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Interventions to combat or prevent drug counterfeiting: a systematic review

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ABSTRACT

Objective: Drug counterfeiting has serious public health and safety implications. The objective of this study was to systematically review the evidence on the effectiveness of interventions to combat or prevent drug counterfeiting.

Data sources: We searched multiple electronic databases and the grey literature up to March 2014. Two reviewers completed, in duplicate and independently, the study selection, data abstraction and risk of bias assessment.

Study eligibility criteria, participants and interventions: We included randomised trials, non-randomised studies, and case studies examining any intervention at the health system-level to combat or prevent drug counterfeiting. Outcomes of interest included changes in failure rates of tested drugs and changes in prevalence of counterfeit medicines. We excluded studies that focused exclusively on substandard, degraded or expired drugs, or that focused on medication errors.

Appraisal and synthesis: We assessed the risk of bias in each included study. We reported the results narratively and, where applicable, we conducted meta-analyses.

Results: We included 21 studies representing 25 units of analysis. Overall, we found low quality evidence suggesting positive effects of drug registration (OR=0.23; 95% CI 0.08 to 0.67), and WHO-prequalification of drugs (OR=0.06; 95% CI 0.01 to 0.35) in reducing the prevalence of counterfeit and substandard drugs. Low quality evidence suggests that licensing of drug outlets is probably ineffective (OR=0.66; 95% CI 0.41 to 1.05). For multifaceted interventions (including a mix of regulations, training of inspectors, public-private collaborations and legal actions), low quality evidence suggest they may be effective. The single RCT provided moderate quality evidence of no effect of 'two extra inspections' in improving drug quality.

Conclusions: Policymakers and stakeholders would benefit from registration and WHO-prequalification of drugs and may also consider multifaceted interventions. Future effectiveness studies should address the methodological limitations of the available evidence.

Trial registration number: PROSPERO CRD42014009269.

Strengths and limitations of this study

- This is the first systematic review assessing the effectiveness of interventions to combat or prevent drug counterfeiting.
- The systematic review responds to a policy-relevant priority identified by policymakers and stakeholders from several low-income and middle-income countries.
- We searched multiple databases and included published as well as grey literature.
- Most of the included studies were observational in nature.

INTRODUCTION

Drug counterfeiting is widespread and affects developing as well as developed countries.[1 2] It is believed that up to 10% of all medicines sold worldwide are counterfeit, with higher prevalence in regions where drug regulatory and enforcement systems are weakest.[3 4] Estimates suggest that counterfeited drugs can account for over 30% of all drugs in parts of Africa, Asia and the Middle East, in contrast to less than 1% in the USA and Western Europe.[4–6]

There is still no consensus over what constitutes a counterfeited medicine.[1 7] The WHO defined counterfeit medicines as those which have been deliberately and fraudulently mislabelled with respect to identity and/or source; counterfeit medicines may include medicines with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.[2] Under the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement, counterfeiting refers to the deliberate infringement of trademark on a commercial scale.[7 8] This definition, however, diverts attention from the serious public health implications of poor-quality drugs.[8 9] Thus, the term 'falsified' is increasingly being used as a synonym for counterfeit drugs to avoid the controversy over Intellectual Property issues.[9]

Counterfeit and substandard drugs have often been conflated,[9] with the latter referring to genuine medicines that have failed to meet the quality specifications set by national pharmacopoeia standards.[2] In 2011, the WHO member states incorporated counterfeit and substandard medicines under the new term "substandard/spurious/falsely-labelled/falsified/counterfeit medical products" (SSFFC).[10] This new term has recently been queried as it is felt not to adequately differentiate between the different illicit drug categories, which may entail different solutions.[11]

Counterfeited drugs span the spectrum from lifestyle drugs to lifesaving drugs.[12] They can result in adverse health outcomes and treatment failures, development of drug resistance and decline in confidence in health systems, all of which contribute to the burden of disease and, subsequently, to excess morbidity and mortality.[13] Indeed, significant deaths have been attributed to counterfeited medications.[13–15]

A variety of interventions have been recommended to combat the problem of drug counterfeiting. These include: legal actions and regulations on illicit traders, countermeasures using technologies, consumer education and cooperation with enforcement agencies.[16 17] The need to identify effective anticounterfeiting strategies has recently been raised as a main policy concern by policymakers from several low-income and middle-income countries including the Eastern Mediterranean Region.[18] As a response, the Center for Systematic Review on Health Policy and Systems Research (SPARK) held a stakeholder meeting in Lebanon on January 2014 with 14 policymakers and stakeholders, including representatives from the Ministry of Public Health, Order of Pharmacy, order of physicians and practicing pharmacists. The members were engaged in framing the review question for the current systematic review.

