

Characterizing Medicine Quality by Active Pharmaceutical Ingredient Levels: A Systematic Review and Meta-Analysis across Low- and Middle-Income Countries

Sachiko Ozawa,^{1,2*} Hui-Han Chen,¹ Yi-Fang (Ashley) Lee,¹ Colleen R. Higgins,¹ and Tatenda T. Yemeke¹

¹Division of Practice Advancement and Clinical Education, UNC Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, North Carolina; ²Department of Maternal and Child Health, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina

Abstract. Substandard and falsified medicines are often reported jointly, making it difficult to recognize variations in medicine quality. This study characterized medicine quality based on active pharmaceutical ingredient (API) amounts reported among substandard and falsified essential medicines in low- and middle-income countries (LMICs). A systematic review and meta-analysis was conducted using PubMed, supplemented by results from a previous systematic review, and the Medicine Quality Scientific Literature Surveyor. Study quality was assessed using the Medicine Quality Assessment Reporting Guidelines (MEDQUARG). Random-effects models were used to estimate the prevalence of medicines with < 50% API. Among 95,520 medicine samples from 130 studies, 12.4% (95% confidence interval [CI]: 10.2–14.6%) of essential medicines tested in LMICs were considered substandard or falsified, having failed at least one type of quality analysis. We identified 99 studies that reported API content, where 1.8% (95% CI: 0.8–2.8%) of samples reported containing < 50% of stated API. Among all failed samples ($N = 9,724$), 25.9% (95% CI: 19.3–32.6%) reported having < 80% API. Nearly one in seven (13.8%, 95% CI: 9.0–18.6%) failed samples were likely to be falsified based on reported API amounts of < 50%, whereas the remaining six of seven samples were likely to be substandard. Furthermore, 12.5% (95% CI: 7.7–17.3%) of failed samples reported finding 0% API. Many studies did not present a breakdown of actual API amount of each tested sample. We offer suggested improved guidelines for reporting poor-quality medicines. Consistent data on substandard and falsified medicines and medicine-specific tailored interventions are needed to ensure medicine quality throughout the supply chain.

INTRODUCTION

Poor-quality medicines pose a significant threat to patients and health systems globally because they may be ineffective, resulting in increased length of illness and the need for further treatment.^{1–5} In worse cases, poor-quality medicines can cause severe adverse reactions or lack life-saving active ingredients, resulting in avertable deaths.^{2,3,6,7} In 2017, the World Health Organization (WHO) adopted formal definitions of substandard and falsified medical products to describe poor-quality medicines.⁸ Substandard medicines refer to “authorized medical products that fail to meet either their quality standards or specifications, or both.”⁶ Falsified medicines are defined as “medical products that deliberately or fraudulently misrepresent their identity, composition, or source.”⁶

A variety of testing methods can detect substandard and falsified medicines, including visual and physical inspection, dissolution testing, and analysis of active pharmaceutical ingredient (API) content.³ A WHO review found that 1 in 10 essential medicines in low- and middle-income countries (LMICs) failed tests for quality.² Two recent studies estimated a similar range from 13% to 25%.^{9,10} However, these analyses report all failed samples together, without distinguishing what pharmacopeia standards are being applied and how much the failed samples deviated from these specifications.¹¹ Understanding how much substandard and falsified medicines deviate from pharmacopeial standards for API content would add needed depth to the interpretation of overall prevalence of poor-quality medicines, and has implications for interventions to address them.¹¹

Although many quality attributes (e.g., disintegration, dissolution, degradation, and presence of impurities) can affect treatment outcomes, the API content of a medicine is highly

associated with its therapeutic efficacy and has implications for the development of antimicrobial resistance.¹² Broadly, medicines with insufficient API content reduce therapeutic efficacy and have a more extensive impact on resistance compared with medicines with no API.¹²

The extent of deviation in the API content can indicate where supply chain issues are and allow for better tailoring of interventions. For example, some drugs may deviate only slightly from specifications, most likely indicating inadequate manufacturing or poor storage conditions. On the other hand, medicines with substantially low amounts of API, no API, or an incorrect API may indicate fraud, which may be further investigated by the pharmaceutical company or national medicines regulatory authorities (NMRAs). Because manufacturing falsified medicines is criminal, substandard and falsified medicines have different legal ramifications and require distinct solutions. A 2016 report on quality of lifesaving medicines differentiated samples by levels of deviation to understand the therapeutic effects of the products.¹³ However, studies differentiating poor-quality medicines by API content levels have not previously been documented.

This systematic review and meta-analysis updates prior analyses⁹ and seeks to break down the prevalence of substandard and falsified essential medicines in LMICs by API levels. We examined amounts of API content among essential medicines in studies that tested medicine quality in LMICs. We also offer guidance on how to improve reporting of poor-quality medicines in future medicine quality studies.

MATERIALS AND METHODS

Systematic review. We searched for medicine quality studies in LMICs. First, we used searches from PubMed, EconLit, Global Health, Embase, and Scopus covering publications up to November 3, 2017.⁹ Search terms involved iterations of the terms “substandard and falsified medicines,” “quality of medicines,” and “low- and middle-income

*Address correspondence to Sachiko Ozawa, Practice Advancement and Clinical Education, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, CB#7574, Beard Hall 115G, Chapel Hill, NC 27599. E-mail: ozawa@unc.edu

countries.” Second, we updated this search in PubMed to February 4, 2020. Third, we searched the Infectious Diseases Data Observatory’s Medicine Quality Scientific Literature Surveyor, an online platform that gathers medicine quality studies, from inception through September 10, 2020. This database reviews PubMed, Google Scholar, Embase, the WHO, the U.S. Pharmacopeia, Medical Regulatory Agencies’ websites, and other sources to include scientific reports on medicine quality in English, French, and Spanish.¹⁴ Further details of the search strategy and search terms are included in the supplemental materials.

Studies were included in the systematic review if they assessed medicine quality, examined essential medicines as classified by the WHO, were conducted in LMICs as classified by the World Bank, and reported the quantity of samples tested and failed.¹⁵ Included studies reported original sampling and testing data where samples were taken or purchased directly from markets. To ensure adequate statistical power and study quality, we included studies that tested a minimum of 50 samples. Studies without primary data, publications without full texts, and case reports were excluded.

After removing duplicates, each publication was independently reviewed for potential inclusion by two of four reviewers (H. C., Y. L., C. H., and T. Y.) based on the title and abstract, followed by a full-text review. Any inconsistencies between dual reviewers were addressed by a third independent reviewer (S.O.). Data abstraction was completed independently by three abstractors (H.C., Y.L., and C.H.). Discrepancies between abstracted results were discussed and resolved between the abstractors and S. O. Study data, including the sample size, type of sampling and testing methods, publication year, country where samples were collected, medicine class, and the number of samples tested and failed were extracted in Excel.

We used the 12-item Medicine Quality Assessment Reporting Guidelines (MEDQUARG) to evaluate the reporting standard of medicine quality studies.^{16,17} Studies not included in the previous review were rated by two reviewers (H. C., Y. L.). A Spearman’s correlation coefficient between reviewers was assessed for interrater reliability. Further information on MEDQUARG scoring and interrater reliability is reported in the supplemental materials.

Meta-analysis across substandard and falsified samples.

Two separate meta-analyses were conducted. First, we estimated the prevalence of substandard and falsified medicines across all studies that assessed medicine quality in LMICs using a random-effects model, taking into account study sample sizes and MEDQUARG scores. A subgroup analysis was performed to illustrate the variation in the average weighted prevalence of substandard and falsified medicines across regions and therapeutic categories.

To assess the heterogeneity across studies, we evaluated the results of the random-effects model based on Cochran’s Q and I^2 . Effect modifiers were assessed to identify study features that may be associated with heterogeneity across studies included in the meta-analysis. We tested five potential effect modifiers using a mixed-effects model: publication year, region, medicine category, number of samples tested, and MEDQUARG scores. A Baujat plot analysis was conducted to examine the influence of each study on pooled results.¹⁸ A funnel plot and funnel plot asymmetry test assessed potential publication bias.¹⁹ Additionally, we

examined which studies exerted the most influence on the pooled weighted result using an influence plot analysis.²⁰ These results are reported in the supplemental materials.

Meta-analysis among samples that reported API levels.

A second meta-analysis was conducted among studies that reported API amounts in medicine samples tested. Studies were included if they reported the percentage API of all failed samples or reported the number of samples within API ranges. Studies that reported adequate data were included whether they found any substandard or falsified medicines.

We recorded the number of failed medicine samples reported into categories of API level deviations. We documented whether failed samples were reported to contain 1) no and/or incorrect API, 2) $< 50\%$ API, or 3) $< 80\%$ API. These categories were not mutually exclusive where samples could be classified into more than one category. For example, a sample with 0% API was included in counts containing $< 50\%$ API and in the classification for $< 80\%$ API. On the other hand, a sample that reported to have $< 80\%$ API without specifying the actual API amount was only included in the $< 80\%$ API category. Medicine samples with $< 80\%$ of API are considered to be “extremely deviating” from specifications and in the absence of evidence of falsification these medicines can be considered likely substandard,¹³ whereas those with $< 50\%$ of API can be considered likely falsified.¹¹ Where available, we categorized samples that were documented as having incorrect labeling or false packaging because this is a common sign of falsification. We also recorded when authors claimed the samples were falsified without presenting data.

We estimated the pooled prevalence of medicines with 0% API and/or incorrect API, medicines with $< 50\%$ API, and medicines with $< 80\%$ API using random-effects models weighted by sample size and MEDQUARG scores. Studies with larger samples and higher MEDQUARG scores contributed greater weight. A subgroup analysis was conducted to examine the variation in API levels across regions and therapeutic categories.

This systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO) database (#CRD42020188678). Results are reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

RESULTS

Systematic review. Combined searches resulted in a total of 3,537 articles after removing duplicates, which were screened based on titles and abstracts. After conducting full-text screening of 1,043 studies, 130 studies were included in this systematic review (Figure 1; see supplemental materials for a list of studies).

