## Other findings in published literature

A review of the literature reveals that there are a number of factors contributing to the influx of counterfeit and substandard medications. In terms of counterfeit medications, high prices and lack of availability play a major role in the entry of counterfeit medications into the market,<sup>xxx</sup> as well as the growth of international free trade, inadequate drug regulation,<sup>xxxii</sup> and the complexity of the supply chain.<sup>xxxiii</sup> Substandard medicines result from a variety of factors including poor manufacturing, poor storage, and disregarded expiration dates. It is stated that while programs such as the WHO prequalification program are very important, donors must also encourage more explicit quality requirements in tender mechanisms, and purchasers should insist that producers and distributors comply with international standards.<sup>xxxiiii</sup> A further suggestion has been made that increased provision of free or inexpensive medicines for key diseases would reduce the financial incentive for counterfeit medicines.<sup>iii</sup>

Equally important in the efforts to reduce the prevalence of substandard and counterfeit medications is the development of accurate yet low-cost testing mechanisms that can be easily applied in low-resource settings. The FDA is currently testing the use of a handheld device that helps identify counterfeit or substandard anti-malarial medicines. It is not known at this point if this device will be useful for other drugs. The Institute of Medicine (IOM) recognizes the serious problem that counterfeit and substandard medications pose around the globe. In their book, *Countering the Problem of Falsified and Substandard Drugs*, the IOM outlines a number of ways that countries can address these issues.<sup>xxxv</sup> Criminals are becoming more sophisticated in their abilities to counterfeit medicines; therefore, it is imperative that countries do their best to establish good laboratories for monitoring quality control, not only for locally manufactured drugs, but also for those imported or donated to ensure they meet international and national standards.<sup>xxxvi</sup> The IOM suggests several categories of techniques to analyze pharmaceuticals, including the following: visual inspection of product and packaging; tests for physical properties such as disintegration, reflectance spectroscopy, and refractive index; chemical tests including colorimetry and dissolution; chromatography; spectroscopic techniques; and mass spectrometry. However, the IOM also recognizes the barriers of cost, training, and equipment to such analysis in developing countries. Suggestions such as mobile laboratories, the Global Pharma Health Fund Minilab, and the participation of well-informed consumers are just a few components of the IOM's larger plan to identify counterfeit and substandard medications in resource-poor settings.

## Conclusion

As previously stated, antibiotics are the most counterfeited medicines and account for 28% of global counterfeit medicines; and beta-lactams, which include penicillin and amoxicillin, account for half of the counterfeit antibiotics.<sup>iv</sup> Although Africa and Asia make up 72% of the world's population, they consume only 10.6% of the world's drugs. Yet, the number of counterfeit and substandard medicines reaching these areas is disproportionately high.<sup>iii</sup> While scarce resources are invested in an optimum treatment policy, improving diagnosis, and delivery of treatment, these strategies are significantly weakened when the quality of the available medications is poor.<sup>iii</sup> Counterfeit and substandard medications can lead to adverse clinical outcomes, development of bacterial resistance, toxicity, unpleasant side effects, and death, causing

prescribers and patients to lose confidence both in the treatment, but also in the health care system. Despite regulatory efforts, it is clear that substandard medications continue to be a major concern. As noted by Bates and colleagues, substandard medicines from approved manufacturers still reach the market in relatively high volumes even when there are stringent quality assurance methods in place such as the WHO prequalification program.<sup>viii</sup> Although the FDA has taken further steps to address the harm caused by gentamicin in the United States between 1989 and 1994, it is worth considering that it was not difficult for the substandard API to enter the US pharmaceutical manufacturing system despite heavy regulatory oversight. Weaker regulatory systems in developing countries have far less control over the quality of the antibiotics that are available in their market.

Keeping in mind the potential limitations of the identified studies and reports, our literature review found that counterfeiting of amoxicillin proved to be quite common, while fewer studies have investigated the situation with gentamicin and penicillin. Further, studies have given little to no consideration of pediatric formulations. Where gentamicin was studied, we found that quality issues were evident in multiple areas, including counterfeiting, expired medicines, and substandard API. While the issue of counterfeit and substandard antibiotics is well recognized, further studies need to be conducted with the appropriate methodology, particularly around the various presentations of the antibiotics of interest and specifically pediatric formulations.

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