The objective of this study was to systematically review the evidence on the effectiveness of interventions implemented to combat or prevent drug counterfeiting, particularly in low-income and middle-income countries, given its high priority and prevalence. We could not identify any systematic review in the literature that examined the effectiveness of interventions to combat drug counterfeiting. Thus, the findings can help inform policy-decisions regarding the type of interventions to implement, given their contexts and available resources.

METHODS

We developed a conceptual framework for the different anticounterfeiting strategies, informed by extensive review of the literature. The framework guided us in refining the review question and in developing the eligibility criteria. For details, please refer to figure 1 in the results section.

Protocol and registration

We registered the review protocol in PROSPERO International prospective register of systematic reviews. The protocol can be accessed at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014009269.

Eligibility criteria

The eligibility criteria were:

Types of studies: Randomised trials, non-randomised studies (eg, cohort studies, prospective studies, retrospective studies, cross-sectional studies, before and after studies) and case studies. We excluded editorials, letters to the editors, reflections, proposals, reviews and studies published only in abstract format.

We considered published and unpublished studies.

Problem: Counterfeit/spurious/falsely-labelled/falsified/medicines.

We used the WHO's definition for counterfeit medicines, which includes medicines with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging drugs.[2 19] While the primary focus of our review is on counterfeit drugs, we included substandard drugs only when the study did not differentiate between the two or if it was unclear if the poor-quality medicine was counterfeit or substandard. However, we excluded studies that linked poor quality to degradation or

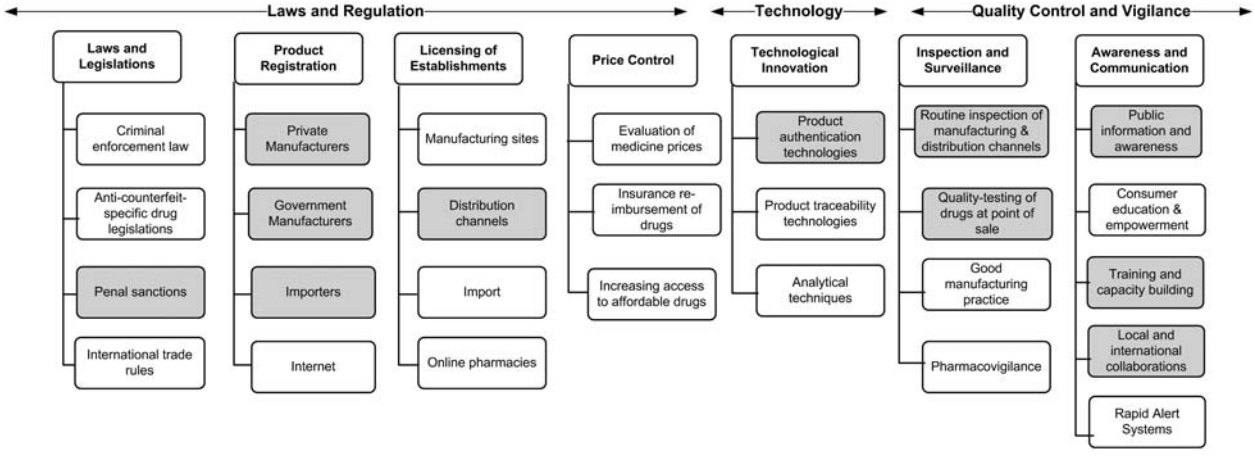

Figure 1 A framework for the different anticounterfeit drug strategies.

expiration of drugs as these were beyond the scope of counterfeit drugs as per the WHO's definition. We also excluded studies that focused exclusively on substandard drugs and studies that focused on herbal medicines/dietary supplements/cosmetics/food.

Types of interventions: We included any intervention at the health system level to combat or prevent drug counterfeiting (eg, anticounterfeit laws and legislations, inspection and quality control, awareness campaigns, technology). We excluded studies that focused on internet/online drug counterfeiting. We also excluded studies on the reliability of analytical techniques (eg, high-performance liquid chromatography and UV-visible spectrophotometry) and studies on interventions to improve the medication administration process or reduce medication errors.

Comparator/control: The comparator was the lack or absence of intervention, either explicitly or implicitly stated.

Type of outcome measures: Changes in failure rates of tested drugs (failure refers to drugs not meeting the minimum requirement for basic testing, quality control lab testing, and/or packaging analysis), changes in the prevalence of counterfeit/spurious/falsely-labelled/falsified/medicines, changes in quality of medicine, changes in behaviour of consumers, seizures of counterfeit drugs and closures of illegal outlets/warehouses/shops.

We did not exclude studies based on date of publication or setting. We excluded studies not published in English, Arabic or French.