Africa (58 studies, 44.6%) and Asia (48 studies, 36.9%) were the primary regions where medicine quality studies were conducted in LMICs, with few studies in South America ($N = 5$, 3.8%),^{21–25} Europe ($N = 1$, 0.8%),²⁶ and Oceania ($N = 1$, 0.8%).²⁷ In addition, we identified 17 studies (13.1%) that collected samples from multiple regions. The majority of the included articles (87 studies, 66.9%) were published in or after 2010, of which 31 studies (23.8%) were published since 2017. Antibiotics (74 studies) and antimalarials (70 studies) remain the most examined therapeutic classes for medicine quality. Additional classes of medicines that were tested for quality and reported in LMICs included analgesics and anti-

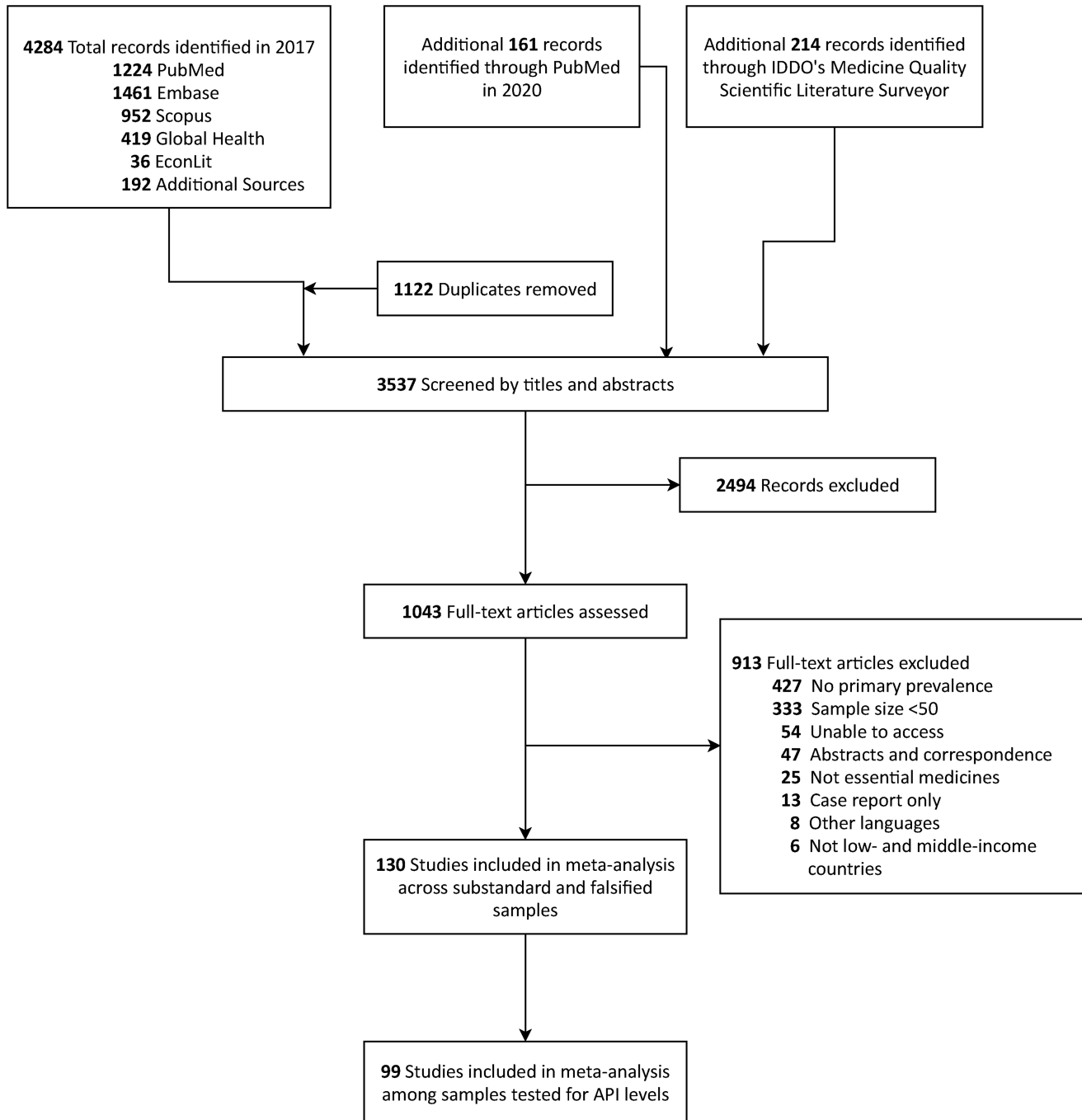


FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram.

inflammatories (27 studies), antihypertensives (17 studies), uterotonics (10 studies), steroids (10 studies), antidiabetics (8 studies), antiparasitics (8 studies), antiretrovirals (8 studies), and others such as vitamins, anticonvulsants, proton pump inhibitors, bronchodilators, opioids, and antifungals (24 studies). Across 130 studies, 95,520 samples were tested in total, with a median sample size of 248 samples per study and an interquartile range of 107 to 544 samples.

Meta-analysis across substandard and falsified samples. Figure 2 presents a forest plot of the weighted prevalence of substandard and falsified essential medicines across 130 included studies, with subgroup analyses by

region and medication category. The overall weighted prevalence of substandard and falsified medicines in LMICs was 12.4% (95% CI: 10.2–14.6%) across all therapeutic categories and geographic regions. Substandard and falsified medicines were most prevalent in Africa at 18.9% (95% CI: 14.3–23.5%), followed by Asia at 10.2% (95% CI: 6.5–13.8%), and in other single-region studies at 8.7% (95% CI: 2.7–14.7%). Among studies that combined samples from multiple regions, the prevalence of substandard and falsified medicines was estimated at 12.0% (95% CI: 8.1–15.8%).

Across 27 studies ($N = 10,719$) that examined labeling, 2.5% (95% CI: 0.5–4.4%) of labels were incorrect. Among

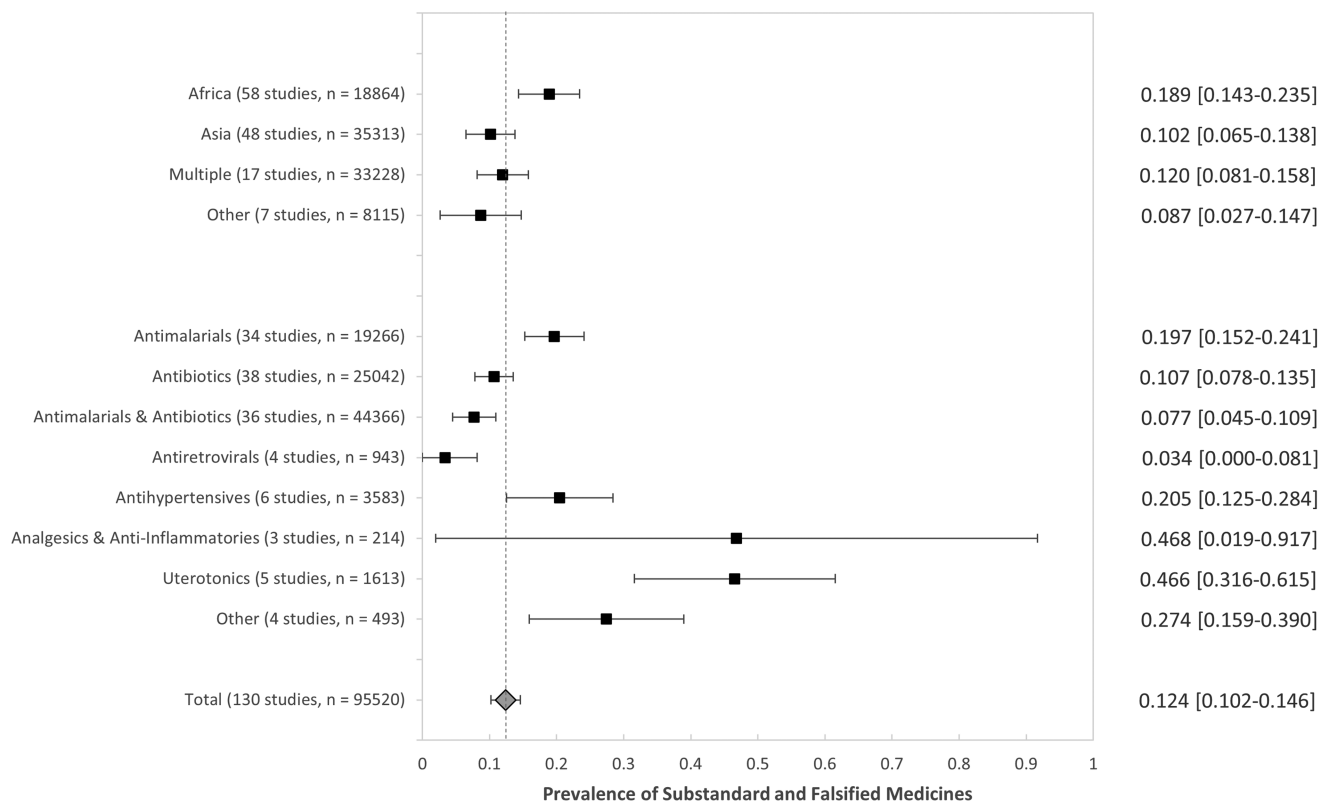


FIGURE 2. Forest plot of overall prevalence of substandard and falsified medicines. Sample size includes all medicine quality study samples tested. Antimalarials include studies that examined antimalarials but not antibiotics. Antibiotics exclude studies that examined antimalarials. Antimalarials and antibiotics category includes studies that examined both together. Sample sizes of 1) antiretrovirals, 2) antihypertensives, 3) analgesics and anti-inflammatories, and 4) uterotonics include studies that investigated the specific therapeutic category but not antibiotics or antimalarials, and may or may not include other therapeutic categories.

six studies ($N = 11,024$) that did not offer data on samples,^{28–33} 1.5% (95% CI: 0.6–2.3%) were samples authors claimed were falsified.