Literature search method

We searched the following electronic databases up to March 2014: Medline, Pubmed, Embase, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Global Health Library, Rx for change, Cochrane Central Register of Controlled Trials (CENTRAL), Health Systems Evidence, Cab Direct, Academic Search Complete, Google Scholar, Mednar, GreylitNetwork and Opengrey.

The search combined various terms for counterfeit drugs and included free text words as well as controlled vocabulary terms such as MeSH (Medical Subject Headings), in addition to various search options available for each resource. We did not use any search filter for study type, language or date of publication. The search strategy was validated by a medical librarian who supports the work of the Center (see online supplementary appendix 1).

We also searched relevant websites such as the WHO, the Food and Drug Administration (FDA), the Center for Disease Control (CDC) and the US Pharmacopeia (USP). Also, we reviewed the reference lists of included studies and contacted the authors of relevant articles for further information or additional potentially relevant studies.

Selection process

Two reviewers screened the titles and abstracts of identified citations, in duplicate and independently, for potential eligibility. All reviewers hold at least a Master's degree (with some having PhDs) in public health or other health-related field and they have all been trained in conducting systematic reviews.

We conducted a calibration exercise to ensure validity of the selection process. We retrieved the full text for studies judged as potentially eligible by at least one of the two reviewers. Two reviewers screened the full texts in duplicate and independently for eligibility. They used a standardised and pilot tested screening form. They resolved disagreements by discussion.

Data abstraction process

Two reviewers abstracted data from eligible studies in duplicate and independently. They used a standardised data abstraction form to collect data on study design, definition, setting, drug type, intervention, comparison group, outcomes evaluated, statistical and non-statistical results, funding and reported conflicts of interests. They resolved disagreements by discussion.

Risk of bias assessment

Two reviewers independently assessed the risk of bias. They resolved disagreements by discussion. We used the Cochrane Risk of Bias tool to assess the risk of bias in randomised trials and a modified version of the Cochrane Risk of Bias tool to assess the risk of bias in non-randomised studies.[20] We graded each potential source of bias as low, high or unclear risk of bias.

Data analysis and synthesis

We calculated the κ statistic to assess the agreement between the reviewers in judging full texts for eligibility. We conducted meta-analyses, stratified by the type of intervention. We calculated the unadjusted OR by entering the raw data in RevMan and planned a priori to pool the results using a random-effects model. The latter is recommended when heterogeneity between studies is assumed, particularly among observational studies.[21 22] We tested the results for homogeneity across studies using the I^2 test and considered heterogeneity present if I^2 was greater than 50%. We also reported the results narratively when the data were not reported in a way to allow their inclusion in the meta-analysis.

RESULTS

The first two sections, respectively, provide an overview of the search results and a description of included studies, including their risk of biases. Afterwards the effects of the interventions are specifically addressed.

Results of the search

Figure 2 shows the study flow. Of the 10 220 studies identified through database and website searches, 20 studies met our inclusion criteria. One additional study was identified through screening the reference lists of the included studies. The 21 included studies represented

25 units of analysis (3 studies examined more than one type of strategy). We excluded 166 full texts (see online supplementary appendix 2). The value of κ statistic for full-text screening was 0.638, reflecting good agreement between the reviewers.

Online supplementary tables S1 and S2 show the characteristics of the included studies. The most common study design was cross-sectional (14/21). There were also five before–after studies, one retrospective study and one case study. Among the 21 included studies, we also identified 1 randomised trial that was conducted in parallel and on the same study population as 1 of the pre–post studies.[23] Only one article was reported in French language.[24] Sixteen articles were published in academic journals, three were reports from the WHO and two were reports from the USP. All studies were conducted in low-income and middle-income countries. However, none was from the Eastern Mediterranean Region.

Figure 1 shows the conceptual framework we developed for the different anticounterfeit interventions/strategies. The shaded cells in the framework portray areas where evidence about the intervention exists. We could not establish whether evidence exists for counterfeit drugs bought online as this was beyond the scope of the review.

The 21 included studies examined various types of interventions (table 1). In all included studies, except the randomised trial, the comparator was the absence of intervention or strategy (explicitly or implicitly stated). For the randomised trial, two different levels of the intervention were compared to each other and to the absence of intervention. The types of outcomes measured were: changes in failure rates of tested drugs

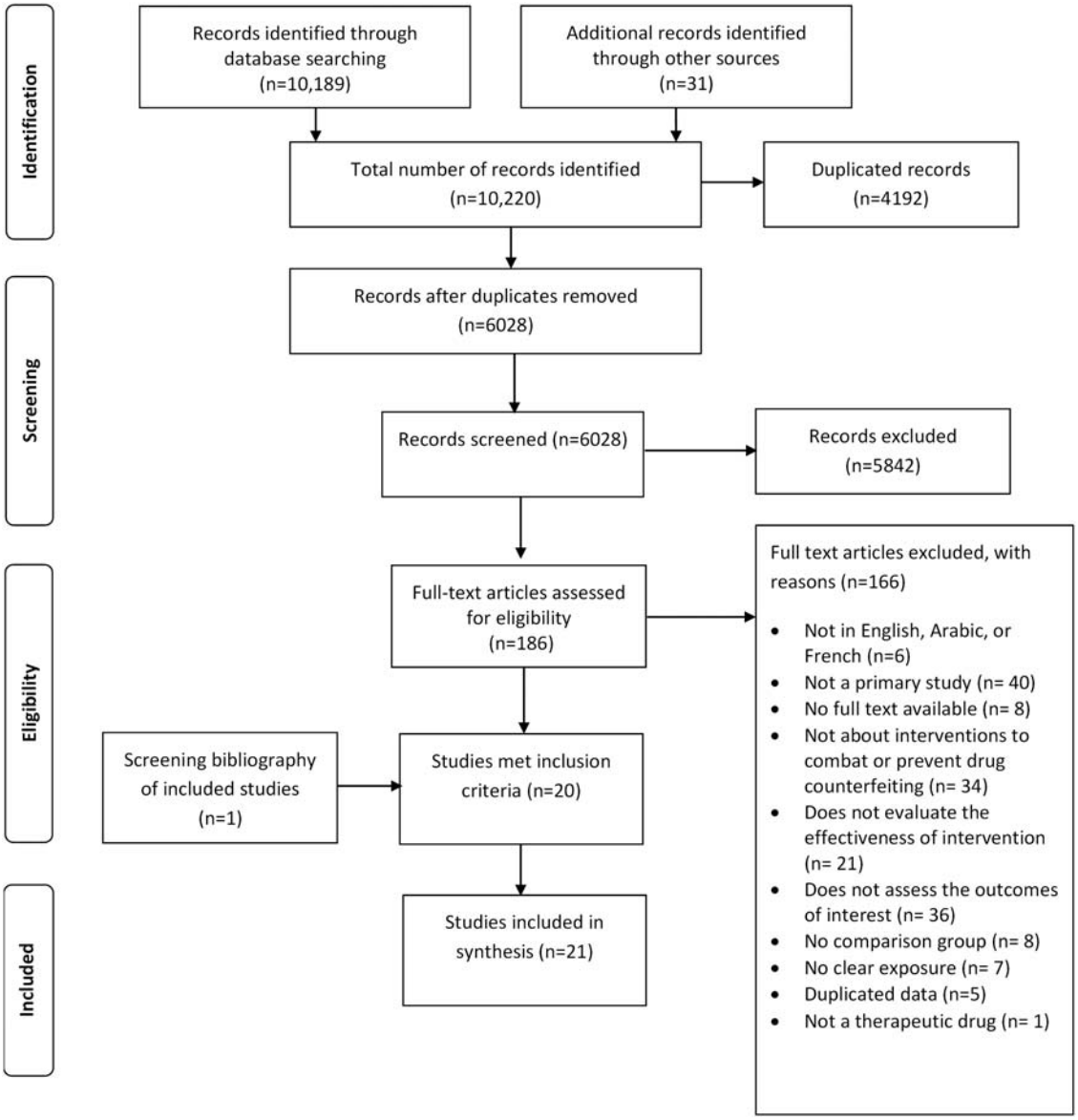

Figure 2 Flowchart for results of search strategy.

Table 1 Key characteristics of the interventions included in the systematic review