Across therapeutic classes, substandard and falsified medicines were most prevalent among analgesics and antiinflammatories at 46.8% (95% CI: 1.9–91.7%), and uterotonics at 46.6% (95% CI: 31.6–61.5%), although both demonstrated large uncertainty due to small numbers of studies and samples tested. The prevalence of substandard and falsified antihypertensives was 20.5% (95% CI: 12.5–28.4%), antimalarials was 19.7% (95% CI: 15.2–24.1%), and antibiotics was 10.7% (95% CI: 7.8–13.5%). Among studies that combined the results of antimalarials and antibiotics, 7.7% (95% CI: 4.5–10.9%) of medicines were found to be substandard or falsified. Antiretrovirals were found to have the lowest substandard and falsified prevalence among therapeutic classes of medicines tested at 3.4% (95% CI: 0.0–8.1%).

The random-effects model showed considerable heterogeneity between studies ($I^2 = 99.92\%$) and funnel plot asymmetry showed publication bias ($P < 0.001$). Effect modifiers for the number of samples tested and region were significant ($P < 0.05$) in explaining some of the heterogeneity between studies (see supplemental materials). The heterogeneity demonstrated that studies in Africa and Asia, and those testing fewer samples tended to have higher prevalence of substandard and falsified medicines.

Meta-analysis among samples that reported API levels.

From the second meta-analysis, we found that 99 of the 130 studies (76.2%) included information on API levels

(Table 1).^{4,13,21–24,26–31,34–120} Many studies reported the number of samples that contained API amounts below a cutoff rather than the exact API amount of each sample. Overall weighted prevalence of medicines that were reported to contain < 50% API was 1.8% (95% CI: 0.8–2.8%) across all essential medicines in LMICs (see supplemental materials for forest plot). Regional prevalence of medicines with < 50% API was marginally higher in Asia and Africa at 2.8% (95% CI: 0.0–5.6%) and 2.2% (95% CI: 0.5–3.9%), respectively. On average, prevalence of medicines with < 50% API was 3.7% (95% CI: 0.0–8.8%) for uterotonics, 3.6% (95% CI: 1.0–7.2%) for antimalarials, and 1.6% (95% CI: 0.1–2.1%) for antibiotics. Across the 99 studies, we found that 1.6% (95% CI: 0.6–2.6%) of samples were reported to contain 0% API.

Among the 99 studies that included information on API levels and found medication samples that failed quality testing (9,724 samples), we found 25.9% (95% CI: 19.3–32.6%) that were reported to contain < 80% API (Figure 3). The remainder failed other quality tests (e.g., disintegration, dissolution, degradation, presence of impurities, visual and physical inspection), contained API levels > 80% but below pharmacopeia standards or had API levels > 100%. Moreover, 13.8% (95% CI: 9.0–18.6%) of failed samples were reported to contain < 50% API, and 12.5% (95% CI: 7.8–17.3%) reported finding no or incorrect API.

Figure 4 presents a subgroup analysis. The proportion of samples reported to contain < 50% API was highest in Asia at 23.4% (95% CI: 11.2–35.7%), compared with 12.7%

TABLE 1
Studies reporting active pharmaceutical ingredient (API) amounts of samples that failed medicine quality tests, by therapeutic class

Author (year)	Countries	Sample size	Incorrect or no API count (%)	< 50% API count (%)	< 80% API count (%)
Analgesics and anti-inflammatories					
Roy et al. ³⁴ (1993)	Bangladesh	53	0 (0.00%)	0 (0.00%)	16 (30.19%)
Antibiotics					
Alotaibi et al. ³⁵ (2018)	Haiti, Ghana, Sierra, Leone, Democratic Republic of Congo, India, Papua New Guinea, Ethiopia	290	0 (0.00%)	0 (0.00%)	4 (1.38%)
Bate et al. ³⁶ (2012)	Angola, Brazil, China, DRC, Egypt, Ethiopia, Ghana, India, Kenya, Mozambique, Nigeria, Russia, Rwanda, Tanzania, Thailand, Turkey, Uganda, Zambia	1,437	59 (4.11%)	59 (4.11%)	142 (9.88%)
Bate et al. ²⁹ (2013)	Angola, DRC, Egypt, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, Tanzania, Uganda, Zambia, India, Thailand, China, Turkey, Russia, Brazil	713	0 (0.00%)	29 (4.07%)	65 (9.12%)
Bate et al. ³⁷ (2014)	Angola, DRC, Egypt, Ethiopia, Ghana, Kenya, Nigeria, Rwanda, Tanzania, Uganda, Zambia, India, Thailand, China, Turkey, Russia, Brazil, Mozambique	1,470	57 (3.88%)	57 (3.88%)	160 (10.88%)
Bate et al. ²⁴ (2018)	Argentina	687	14 (2.04%)	14 (2.04%)	48 (6.99%)
Boadu et al. ³⁸ (2015)	Ghana	54	0 (0.00%)	8 (14.81%)	16 (29.63%)
Exebio et al. ²³ (2010)	Peru	4,917	68 (1.38%)	68 (1.38%)	68 (1.38%)
Islam et al. ³⁹ (2018)	Myanmar	235	3 (1.28%)	3 (1.28%)	3 (1.28%)
Kamau et al. ⁴⁰ (2003)	Kenya	57	0 (0.00%)	2 (3.51%)	5 (8.77%)
Khan et al. ⁴¹ (2013)	India	59	0 (0.00%)	0 (0.00%)	0 (0.00%)
Khurelbat et al. ⁴² (2014)	Mongolia	1,236	0 (0.00%)	0 (0.00%)	0 (0.00%)
Khurelbat et al. ⁴³ (2020)	Mongolia	1,770	0 (0.00%)	0 (0.00%)	73 (4.12%)
Kumar et al. ⁴⁴ (2018)	India	3,925	90 (2.29%)	90 (2.29%)	110 (2.80%)
Kitutu et al. ⁴⁵ (2015)	Uganda	179	3 (1.68%)	3 (1.68%)	10 (5.59%)
Laserson et al. ⁴⁶ (2001)	Colombia, Estonia, India, Latvia, Russia, Vietnam	71	0 (0.00%)	0 (0.00%)	2 (2.82%)
Lawal et al. ⁴⁷ (2019)	Nigeria	112	3 (2.68%)	3 (2.68%)	39 (34.82%)
Myers et al. ⁴⁸ (2019)	Kenya	189	0 (0.00%)	0 (0.00%)	13 (6.88%)
Nabirova et al. ⁴⁹ (2017)	Kazakhstan	854	0 (0.00%)	0 (0.00%)	36 (4.22%)
Nazerli et al. ⁵⁰ (1998)	Zimbabwe	840	0 (0.00%)	0 (0.00%)	94 (11.19%)
Obaid et al. ⁵¹ (2009)	Pakistan	96	0 (0.00%)	0 (0.00%)	3 (3.13%)
Patel et al. ⁵² (2012)	South Africa	135	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sabartova et al. ²⁶ (2011)	Armenia, Azerbaijan, Belarus, Estonia, Kazakhstan, Latvia, Moldova, Ukraine, Uzbekistan	291	0 (0.00%)	0 (0.00%)	1 (0.34%)
Sakolkhai et al. ⁵³ (1991)	Thailand	62	0 (0.00%)	0 (0.00%)	3 (4.84%)
Schafermann et al. ⁵⁴ (2018)	Togo	92	0 (0.00%)	1 (1.09%)	1 (1.09%)
Taberner et al. ⁵⁵ (2019)	Laos	1,025	0 (0.00%)	0 (0.00%)	2 (0.20%)
Tshilumba et al. ⁵⁶ (2015)	Democratic Republic of Congo	60	0 (0.00%)	0 (0.00%)	0 (0.00%)
Wahidullah et al. ⁵⁷ (2011)	Afghanistan	348	0 (0.00%)	1 (0.29%)	1 (0.29%)
Wang et al. ⁵⁸ (2015)	South Africa, United States, China, Ethiopia, Thailand, Laos, Mexico, Nigeria	88	0 (0.00%)	0 (0.00%)	0 (0.00%)
WHO ¹³ (2016)	Burkina Faso, Kenya, Madagascar, Nepal, Nigeria, Tajikistan, Tanzania, Uganda, Viet Nam, Zimbabwe	204	1 (0.49%)	1 (0.49%)	5 (2.45%)

(continued)