Intervention	Study design	Characteristics
Laws and regulations (13 studies with 16 units of analysis)		
Drug registration[25–29]	5 cross-sectional studies	A form of regulation to ensure access to effective and safe medicines. It involves assessments by relevant drug regulatory authorities of manufacturers of all components of drugs to ensure they are certified as meeting the international standards for GMP before authorising the drug for sale.
WHO-prequalification of drugs[25 30 31]	3 cross-sectional studies	A service provided by the WHO to "facilitate access to medicines that meet unified standards of quality, safety and efficacy primarily for HIV/AIDS, malaria TB and reproductive health".[31]
Licensing of drug outlet[25 28 32–37]	8 cross-sectional studies	This refers to the authorisation of pharmaceutical establishments by drug regulatory authorities with the aim of ensuring that the supply and sale of drugs are carried out by qualified personnel on premises that meet regulatory requirements.
Technological innovations (1 study)		
Product authentication technology[38]	1 retrospective study	This involved the deployment of six handheld laser (Raman) spectrometers by the National Agency for Food and Drug Administration and Control for immediate authentication of drugs at the point of sale.
Awareness and communication (2 studies)		
Increased public information[24]	1 cross-sectional study	A public awareness campaign, mainly using TV and radio announcements, to promote public awareness of the dangers of counterfeit medicine from the illicit drug market. The campaign was designed based on previous survey data collected to evaluate the purchasing practices of consumers.
Local and international collaboration[39]	1 case study	An international cross-disciplinary model of interaction and collaboration between WHO officials, physicians, pharmacists and scientists, and the Interpol, to investigate the source of counterfeit drugs in South East Asia.
Multifaceted interventions (5 studies with 6 units of analysis)		
The PQM Program[40–43]	4 pre–post studies	A mechanism for MQM funded by the USAID and implemented by the USP. It is characterised by (1) early detection of poor-quality medicines (substandard and counterfeit) using a three-level testing approach of increasingly complex levels of analysis, (2) collaborations with a country's medicine regulatory authorities and international partners, and (3) strengthening of regulatory authorities' capacities for enforcement of actions based on field evidence.
Quality assurance system within the NDPP[23]	1 pre–post study	The system encompassed three main features: (1) development of regulations, for example, improvement of drug registration system and increased requirement for imported drugs, (2) training of drug inspectors in good manufacturing and pharmacy practice, and (3) implementation of legal actions, for example, fines and product recall.
Regulatory intervention on private pharmacy services[23]	1 randomised trial	The regulatory interventions focused on improving the quality of private pharmacy services. The regular intervention package consisted of four high-quality annual inspections, sanctions for any violation, distribution of regulation documents to the private pharmacies and provision of information to the drug sellers about particular areas needing improvement. The active intervention package included these components, and was actively promoted through intensified supervision and additional training for the district drug inspectors.

GMP, good manufacturing practice; MQM, Medicine Quality Monitoring; NDPP, National Drug Policy Programme; USAID, US Agency for International Development; USP, US Pharmacopeia; TB, tuberculosis.

(19 studies); changes in prevalence of counterfeit drugs (4 studies); confiscation of counterfeit drugs (2 studies); closure of illegal outlets (2 studies); and changes in behaviour of consumers (1 study). Some studies reported more than one type of outcome. Most of the studies used failure rates to measure changes in the quality of medicines without distinguishing between counterfeit and substandard drugs.

Risk of bias

Online supplementary tables S3 and S4, respectively, show the assessments of the risk of bias for the observational studies and the single randomised trial. Online supplementary figures S1 and S2 show the corresponding risk of bias summary figures.

Effects of interventions

This section addresses the type and evidence for each intervention separately. We present the results of single-intervention studies in the order they appear in the framework followed by the multifaceted intervention studies that cut across the different elements in the framework.

Registration

Five cross-sectional studies examined the association between registration of medicines and changes in failure rates, and prevalence of counterfeit drugs.[25–29] We were able to pool the results for four studies. The pooled association estimate was OR=0.23 (95% CI 0.08 to 0.67), with I^2 of 88% (see online supplementary figure S3).

Of the four studies included in the meta-analysis, one conducted statistical tests and found a statistically significant association between drug registration and decreased prevalence of counterfeit drugs (adjusted OR=6.24, p<0.05, 95% CI 1.77 to 22.05).[28] Only one report found a higher failure rate among registered medicines than unregistered medicines (30% vs 20%, respectively).[25] Segregation of the results for this study by imported and local production status showed a higher failure rate among locally registered medicines than unregistered medicine (51% vs 18%, respectively), with similar failure rates observed for imported medicines (23% vs 26%, respectively). We did not include the study by Bate *et al*,[27] in the meta-analysis because it did not report the statistical data required to calculate the OR. The study found that drug registration remained strongly correlated with drugs passing the most stringent test even after adding city-fixed effects (ie, city-specific regulation enforcements such as maximum penalty, taxes and price regulations). The calculated marginal effect was 0.489 (t=7.844, p<0.01).

WHO-prequalification of drugs

Three cross-sectional studies examined the association between WHO-prequalification of drugs and changes in failure rates.[25 30 31] We pooled all three studies in a meta-analysis. The overall result showed a statistically significant association between WHO-prequalification and decreasing failure rates among tested samples. The pooled association estimate was OR=0.06 (95% CI 0.01 to 0.35), with I^2 of 78% (see online supplementary figure S4).

Licensing of drug outlets

Six cross-sectional studies examined the association of licensing of drug outlets on failure rates,[25 32–35 37] and another two examined such association on the prevalence of counterfeit drugs.[28 36] We were able to pool the results for four of the six studies that reported the outcomes as failure rates.[25 32 35 37] The overall result showed a non-statistically significant association of licensing of drug outlets on failure rates of medicines. The pooled association was OR=0.40 (95% CI 0.11 to 1.37), with I^2 of 86% (see online supplementary figure S5).

The pooled results for the two studies reporting on the prevalence of counterfeited drugs found a non-statistically significant association between licensing of drug outlets and decreased prevalence of counterfeit drugs. The pooled association estimate was OR=0.66 (95% CI 0.41 to 1.05) with I^2 of 0% (figure 3).

Of the eight included studies on licensing of drug outlets, three conducted statistical tests, and found no statistically significant association of licensing of drug outlets on failure rates[33] and prevalence of counterfeit drugs.[28 36] Only 1 study (of 8) found a higher failure rate among licensed drug outlets compared to unlicensed drug outlets (34% vs 16%, respectively).[32]

Spectrometry technology

Bate and Mathur[38] conducted a retrospective study to assess the effects of deploying six hand-held laser Truscan (Raman) spectrometers at several inspection points. Samples were collected in 2007, 2009 and 2010, to compare the quality of drugs before and after the spectrometers were introduced in 2009. Minilab tests were used

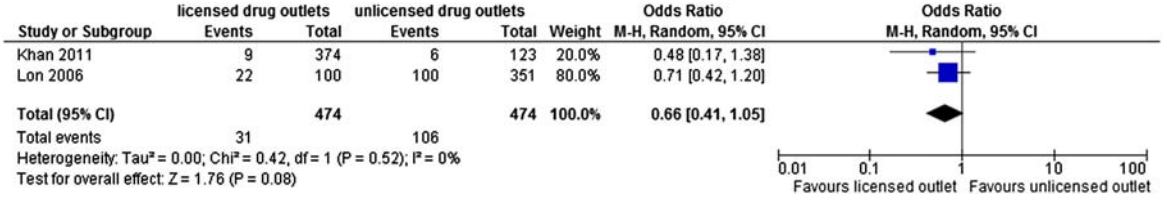

Figure 3 Forest plot for licensing of drug outlet intervention, outcome: prevalence of counterfeit drugs.

to run semiquantitative thin-layer chromatography and disintegration tests, to determine the presence and relative concentration of active ingredients. This was followed by spectrometry testing to reflect on all the contents of the sample. The authors reported a significant increase in the number of drugs passing the minilab tests (89% vs 81%, respectively) and spectrometry tests (88% vs 78%, respectively) postintroduction of the spectrometers. Similarly, disaggregation of the results by drug type showed a higher percentage of samples passing each test postintroduction of the technology.

Public awareness campaigns

Abdoulaye *et al*[24] conducted a cross-sectional study to examine the association between a public awareness campaign on the dangers of counterfeit medicines from illicit drug markets and changes in the behaviour of consumers. The study found that 51.5% of households that previously bought medicines from street markets reported declining this practice. Specifically, respondents who received the awareness messages were six times more prone to divert from the illicit drug market than those who did not (OR=6.38, 95% CI 1.9 to 21.37 p=0.0027). Those who received messages about the dangers of the street medicine market changed their behaviours 60.9% of the times against 22.2% for those who did not receive any message (p=0.033). Those who received messages about the availability of cheaper medicine at the pharmacies and clinics stopped buying from the informal market 73.8% of the time compared with 51.2% for those who did not receive any message (p=0.003).

Collaborative model

A case study by Newton *et al*[39] examined an international cross-disciplinary model of collaboration in quantifying and identifying the source of the counterfeit antimalarial drug, artesunate, in South East Asia. Of the 391 samples of artesunate analysed, the investigators found 16 different fake hologram types. Chemical analysis detected a wide range of wrong active ingredients, including raw materials for the manufacture of methylenedioxymethamphetamine (ecstasy), which suggested the counterfeits may be coming from these factories. Biological analyses of pollen grains inside packages allowed investigators to trace the origin of some of the counterfeited artesunate to Southern China. These results stimulated the Chinese Government to act against the counterfeiters resulting in arrests, seizures and closure of illegal outlets. The model of collaboration was successful in the investigation of the problem of counterfeit artesunate in South East Asia.

Multifaceted interventions

Five studies (representing 6 units of analysis) examined the effects of multifaceted interventions on the prevalence of counterfeit and substandard drugs.

Promoting quality of medicine (PQM) Program

Four pre–post studies examined the effects of the PQM Program.[40–43] Table 2 summarises the key findings from each study. In all four studies, PQM was implemented and expanded, in collaboration with the country's medicine regulatory authorities and other health entities. In Krech *et al*,[41] the PQM Program was implemented alongside other interventions to combat poor-quality drugs.