TABLE 1
Continued

Author (year)	Countries	Sample size	Incorrect or no API count (%)	< 50% API count (%)	< 80% API count (%)
Yoshida et al. ²⁸ (2014)	Cambodia	325	0 (0.00%)	0 (0.00%)	0 (0.00%)
Antihypertensives					
Antignac et al. ⁵⁹ (2017)	Benin, Burkina Faso, Republic of the Congo, the Democratic Republic of Congo, Guinea, Côte d'Ivoire, Mauritania, Niger, Senegal, Togo	1,530	0 (0.00%)	0 (0.00%)	24 (1.57%)
Ndichu et al. ⁶⁰ (2019)	Nigeria	102	0 (0.00%)	0 (0.00%)	6 (5.88%)
Rahman et al. ⁶¹ (2019)	Cambodia	372	0 (0.00%)	6 (1.61%)	7 (1.88%)
Redfern et al. ⁶² (2019)	Nigeria	361	0 (0.00%)	0 (0.00%)	0 (0.00%)
Antimalarials					
Amin et al. ⁶³ (2005)	Kenya	116	1 (0.86%)	1 (0.86%)	1 (0.86%)
Basco et al. ⁶⁴ (2004)	Cameroon	284	76 (26.76%)	76 (26.76%)	84 (29.58%)
Belew et al. ⁶⁵ (2019)	Ethiopia	74	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bjorkman et al. ⁶⁶ (2012)	Uganda	558	108 (19.35%)	108 (19.35%)	108 (19.35%)
Dondorp et al. ⁶⁷ (2004)	Myanmar, Lao PDR, Vietnam, Cambodia, Thailand	232	99 (42.67%)	103 (44.40%)	103 (44.40%)
Evans et al. ²¹ (2012)	Guyana and Suriname	135	2 (1.48%)	2 (1.48%)	12 (8.89%)
Guo et al. ⁶⁸ (2017)	Myanmar	153	1 (0.65%)	1 (0.65%)	1 (0.65%)
Idowu et al. ⁶⁹ (2006)	Nigeria	50	3 (6.00%)	3 (6.00%)	3 (6.00%)
loset et al. ⁷⁰ (2009)	13 countries in Asia, South America and Africa including Kenya, Nigeria, Vietnam; does not name all 13	171	2 (1.17%)	2 (1.17%)	2 (1.17%)
Kaur et al. ⁷¹ (2008)	Tanzania	304	0 (0.00%)	0 (0.00%)	0 (0.00%)
Kaur et al. ⁷² (2016)	Equatorial Guinea (Bioko Island), Cambodia, Ghana, Nigeria, Rwanda, Tanzania	10,079	98 (0.97%)	98 (0.97%)	98 (0.97%)
Khin et al. ⁷³ (2016)	Myanmar	51	2 (3.92%)	2 (3.92%)	2 (3.92%)
Lalani et al. ⁷⁴ (2015)	Afghanistan	134	0 (0.00%)	0 (0.00%)	0 (0.00%)
Maponga et al. ⁷⁵ (2003)	Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	288	0 (0.00%)	0 (0.00%)	13 (4.51%)
Mufusama et al. ⁷⁶ (2018)	Democratic Republic of the Congo	150	4 (2.67%)	6 (4.00%)	19 (12.67%)
Mziray et al. ⁷⁷ (2017)	Tanzania	1,444	1 (0.07%)	1 (0.07%)	1 (0.07%)
Newton et al. ⁷⁸ (2001)	Cambodia, Laos, Myanmar, Thailand, Vietnam	104	39 (37.50%)	39 (37.50%)	39 (37.50%)
Newton et al. ⁷⁹ (2008)	Vietnam, Cambodia, Lao PDR, Myanmar, Thai/Myanmar border	391	195 (49.87%)	195 (49.87%)	195 (49.87%)
Ochekpe et al. ⁸⁰ (2010)	Nigeria	70	2 (2.86%)	2 (2.86%)	20 (28.57%)
Ogwal-Okeng et al. ⁸¹ (1998)	Uganda	88	0 (0.00%)	0 (0.00%)	11 (12.50%)
Osei-Safo et al. ⁸² (2014)	Ghana, Togo	124	1 (0.81%)	1 (0.81%)	6 (4.84%)
Phanouvong et al. ⁸³ (2013)	Cambodia	374	8 (2.14%)	17 (4.55%)	31 (8.29%)
Taberner et al. ⁸⁴ (2015)	Laos	158	0 (0.00%)	0 (0.00%)	3 (1.90%)
Tipke et al. ⁸⁵ (2008)	Burkina Faso	77	1 (1.30%)	1 (1.30%)	13 (16.88%)
Visser et al. ⁸⁶ (2015)	Gabon	432	1 (0.23%)	2 (0.46%)	2 (0.46%)
WHO ⁸⁷ (2009)	Madagascar, Senegal, Uganda	197	0 (0.00%)	0 (0.00%)	0 (0.00%)
WHO ⁸⁸ (2011)	Cameroon, Ethiopia, Ghana, Kenya, Nigeria, Tanzania	267	2 (0.75%)	3 (1.12%)	8 (3.00%)
Yeung et al. ⁸⁹ (2015)	Cambodia	291	0 (0.00%)	2 (0.69%)	50 (17.18%)
Antimalarials and antibiotics					
Baratta et al. ⁹⁰ (2012)	Congo, Ethiopia, India, Malawi, CAR, Guinea Conakry, Uganda, Brazil, Guinea Bissau, Madagascar, Kenya, Angola, Rwanda, Cameroon, Chad	221	4 (1.81%)	4 (1.81%)	4 (1.81%)

(continued)

TABLE 1
Continued

Author (year)	Countries	Sample size	Incorrect or no API count (%)	< 50% API count (%)	< 80% API count (%)
Bate et al. ⁹¹ (2010)	Ghana, Tanzania, Uganda, Nigeria, Angola, Zambia, Kenya, India, Thailand, China, Turkey, Russia, Brazil	2,065	0 (0.00%)	0 (0.00%)	210 (10.17%)
Central Drug Standard Control Organization ⁹² (2009)	India	2,976	0 (0.00%)	0 (0.00%)	0 (0.00%)
Food and Drug Department ⁹³ (2010)	Lao	1,567	10 (0.64%)	10 (0.64%)	18 (1.15%)
Food and Drug Department ⁹⁴ (2014)	Lao	114	0 (0.00%)	0 (0.00%)	0 (0.00%)
Frimpong et al. ⁹⁵ (2018)	Ghana	68	0 (0.00%)	5 (7.35%)	15 (22.06%)
Hajjou et al. ⁹⁶ (2015)	Ghana, Ethiopia, Liberia, Kenya, and Mozambique, Cambodia, Indonesia, Laos, Myanmar, Philippines, Thailand, Vietnam, China, Colombia, Ecuador, Guyana, Peru	15,063	81 (0.54%)	81 (0.54%)	81 (0.54%)
Hetzel et al. ²⁷ (2014)	Papua New Guinea	360	0 (0.00%)	2 (0.56%)	25 (6.94%)
Kaale et al. ⁹⁷ (2016)	Tanzania	242	0 (0.00%)	5 (2.07%)	14 (5.79%)
Khan et al. ³⁰ (2011)	Cambodia	679	0 (0.00%)	0 (0.00%)	0 (0.00%)
Khuluza et al. ⁹⁸ (2017)	Malawi	56	1 (1.79%)	2 (3.57%)	3 (5.36%)
Kibwage et al. ⁹⁹ (1999)	Kenya	262	1 (0.38%)	1 (0.38%)	17 (6.49%)
Lon et al. ¹⁰⁰ (2006)	Cambodia	451	90 (19.96%)	90 (19.96%)	114 (25.28%)
Petersen et al. ⁴ (2017)	Cameroon, Democratic Republic of the Congo, India, Ghana, Kenya, Nigeria, Uganda	869	12 (1.38%)	19 (2.19%)	20 (2.30%)
Phanouvong et al. ¹⁰¹ (2013)	Thailand	709	4 (0.56%)	6 (0.85%)	6 (0.85%)
Pribluda et al. ²² (2012)	Bolivia, Brazil, Colombia, Ecuador, Guyana, Suriname, Venezuela	1,663	0 (0.00%)	0 (0.00%)	0 (0.00%)
Risha et al. ³¹ (2008)	Tanzania	1,257	0 (0.00%)	0 (0.00%)	0 (0.00%)
Schiavetti et al. ¹⁰² (2018)	Democratic Republic of the Congo	239	0 (0.00%)	0 (0.00%)	8 (3.35%)
Seear et al. ¹⁰³ (2011)	India	300	0 (0.00%)	0 (0.00%)	0 (0.00%)
Shakoore et al. ¹⁰⁴ (1997)	Nigeria, Thailand	96	6 (6.25%)	6 (6.25%)	6 (6.25%)
Stenson et al. ¹⁰⁵ (1998)	Laos	366	12 (3.28%)	12 (3.28%)	17 (4.64%)
Syhakhang et al. ¹⁰⁶ (2002)	Laos	666	15 (2.25%)	15 (2.25%)	20 (3.00%)
Taylor et al. ¹⁰⁷ (2001)	Nigeria	581	6 (1.03%)	13 (2.24%)	32 (5.51%)
Uganda Medicines Transparency Alliance ¹⁰⁸ (2014)	Uganda	105	0 (0.00%)	0 (0.00%)	5 (4.76%)
Wondemagegnehu et al. ¹⁰⁹ (1999)	Myanmar, Vietnam	500	1 (0.20%)	3 (0.60%)	14 (2.80%)
WHO ¹¹⁰ (1995)	Cameroon, Madagascar, Chad	429	17 (3.96%)	17 (3.96%)	58 (13.52%)
Antiretrovirals					
Kuwana et al. ¹¹¹ (2017)	Burkina Faso, Democratic Republic of the Congo, Nigeria, Rwanda, Zambia	126	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ministry of Medical Services ¹¹² (2012)	Kenya	272	0 (0.00%)	0 (0.00%)	0 (0.00%)
WHO ¹¹³ (2007)	Cameroon, Democratic Republic of the Congo, Kenya, Nigeria, Tanzania, Uganda, Zambia	394	0 (0.00%)	0 (0.00%)	0 (0.00%)

(continued)

TABLE 1
Continued

Author (year)	Countries	Sample size	Incorrect or no API count (%)	< 50% API count (%)	< 80% API count (%)
Uterotonics					
Anyakora et al. ¹¹⁴ (2018)	Nigeria	637	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hall et al. ¹¹⁵ (2016)	Bangladesh, Egypt, Cambodia, Kenya, India, Mexico, Nigeria, Pakistan, Peru, Vietnam, Nigeria, Nepal, Pakistan, Bangladesh, Argentina, Indonesia, Peru, Philippines, Kazakhstan	215	14 (6.51%)	14 (6.51%)	14 (6.51%)
Karikari-Boateng et al. ¹¹⁶ (2013)	Ghana	279	5 (1.79%)	5 (1.79%)	5 (1.79%)
Stanton et al. ¹¹⁷ (2012)	Ghana	101	1 (0.99%)	25 (24.77%)	57 (56.40%)
Stanton et al. ¹¹⁸ (2014)	India	381	0 (0.00%)	16 (4.20%)	44 (11.53%)
Other*					
Laroche et al. ¹¹⁹ (2005)	Mauritania	146	0 (0.00%)	0 (0.00%)	5 (3.42%)
Suleman et al. ¹²⁰ (2014)	Ethiopia	106	0 (0.00%)	0 (0.00%)	1 (0.94%)

* Other includes phenobarbital, mebendazole, albendazole, and tinidazole.

(95% CI: 3.6–21.7%) for other single-region studies, 11.4% (95% CI: 4.2–18.5%) in Africa, and 9.3% (95% CI: 3.5–15.2%) in multiple-region studies. Across medicine samples reported to be substandard or falsified, antimalarials and antibiotics were most likely to be reported to contain < 50% API at 18.0% (95% CI: 6.1–29.9%) and 16.7% (95% CI: 9.1–24.4%), respectively. Studies that combined the results of antibiotics and antimalarials found 10.3% (95% CI: 3.7–16.9%) of samples contained < 50% API. Among poor-quality uterotonics, 7.8% (95% CI: 0.3–15.4%) were reported to contain < 50% API.

DISCUSSION

Our results demonstrate that a quarter of the medicines that failed API quality tests in LMICs were reported to contain

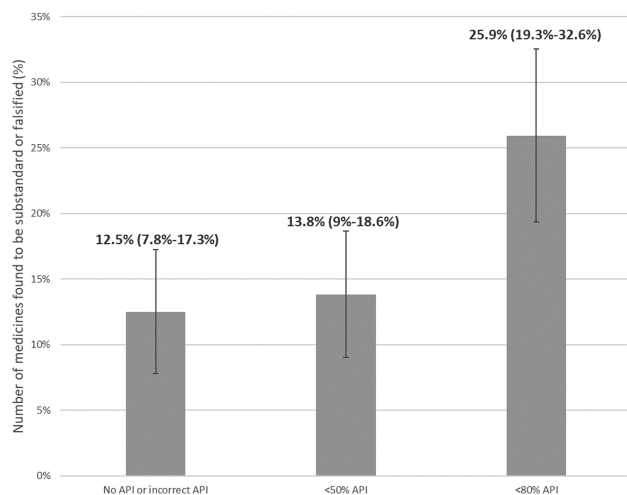


FIGURE 3. Proportion of samples that failed medicine quality tests by active pharmaceutical ingredient (API) levels. Sample size (99 studies, N = 9,724) includes studies with enough information to distinguish proportions of failed samples for no or incorrect API, > 50% API, and > 80% API.

reduced API of < 80% of the stated amount. Only 12.5% of failed samples were found to have no API at all, an incorrect API, or both. This is an important finding because falsified medicines dealing with criminal activity tend to attract more attention than substandard medicines. Yet our results demonstrate that medicines with reduced API are also a pervasive problem, one that governments and policy makers need to allocate more resources toward combatting. Because both substandard and falsified medicines pose a threat to public health, it is critical to direct resources at them differently.

Our results provide some insight into where NMRAs should focus their attention. Medicines deviating from specifications with API < 80% were most commonly reported in Africa, followed by Asia. The prevalence of poor-quality analgesics and anti-inflammatories (46.8%) as well as uterotonics (46.6%), which are likely substandard, is alarming. Substandard medicines slightly deviating from standards can indicate, or are likely to arise from limited technical capacity, and deficient storage conditions at dispensing sites, where interventions should aim at ensuring sound practices.^{3,121} Substandard medicines can be reduced by strengthening Good Manufacturing Practices (GMP), Good Distribution Practices (GDP), Good Storage Practices (GSP), alongside medicine registration, prequalification of suppliers, and recalls.^{122,123}

On the other hand, medicines reporting to contain < 50% API comprised a larger portion of poor-quality medicines in Asia (23.4%) compared with Africa (11.4%). Moreover, anti-malarials and antibiotics were the therapeutic classes most likely reported to contain low API of < 50% API (18.0% and 16.7% of all poor-quality samples, respectively). This could be a sign of more falsification of these medicines, something that would require further testing and confirmation by NMRAs. Tackling falsified medicines requires coordination with law enforcement or customs authorities and may involve increased regulatory oversight, legal framework for prosecution, customs screening, post-market surveillance, and medication safety alerts. Falsification tends to flourish under high demand for medicines and poor governance,

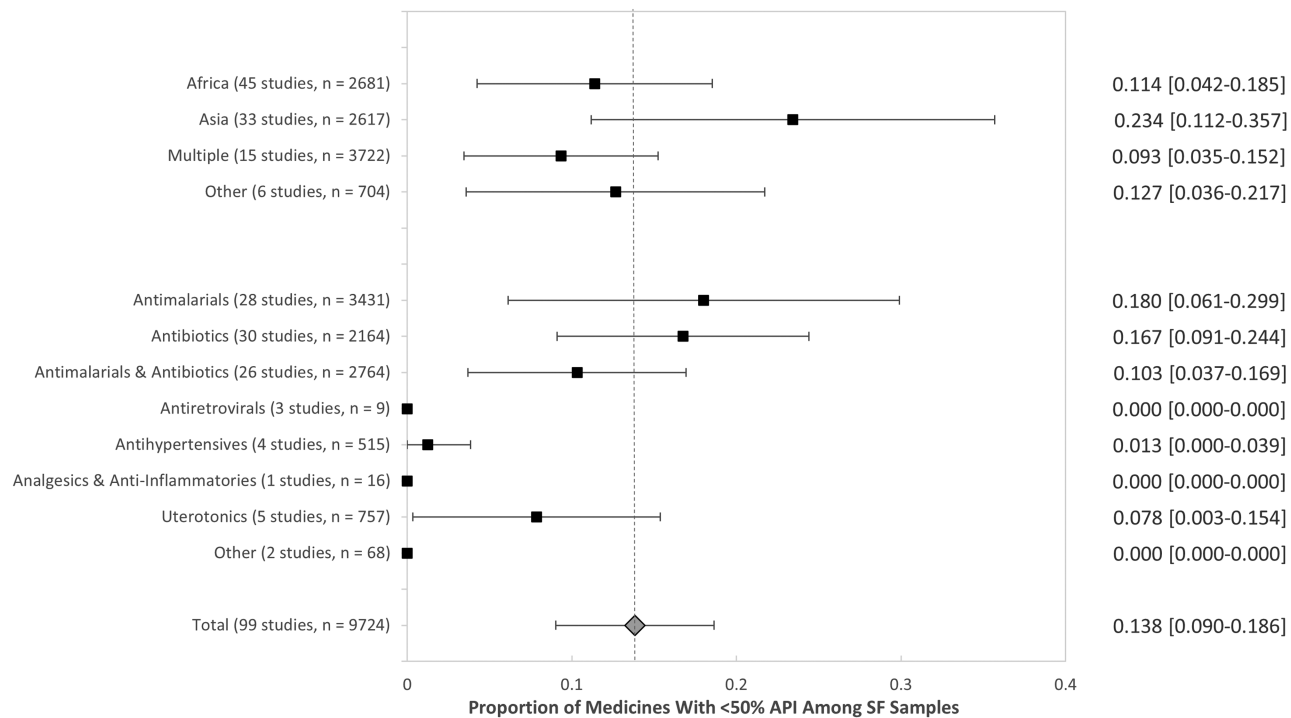


FIGURE 4. Medicines with < 50% active pharmaceutical ingredient (API) among samples that failed medicine quality tests. Sample size includes medicines found to be substandard or falsified across medicine quality studies. Classifications among therapeutic classes are the same as in Figure 2.

where criminals intend to make a profit.^{24,124} Therefore, preventing shortages or stock-outs and ensuring medication access are important parts of the solution.³

According to the WHO definition, a falsified medical product is one that intends to deceive.⁶ However, intention is difficult to assess. We found that most medicine quality studies do not report whether the product authenticity was confirmed by the manufacturer. Therefore, we used API amounts as a proxy to assess whether medicines are likely substandard or falsified. Although it is generally agreed upon that medicines with no or incorrect API are falsified,¹¹ this cutoff would miss other falsified medicines intentionally manufactured with reduced amounts of API. We reasoned that medicines with < 50% API are likely to be falsified given that there was likely to be deliberate intent to make such medicines where no confirmation of intent was provided. In the absence of ability to confirm the intent to deceive, we consider that medicines containing < 50% API without evidence of decomposition is reasonable to denote likely falsification.¹¹

Furthermore, we endorse the earlier call¹¹ to improve reporting guidelines for medicine quality studies to distinguish substandard from falsified medicines (Table 2). Most medicines reported to be of poor-quality in LMICs did not specifically report the API amount of each sample. This makes our meta-analysis among samples reporting API levels conservative, because data were not available to classify every tested sample clearly and definitively. Currently, inconsistencies in reporting and combined results across countries, medicines, and sampled locations make it difficult to adequately assess risks and devise targeted interventions. We suggest that authors include exact API amounts rather than reporting only the number of samples that failed testing or API ranges, with

further information on how and where those samples were obtained. We recommend that visual inspection, which can signal potential falsification,¹²⁵ be accompanied by chemical testing to assess API amounts, along with an attempt to communicate with the manufacturer to confirm the original source. For medications with < 80% API, we suggest that studies report whether evidence of degradation exists to differentiate between samples that had degraded after manufacture and samples that were produced with insufficient API amounts. We also suggest that results of dissolution or disintegration tests be reported alongside API results when assessing the quality of tablets. Consistent and accurate reporting of medicine quality would not only aid in comparability of results but also inform countermeasures.