National Drug Policy Program (NDPP)

Syhakhang *et al*[23] evaluated the impact of two different aspects of the National Drug Policy Program (NDPP). A pre–post study design evaluated the impact of implementing the Quality Assurance system, while a randomised trial evaluated two different levels of the regulatory interventions. The investigators found a statistically significant decrease in substandard drugs from 46% (169 of 366) to 22% (66 of 300) between 1997 and 1999 (p<0.001). Samples with no active ingredients (likely to be counterfeited) decreased from 3.3% to 1% (p=0.048). Samples with lower or higher content of active ingredient than approved limits decreased from 12% to 4% (p<0.001). Weight variations outside approved limits decreased from 35% to 14% (p<0.001). The randomised trial, which assessed the impact of regulatory intervention on private pharmacy services, found no statistically significant differences in the percentages of substandard drugs between the active and regular intervention pharmacies (25% vs 20%, respectively; p=0.215).

Assessment of the quality of evidence

Within the individual observational studies, we judged the risk of biases associated with exposure and outcome measurements as generally low, and controlling for confounding variables as unclear. We judged the overall quality of evidence from observational studies as low due to study design. We also considered the presence of heterogeneity when we rated down the quality of evidence as a factor that limits our confidence in pooled effect estimate.[44] The evidence for the randomisation trial was judged as moderate due to lack of blinding and insufficient information on allocation concealment. We were unable to assess publication and reporting biases due to the small number of studies, and the absence of published protocols, respectively. Although we had initially planned to construct funnel plots, we eventually opted against that since the number of included studies in the meta-analyses was fewer than 10. Lau *et al*[45] state that funnel plots are only encouraged for interventions that include at least 10 studies, with a substantially higher number in the presence of significant heterogeneity.[22]

DISCUSSION

While the findings of the systematic review provide valuable insights into policy and practice, the evidence base on the effectiveness of anticounterfeit drug interventions

Table 2 A summary of the findings from the studies on the PQM Program*

Study	Country	Date of implementation	Key findings
Krech *et al*[41]	Cambodia	PQM was implemented in 2009	Comparing the period from 2005–2008 with the period from 2009 onwards, there has been a statistically significant reduction in the failure rate from 3.8% (33 of 877, 95% CI 2.7 to 5.2) to 2.1% (73 of 3484, 95% CI 1.7 to 2.6) (p=0.0065). Twenty-eight counterfeit medicines were found from 2005–2009 and none were found from 2010–2012. By the end of 2011, Cambodia had reportedly closed over 99% of illegal pharmacy outlets through the Inter-Ministerial Committee to Fight against Counterfeit and Substandard Medicines.
MOH FDD[43]	(Lao PDR)	PQM was implemented in 2005 and expanded from 2005–2009	The failure rates decreased from 3.2% in 2005 to 0.6% in 2009. During that same period, the number of samples tested increased from 158 in 2005 to 346 in 2009. The percentage of counterfeit drugs fluctuated on a year by year basis, with an initial rate of 2.5% (4 of 158) in 2005 and an average of 0.4% (6 of 1409) from 2006–2009. Numerous confiscations, fines and arrests were also reported.
PQM[40]†	Southeast Asia	PQM was implemented in 2003 and expanded in 2006–2007	*Thailand*: The failure rate decreased from an initial 2.4% in 2005 to 1% in 2009. *Vietnam*: While the initial failure was zero in 2005, the failure rate decreased from 2.3% in 2006 to 0.3% in 2009. *The Philippines*: Statistical data were not available for the Philippines, but the authors reported that since the establishment of the PQM's MQM Program for tuberculosis medicine in 2009, "none of the anti-tuberculosis medicines tested within six months have been found to be substandard".
Pribluda *et al*[42]	Amazon Basin countries	PQM was implemented in 2005	With the exception of two countries, the results for over 100 samples per country were submitted, and since 2008 "most indicated a significant decrease in the percentages that did not pass quality control testing (failures)". For instance, in Brazil, 18.7% (29 of 155) of samples tested in 2008 failed while none of the 60 samples tested in 2010 failed. In Ecuador, 25% (18 of 72) of samples tested in 2008 failed in contrast to 0.81% (1 of 122) in 2010.