There are several limitations to our analysis. First, systematic reviews are inherently limited by the search strategies used, databases searched, and inclusion and exclusion criteria applied. Our review update focused on PubMed as previous findings showed that few unique articles were identified from other databases.⁹ By cross-referencing with the Medicine Quality Scientific Literature Surveyor database, we believe we have captured the most pertinent literature. Second, meta-analyses are limited by the quality of included studies and the biases they contain.¹²⁶ To minimize the impact of poor-quality studies in our analysis, we selected studies that tested 50 or more samples and weighted our meta-analyses by study sample size and MEDQUARG scores. Third, we observed considerable heterogeneity across medicine quality studies in reporting. For example, a considerable number of publications only reported API amounts below a cutoff rather than presenting a breakdown of actual API amounts of each sample. This prevented us from being able to develop mutually exclusive categories in our analysis. Our results for samples with 0% or < 50% API

TABLE 2
Suggested guidelines for reporting poor-quality medicines as substandard or falsified medicines

Medicine quality	WHO definition	Operational characterizations of medicine quality	Suggested guidelines for medicine quality reporting
Falsified	Medical products that deliberately/fraudulently misrepresent their identity, composition or source	If at least one of the following is true: - Contains 0% - Contains an incorrect API - Manufacturer credibly confirms the packaging misrepresents the identity of the medicine - Analysis of the packaging gives conclusive evidence for falsification (e.g., the stated manufacturer does not exist)	<ul style="list-style-type: none"> Report numerical values of % API for every medicine tested, denoting the medicine, country, and region it was obtained from, sampled location (e.g., entry ports, warehouses, district hospitals, health centers, pharmacies, informal outlets), and method obtained (e.g., overt, mystery client). Visual inspection of packaging should be accompanied by findings from chemical testing to assess % API and results of communication with the manufacturer to confirm the source.
Likely Falsified		Contains < 50% API and there is no evidence of decomposition	
Likely Substandard	Authorized medical products that fail to meet either their quality standards, specifications, or both	Extreme deviation ¹³ - The content of API deviates by more than 20% from the declared content and/or - For tablets, an average dissolution value of tested units below pharmacopoeial Q value minus 25% Other deviations	<ul style="list-style-type: none"> Report if evidence for degradation exists (e.g., exhibiting multiple peaks in HPLC chromatogram) for samples containing < 80% API. Performance tests such as dissolution or disintegration test results should be reported for tablets alongside information on % API (e.g., results of Minilab tablet disintegration procedure).

API = active pharmaceutical ingredient; HPLC = high-performance liquid chromatography.

categories may be conservative because we were not able to assess the actual API amounts in some publications. Many publications were missing information on the criteria used to determine that a sample had failed. We suggest guidelines for reporting medicine quality studies to reduce reporting inconsistencies in the future. Lastly, our meta-analysis is likely influenced by publication bias where many studies are conducted in Africa and Asia testing antimalarials and antibiotics. Testing and reporting the quality of a wider range of medical products around the world will lend to a more comprehensive picture of the risks posed by substandard and falsified medicines. Despite these limitations, this meta-analysis offers a comprehensive and scientifically grounded method for differentiating poor-quality medicines across LMICs by reported API levels.

CONCLUSION

This study contributes to the existing literature by providing an estimate of the magnitude of the problem of substandard and falsified medicines and examining the amounts of API in medicine samples that fail quality testing. Our findings of 12.4% overall prevalence of substandard and falsified medicines are consistent with previous analyses and WHO reports.^{1,9,17,127–129} Our analysis goes further by finding that nearly one in seven poor-quality medicine samples were likely to be falsified based on reported API amounts of < 50%, whereas the remaining six in seven samples were likely to be substandard. Separating out substandard from falsified medicines is essential to better inform tailored interventions to ensure medicine quality throughout the supply chain. Furthermore, we propose improved guidelines

for reporting medicine quality in publications to better differentiate among poor-quality medicines. Governments and policy makers should use these results to target interventions to mitigate the threats of substandard and falsified medicines.

Received October 26, 2021. Accepted for publication February 3, 2022.

Note: Supplemental appendices appear at www.ajtmh.org.

Acknowledgment: We thank Lutz Heide and Cathrin Hauk for their helpful insights and guidance. We also thank Anita Zahra Trippe for early inspirations for this work.

Financial support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' addresses: Sachiko Ozawa, Hui-Han Chen, Yi-Fang (Ashley) Lee, Colleen R. Higgins, and Tatenda T. Yemeke, University of North Carolina at Chapel Hill, Chapel Hill, NC, E-mails: ozawa@unc.edu, huihanc@unc.edu, yifang@live.unc.edu, collhigg@live.unc.edu, and tyemeke@email.unc.edu.

This is an open-access article distributed under the terms of the Creative Commons Attribution (CC-BY) License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

REFERENCES

- Nayyar GM, Breman JG, Newton PN, Herrington J, 2012. Poor-quality antimalarial drugs in southeast Asia and sub-Saharan Africa. *Lancet Infect Dis* 12: 488–496.
- World Health Organization, 2017. *A Study on the Public Health and Socioeconomic Impact of Substandard and Falsified Medical Products*. Geneva, Switzerland: WHO.

3. World Health Organization, 2017. *WHO Global Surveillance and Monitoring System for substandard and falsified medical products*. Geneva, Switzerland: WHO.
4. Petersen A, Held N, Heide L, Difam EPNMSG, 2017. Surveillance for falsified and substandard medicines in Africa and Asia by local organizations using the low-cost GPHF Minilab. *PLoS One* 12: e0184165.
5. Funestrland H, Liu R, Lundin S, Troein M, 2019. Substandard and falsified medical products are a global public health threat. A pilot survey of awareness among physicians in Sweden. *J Public Health (Oxf)* 41: e95–e102.
6. World Health Organization, 2018. *Substandard and Falsified Medical Products*. Updated January 31, 2018. Available at: <https://www.who.int/en/news-room/fact-sheets/detail/substandard-and-falsified-medical-products>. Accessed May 20, 2020.
7. Buckley GJ, Gostin LO, 2013. *Countering the Problem of Falsified and Substandard Drugs*. Washington, DC: National Academies Press.
8. World Health Organization, 2017. *What Do SSSFFC Medical Products Contain?* Available at: https://www.who.int/medicines/regulation/ssffc/faq-ssffc_1-10/en/index2.html. Accessed May 21, 2020.
9. Ozawa S et al., 2018. Prevalence and estimated economic burden of substandard and falsified medicines in low- and middle-income countries: a systematic review and meta-analysis. *JAMA Netw Open* 1: e181662.
10. McManus D, Naughton BD, 2020. A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: a focus on context, prevalence, and quality. *BMJ Glob Health* 5: e002393.
11. Hauk C, Hagen N, Heide L, 2021. Identification of substandard and falsified medicines: influence of different tolerance limits and use of authenticity inquiries. *Am J Trop Med Hyg* 104: 1936–1945.
12. Pisani E, 2015. *Antimicrobial Resistance: What Does Medicine Quality Have to Do with It?* Available at: <https://amr-review.org/sites/default/files/ElizabethPisaniMedicinesQualitypaper.pdf>. Accessed December 8, 2021.
13. World Health Organization, 2016. *Survey of the Quality of Medicines Identified by the United Nations Commission on Life-Saving Commodities for Women and Children*. Geneva, Switzerland: WHO.
14. Infectious Diseases Data Observatory, 2020. *Medicine Quality Scientific Literature Surveyor*. Available at: <https://www.iddo.org/mq-scientific-literature-surveyor>. Accessed September 10, 2020.
15. World Bank Group, 2020. *World Bank Country and Lending Groups*. Available at: <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>. Accessed September 1, 2020.
16. Newton PN et al., 2009. Guidelines for field surveys of the quality of medicines: a proposal. *PLoS Med* 6: e52.
17. Almuzaini T, Choonara I, Sammons H, 2013. Substandard and counterfeit medicines: a systematic review of the literature. *BMJ Open* 3: e002923.
18. Baujat B, Mahé C, Pignon JP, Hill C, 2002. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. *Stat Med* 21: 2641–2652.
19. Borenstein M, Hedges LV, Higgins JP, Rothstein HR, 2011. *Introduction to Meta-analysis*. Hoboken, NJ: John Wiley & Sons.
20. Viechtbauer W, Cheung MW, 2010. Outlier and influence diagnostics for meta-analysis. *Res Synth Methods* 1: 112–125.
21. Evans L 3rd et al., 2012. Quality of anti-malarials collected in the private and informal sectors in Guyana and Suriname. *Malar J* 11: 203.
22. Pribluda VS et al., 2012. Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005–2010 period. *Malar J* 11: 202.
23. Exebio LEM, Rodríguez J, Sayritupac F, 2010. Los medicamentos falsificados en Perú. *Rev Panam Salud Publica* 27: 138–143.
24. Bate R, Mathur A, 2018. Corruption and medicine quality in Latin America: a pilot study. *BE J Econ Anal Policy* 18.
25. South America Infectious Diseases Initiative (SAIDI-Peru), 2009. *USP DQI USAID—Peru and Dirección de Salud Callao (DISA) Resumen del Segundo Estudio para Determinar la Calidad de Antimicrobianos y Antituberculosos Utilizados en la Red BEPECA de la Dirección de Salud Callao*. Lima, Perú: Ministerio de Salud del Perú.
26. World Health Organization, 2011. *Survey of the Quality of Anti-tuberculosis Medicines Circulating in Selected Newly Independent States of the Former Soviet Union*. Geneva, Switzerland: WHO.
27. Hetzel MW et al., 2014. Quality of antimalarial drugs and antibiotics in Papua New Guinea: a survey of the health facility supply chain. *PLoS One* 9: e96810.
28. Yoshida N et al., 2014. A cross-sectional investigation of the quality of selected medicines in Cambodia in 2010. *BMC Pharmacol Toxicol* 15: 13.
29. Bate R, Jensen P, Hess K, Mooney L, Milligan J, 2013. Substandard and falsified anti-tuberculosis drugs: a preliminary field analysis. *Int J Tuberc Lung Dis* 17: 308–311.
30. Khan MH et al., 2011. Counterfeit medicines in Cambodia—possible causes. *Pharm Res* 28: 484–489.
31. Risha PG, Msuya Z, Clark M, Johnson K, Ndomondo-Sigonda M, Layloff T, 2008. The use of minilabs to improve the testing capacity of regulatory authorities in resource limited settings: Tanzanian experience. *Health Policy (Amsterdam, Netherlands)* 87: 217–222.
32. Krech LA et al., 2014. Cambodian ministry of health takes decisive actions in the fight against substandard and counterfeit medicines. *Trop Med Surg* 2: 10.4172/2329-9088.1000166.
33. Ratanawijitrasin S, Phanouvong S, 2018. *The State of Medicine Quality in the Mekong Sub-region*. Bangkok, Thailand: Research Institute for Contemporary Southeast Asia.
34. Roy J, Saha P, Rahman A, Zakaria M, 1993. Quality of marketed paracetamol tablets in Bangladesh—an analytical overview. *J Inst Postgrad Med Res* 8: 49–53.
35. Alotaibi N et al., 2018. Toward point-of-care drug quality assurance in developing countries: comparison of liquid chromatography and infrared spectroscopy quantitation of a small-scale random sample of amoxicillin. *Am J Trop Med Hyg* 99: 477–481.
36. Bate R, Jin GZ, Mathur A, 2012. *Counterfeit or Substandard? The Role of Regulation and Distribution Channel in Drug Safety*. NBER Working Paper 18073. Cambridge, MA: National Bureau of Economic Research, Inc.
37. Bate R, Jin GZ, Mathur A, Attaran A, 2014. *Poor Quality Drugs and Global Trade: A Pilot Study*. NBER Working Paper 20469. Cambridge, MA: National Bureau of Economic Research, Inc.
38. Boadu RF, Agyare C, Adarkwa-Yiadom M, Adu F, Boamah VE, Boakye YD, 2015. In vitro activity and evaluation of quality of some selected penicillins on the Ghanaian market using developed HPLC methods. *Med Chem* 5: 001–014.
39. Islam MR et al., 2018. An investigation into the quality of medicines in Yangon, Myanmar. *Pharmacy (Basel)* 6.
40. Kamau F, Thoithi G, Ngugi J, King'ondo O, Kibwage IO, 2003. Quality of amoxicillin preparations on the Kenyan market. *East Cent Afr J Pharm Sci* 6: 57–60.
41. Khan MH et al., 2013. Effects of packaging and storage conditions on the quality of amoxicillin-clavulanic acid—an analysis of Cambodian samples. *BMC Pharmacol Toxicol* 14: 33.
42. Khurelbat D et al., 2014. Prevalence estimates of substandard drugs in Mongolia using a random sample survey. *Springerplus* 3: 709.
43. Khurelbat D et al., 2020. A cross-sectional analysis of falsified, counterfeit and substandard medicines in a low-middle income country. *BMC Public Health* 20: 743.
44. Kumar P, 2018. A study on spurious and not of standard quality drugs in the state of Andhra Pradesh. *Afr J Pharm Pharmacol* 12: 130–135.
45. Kitutu F, 2015. *Screening Drug Quality Project Report*. Kampala, Uganda: Medicines Transparency Alliance (MeTa).
46. Laserson KF, Kenyon AS, Kenyon TA, Layloff T, Binkin NJ, 2001. Substandard tuberculosis drugs on the global market and their simple detection. *Int J Tuberc Lung Dis* 5: 448–454.
47. Lawal MG, Mukhtar MD, Magashi AM, 2019. Quality assessment of antibiotic oral drug formulations marketed in Katsina State, Nigeria. *Asian J Pharm Res Dev* 7: 6–10.
48. Myers NM et al., 2019. Lab on paper: assay of beta-lactam pharmaceuticals by redox titration. *Anal Methods* 11: 4741–4750.

49. Nabirova D et al., 2017. Assessment of the quality of anti-tuberculosis medicines in Almaty, Kazakhstan, 2014. *Int J Tuberc Lung Dis* 21: 1161–1168.
50. Nazerali H, Hogerzeil HV, 1998. The quality and stability of essential drugs in rural Zimbabwe: controlled longitudinal study. *BMJ* 317: 512–513.
51. Obaid A, 2009. Quality of ceftriaxone in Pakistan: reality and resonance. *Pak J Pharm Sci* 22: 220–229.
52. Patel A, Gauld R, Norris P, Rades T, 2012. Quality of generic medicines in South Africa: perceptions versus reality—a qualitative study. *BMC Health Serv Res* 12: 297.
53. Sakolchai S et al., 1991. A survey on qualities of drugs commercially available in Thailand. *Srinagarind Med J* 6: 155–164.
54. Schäfermann S, Wemakor E, Hauk C, Heide L, 2018. Quality of medicines in southern Togo: investigation of antibiotics and of medicines for non-communicable diseases from pharmacies and informal vendors. *PLoS One* 13: e0207911.
55. Tabemero P et al., 2019. A random survey of the prevalence of falsified and substandard antibiotics in the Lao PDR. *J Antimicrob Chemother* 74: 2417–2425.
56. Tshilumba PM et al., 2015. Survey of some counterfeit anti-infective agents administered orally and marketed in the city of Lubumbashi/Enquête sur la contrefaçon de quelques anti-infectieux administrés per os commercialisés dans la ville de Lubumbashi. *Pan Afr Med J* 22: 318.
57. Yusuf I, Lee D, Fatehzada Z, Karwar W, Morris M, Omari MZ, Noorzaee A, Layloff T, 2011. *Afghanistan Medicines Sampling and Testing—A Quantitative Survey*. Arlington, VA: Strengthening Pharmaceutical Systems, Center for Pharmaceutical Management, Management Sciences for Health.
58. Wang T, Hoag SW, Eng ML, Polli J, Pandit NS, 2015. Quality of antiretroviral and opportunistic infection medications dispensed from developing countries and internet pharmacies. *J Clin Pharm Ther* 40: 68–75.
59. Antignac M et al., 2017. Fighting fake medicines: first quality evaluation of cardiac drugs in Africa. *Int J Cardiol* 243: 523–528.
60. Ndichu ET, Ohiri K, Sekoni O, Makinde O, Schulman K, 2019. Evaluating the quality of antihypertensive drugs in Lagos State, Nigeria. *PLoS One* 14: e0211567.
61. Rahman MS et al., 2019. A cross-sectional investigation of the quality of selected medicines for noncommunicable diseases in private community drug outlets in Cambodia during 2011–2013. *Am J Trop Med Hyg* 101: 1018–1026.
62. Redfern J et al., 2019. Equivalence in active pharmaceutical ingredient of generic antihypertensive medicines available in Nigeria (EQUIMEDS): a case for further surveillance. *Glob Heart* 14: 327–333.
63. Amin AA, Snow RW, Kokwaro GO, 2005. The quality of sulphadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. *J Clin Pharm Ther* 30: 559–565.
64. Basco LK, 2004. Molecular epidemiology of malaria in Cameroon. XIX. Quality of antimalarial drugs used for self-medication. *Am J Trop Med Hyg* 70: 245–250.
65. Belew S et al., 2019. Quality of fixed dose artemether/lumefantrine products in Jimma Zone, Ethiopia. *Malar J* 18: 236.
66. Bjorkman Nyqvist M, Svensson J, Yanagizawa-Drott D, 2012. *Can Good Products Drive Out Bad? Evidence from Local Markets for (fake?) Antimalarial Medicine in Uganda*. CEPR Discussion Paper 9114. Washington, DC: Center for Economic Policy and Research.
67. Dondorp AM et al., 2004. Fake antimalarials in Southeast Asia are a major impediment to malaria control: multinational cross-sectional survey on the prevalence of fake antimalarials. *Trop Med Int Health* 9: 1241–1246.
68. Guo S et al., 2017. Quality testing of artemisinin-based antimalarial drugs in Myanmar. *Am J Trop Med Hyg* 97: 1198–1203.
69. Idowu OA, Apalara SB, Lasisi AA, 2006. Assessment of quality of chloroquine tablets sold by drug vendors in Abeokuta, Nigeria. *Tanzan Health Res Bull* 8: 45–46.
70. Ioset JR, Kaur H, 2009. Simple field assays to check quality of current artemisinin-based antimalarial combination formulations. *PLoS One* 4: e7270.
71. Kaur H et al., 2008. A nationwide survey of the quality of antimalarials in retail outlets in Tanzania. *PLoS One* 3: e3403.
72. Kaur H et al., 2016. Fake anti-malarials: start with the facts. *Malar J* 15: 86.
73. Khin C et al., 2016. Quality assessment of antimalarials in two border areas (Tamu and Muse). *Myanmar Health Sci Res J* 28: 48–52.
74. Lalani M et al., 2015. Substandard antimalarials available in Afghanistan: a case for assessing the quality of drugs in resource poor settings. *Am J Trop Med Hyg* 92 (Suppl): 51–58.
75. Maponga C, Ondari C, 2003. *The Quality of Antimalarials: A Study in Selected African Countries*. Geneva, Switzerland: World Health Organization.
76. Mufusama JP, Ndjoko Ioset K, Feineis D, Hoellein L, Holzgrabe U, Bringmann G, 2018. Quality of the antimalarial medicine artemether—lumefantrine in 8 cities of the Democratic Republic of the Congo. *Drug Test Anal* 10: 1599–1606.
77. Mziray S et al., 2017. Post marketing surveillance of anti-malarial medicines in Tanzania. *Pharm Regul Aff* 6: 1–5.
78. Newton P et al., 2001. Fake artesunate in southeast Asia. *Lancet* 357: 1948–1950.
79. Newton PN et al., 2008. A collaborative epidemiological investigation into the criminal fake artesunate trade in South East Asia. *PLoS Med* 5: e32.
80. Ochekepe NA, Agbowuro AA, Attah SE, 2010. Correlation of price and quality of medicines: assessment of some artemisinin antimalarials in Nigeria based on GPHF Minilab. *Int J Drug Dev Res* 2: 211–218.
81. Ogwal-Okeng JW, Okello DO, Odyek O, 1998. Quality of oral and parenteral chloroquine in Kampala. *East Afr Med J* 75: 692–694.
82. Osei-Safo D et al., 2014. Evaluation of the quality of artemisinin-based antimalarial medicines distributed in Ghana and Togo. *Malar Res Treat* 2014: 806416.
83. Phanouvong S et al., 2013. The quality of antimalarial medicines in western Cambodia: a case study along the Thai–Cambodian border. *Southeast Asian J Trop Med Public Health* 44: 349–362.
84. Tabemero P et al., 2015. A repeat random survey of the prevalence of falsified and substandard antimalarials in the Lao PDR: a change for the better. *Am J Trop Med Hyg* 92 (Suppl): 95–104.
85. Tipke M et al., 2008. Substandard anti-malarial drugs in Burkina Faso. *Malar J* 7: 95.
86. Visser BJ et al., 2015. Assessing the quality of anti-malarial drugs from Gabonese pharmacies using the MiniLab(R): a field study. *Malar J* 14: 273.
87. World Health Organization, 2009. *Survey of the Quality of Selected Antimalarial Medicines Circulating in Madagascar, Senegal, and Uganda*. Geneva, Switzerland: WHO.
88. World Health Organization, 2011. *Survey of the Quality of Selected Antimalarial Medicines Circulating in Six Countries of Sub-Saharan Africa*. Geneva, Switzerland: WHO.
89. Yeung S et al., 2015. Quality of antimalarials at the epicenter of antimalarial drug resistance: results from an overt and mystery client survey in Cambodia. *Am J Trop Med Hyg* 92 (Suppl): 39–50.
90. Baratta F, Germano A, Brusa P, 2012. Diffusion of counterfeit drugs in developing countries and stability of galenics stored for months under different conditions of temperature and relative humidity. *Croat Med J* 53: 173–184.
91. Bate R, Mooney L, Hess K, 2010. Medicine registration and medicine quality: a preliminary analysis of key cities in emerging markets. *Res Rep Trop Med* 1: 89–93.
92. Central Drug Standard Control Organization, Ministry of Health and Family Welfare, Government of India, 2009. *Report on Countrywide Survey for Spurious Drugs*. Delhi, India: CDSCO.
93. Food and Drug Department, Food and Drug Quality Control Center, 2010. *Country Report on Medicines Quality Monitoring Program in Laos (2005–2009)*. Available at: http://www.fdd.gov.la/download/contents_documents/1407835610country%20report%20in%20MQM%20progam%202005-2009.pdf. Accessed December 3, 2020.
94. Food and Drug Department, Food and Drug Quality Control Center, 2014. *Comparative Study of the Quality, Availability, and Source of Antimalarial Medicines in Cambodia, Laos, Thailand, and Vietnam in PQM-MQM Covered and Non-covered Areas in Mekong Sub-Region*. Available at:

- http://www.fdd.gov.la/download/contents_documents/1411697106Lao%20Comparative%20Study%20Final.pdf. Accessed December 3, 2020.
95. Frimpong G et al., 2018. Quality assessment of some essential children's medicines sold in licensed outlets in Ashanti Region, Ghana. *J Trop Med* 2018: 1494957.
 96. Hajjou M et al., 2015. Monitoring the quality of medicines: results from Africa, Asia, and South America. *Am J Trop Med Hyg* 92 (Suppl): 68–74.
 97. Kaale E et al., 2016. The quality of selected essential medicines sold in accredited drug dispensing outlets and pharmacies in Tanzania. *PLoS One* 11: e0165785.
 98. Khuluza F, Kigera S, Heide L, 2017. Low prevalence of substandard and falsified antimalarial and antibiotic medicines in public and faith-based health facilities of southern Malawi. *Am J Trop Med Hyg* 96: 1124–1135.
 99. Kibwage I et al., 1999. Drug quality control work in drug analysis and research unit: observation during 1991–1995. *East Cent Afr J Pharm Sci* 2: 32–36.
 100. Lon CT et al., 2006. Counterfeit and substandard antimalarial drugs in Cambodia. *Trans R Soc Trop Med Hyg* 100: 1019–1024.
 101. Phanouvong S et al., 2013. The quality of antimalarial medicines in eastern Thailand: a case study along the Thai–Cambodian border. *Southeast Asian J Trop Med Public Health* 44: 363–373.
 102. Schiavetti B et al., 2018. The quality of medicines used in children and supplied by private pharmaceutical wholesalers in Kinshasa, Democratic Republic of Congo: a prospective survey. *Am J Trop Med Hyg* 98: 894–903.
 103. Seear M, Gandhi D, Carr R, Dayal A, Raghavan D, Sharma N, 2011. The need for better data about counterfeit drugs in developing countries: a proposed standard research methodology tested in Chennai, India. *J Clin Pharm Ther* 36: 488–495.
 104. Shakoor O, Taylor RB, Behrens RH, 1997. Assessment of the incidence of substandard drugs in developing countries. *Trop Med Int Health* 2: 839–845.
 105. Stenson B, Lindgren BH, Syhakhang L, Tomson G, 1998. The quality of drugs in private pharmacies in the Lao People's Democratic Republic. *Int J Risk Saf Med* 11: 243–249.
 106. Syhakhang L, 2002. *The Quality of Private Pharmacy Services in a Province of Lao PDR: Perceptions, Practices and Regulatory Enforcements*. Stockholm, Sweden: Karolinska Institutet, Division of International Health, Department of Public Health Sciences.
 107. Taylor RB et al., 2001. Pharmacopoeial quality of drugs supplied by Nigerian pharmacies. *Lancet* 357: 1933–1936.
 108. Uganda Medicines Transparency Alliance, 2014. *Screening Drug Quality Project Report*. Kampala, Uganda: UMTA.
 109. Wondemagegnehu E, 1999. *Counterfeit and Substandard Drugs in Myanmar and Viet Nam. WHO Report WHO/EDM/QSM99.3*. Geneva, Switzerland: World Health Organization.
 110. World Health Organization Action Programme on Essential Drugs, 1995. *La Qualité des médicaments sur le marché pharmaceutique africain: étude analytique dans trois pays, Cameroun, Madagascar, Tchad*. Geneva, Switzerland: WHO.
 111. Kuwana R, Sabartova J, 2017. Survey of the quality of selected antiretroviral medicines circulating in five African countries. *WHO Drug Inf* 31: 162.
 112. Ministry of Medical Services, Ministry of Public Health and Sanitation Kenya, 2012. *Post Market Survey of Antiretroviral Medicines in Kenya*. Available at: <https://pharmacyboardkenya.org/files/?file=ARV%20Report%20Final%202012.pdf>. Accessed December 3, 2020.
 113. World Health Organization, 2007. *Survey of the Quality of Antiretroviral Medicines Circulating in Selected African Countries*. Geneva, Switzerland: WHO
 114. Anyakora C et al., 2018. Quality medicines in maternal health: results of oxytocin, misoprostol, magnesium sulfate and calcium gluconate quality audits. *BMC Pregnancy Childbirth* 18: 44.
 115. Hall PE, 2016. Quality of medicines: quality of misoprostol products. *WHO Drug Inf* 30: 35–39.
 116. Karikari-Boateng E, Ghana F, Boateng KP, 2013. *Post-Market Quality Surveillance Project Maternal Health Care Products (Oxytocin and Ergometrine) on the Ghanaian Market*. Accra, Ghana: Ghana Food and Drugs Authority.
 117. Stanton C, Koski A, Cofie P, Mirzabagi E, Grady BL, Brooke S, 2012. Uterotonic drug quality: an assessment of the potency of injectable uterotonic drugs purchased by simulated clients in three districts in Ghana. *BMJ Open* 2.
 118. Stanton C et al., 2014. Accessibility and potency of uterotonic drugs purchased by simulated clients in four districts in India. *BMC Pregnancy Childbirth* 14: 386.
 119. Laroche ML, Traore H, Merle L, Gaulier JM, Viana M, Preux PM, 2005. Quality of phenobarbital solid-dosage forms in the urban community of Nouakchott (Mauritania). *Epilepsia* 46: 1293–1296.
 120. Suleman S et al., 2014. Quality of medicines commonly used in the treatment of soil transmitted helminths and *Giardia* in Ethiopia: a nationwide survey. *PLoS Negl Trop Dis* 8: e3345.
 121. Hamilton WL, Doyle C, Halliwell-Ewen M, Lambert G, 2016. Public health interventions to protect against falsified medicines: a systematic review of international, national and local policies. *Health Policy Plan* 31: 1448–1466.
 122. World Health Organization, 2019. Good storage and distribution practices for medical products. *WHO Drug Inf* 33: 194–225. Geneva, Switzerland: WHO.
 123. World Health Organization, 2010. *Annex 5 WHO Good Distribution Practices for Pharmaceutical Products*. Geneva, Switzerland: WHO.
 124. Pisani E, Nistor AL, Hasnida A, Parmaksiz K, Xu J, Kok MO, 2019. Identifying market risk for substandard and falsified medicines: an analytic framework based on qualitative research in China, Indonesia, Turkey and Romania. *Wellcome Open Res* 4: 70.
 125. World Health Organization, 2020. *Full List of WHO Medical Product Alerts*. Geneva, Switzerland: WHO. Available at: <https://www.who.int/medicines/publications/drugalerts/en/>. Accessed September 1, 2020.
 126. Walker E, Hernandez AV, Kattan MW, 2008. Meta-analysis: its strengths and limitations. *Cleve Clin J Med* 75: 431–439.
 127. Amin AA, Kokwaro G, 2007. Antimalarial drug quality in Africa. *J Clin Pharm Ther* 32: 429–440.
 128. Kelesidis T, Falagas ME, 2015. Substandard/counterfeit antimicrobial drugs. *Clin Microbiol Rev* 28: 443–464.
 129. Newton PN, Green MD, Fernández FM, Day NP, White NJ, 2006. Counterfeit anti-infective drugs. *Lancet Infect Dis* 6: 602–613.