*For some of the above countries, more than one report was available for the PQM Program. We contacted the respective authors who advised us on the datasets to use to avoid overlaps and duplications.
†The results for Cambodia and Lao PDR were not included because they were captured in the studies by Krech *et al*[41] and Ministry of Health's, Food and Drug Department,[43] respectively.
MOH FDD, Ministry of Health's, Food and Drug Department; Lao PDR; Lao People's Democratic Republic; PQM, promoting quality of medicine.

is weak. Overall, we found low quality evidence suggesting that regulatory measures, specifically drug registration and WHO-prequalification of drugs, may be effective in reducing the prevalence of counterfeit and substandard drugs. The evidence for licensing of drug outlets suggests that by itself it is probably ineffective. For the remaining single interventions, which include the deployment of handheld spectrometry technologies at various inspection points and an international cross-disciplinary model of collaboration, very low quality evidence suggests they may be effective in decreasing the prevalence of counterfeit and substandard drugs. We also found very low quality evidence suggesting that a public awareness campaign on the danger of counterfeit medicine from illegal drug outlets may be effective in changing the purchasing practices of individuals. For multifaceted interventions (including a mix of regulations, training of inspectors, public-private collaborations and legal actions), low quality evidence suggests they may be effective in reducing the prevalence of substandard and counterfeit

drugs. One randomised trial of moderate quality found no significant difference between the active intervention that involved two extra inspections (intensified supervision and additional training for the district drug inspectors) and the regular intervention in improving the quality of medicines.

We pooled the results separately for drug registration, WHO-prequalification and licensing of drug outlets, given their differing nature. With the exception of the meta-analysis on the association between licensing of drug outlets and prevalence of counterfeit drugs, we found significant heterogeneity for each of the remaining meta-analyses. We could not formally explore the potential sources of heterogeneity given the small number of included studies. Possible sources of heterogeneity may include variations across studies in the types of drugs evaluated and methods used to measure failure rate. The latter is plausible given the variety of instruments and pharmacopoeia standards used for assessment of failure rates.

While drug registration and WHO-prequalification of drugs appeared to be effective, the findings for drug registration highlighted the need for routine market surveillance and expansion of regulatory functions to cover local manufacturers and importers. For WHO-prequalification of drugs, the quality of WHO-prequalified medicines still varied depending on the country of procurement. One study found that China had the highest number of drugs of WHO-approved manufacturers that failed quality control testing, followed by India, with the lowest failure rates observed for WHO-prequalified drugs coming from the USA and European Union.[30] Licensing of drug outlets alone appeared to be ineffective in reducing the prevalence of counterfeit and substandard drugs. This may likely be related to ineffective licensing systems and the absence of routine inspection of outlets.

We could only retrieve a single study for the remaining single interventions. The evidence on multifaceted interventions suggests they may be effective in reducing the prevalence of substandard and counterfeit drugs; however, it was difficult to single out the contributions made by the individual types of interventions. More so, poor quality medicines were still reported, necessitating the need for continuous monitoring and collaborations to combat the problem. The success of the PQM Program, in particular, required collaborations with medicine regulatory bodies, qualified personnel and political will, to act on findings.

Our systematic review did not identify eligible studies assessing other relevant types of interventions (see framework in figure 1). In particular, we could not identify primary studies assessing the effectiveness of anticounterfeit packaging and traceability technologies (barcoding and radiofrequency identification systems (RFID)) in reducing the prevalence of counterfeit drugs despite the fact that they have become prominent preventive measures in the fight against drug counterfeiting.[16 46 47]

Existing systematic reviews focused mainly on the prevalence of counterfeit and substandard drugs[13 48 49] or on the risk factors and consequences of drug counterfeiting.[50] One systematic review provided an overview of available analytical technologies for detecting counterfeit and substandard drugs, and compared their suitability in low-income and middle-income countries.[51] Another systematic review focused on the RFID intervention, but it did not include any effectiveness studies.[52]

Strengths and limitations

To our knowledge, this is the first systematic review assessing the effectiveness of interventions to combat or prevent drug counterfeiting. We searched multiple databases and included the published as well as grey literature to increase the comprehensiveness of our search. We also conducted rigorous appraisals of included studies. In addition, our systematic review responds to a policy-relevant priority as identified by policymakers and stakeholders.

Some of the limitations relate to those of the included studies. We identified only one randomised trial of moderate quality. The observational studies suffered from risk of biases related to sampling methods and inadequate control for significant potential confounders. Also, for some interventions, only a single study was retrieved, limiting our ability to draw any conclusion regarding the effectiveness of the intervention. Most of the studies did not distinguish between counterfeit and substandard drugs, referring to changes in quality of medicines collectively as 'failure'. Only four studies[28 29 36 39] reported conducting some form of authentication investigation, which is important to confirm if a medicine is counterfeit, particularly since samples that have passed laboratory tests were still found to be counterfeit on investigation.[29] Another limitation of the review may relate to the fact that we only included studies written in English, Arabic or French.

Implications for policy

Based on the current available evidence, government and regulatory agencies in low-income and middle-income countries may benefit from spending their resources on strengthening the registration procedure to ensure that all drugs, including those of domestic manufacturers and importers, are assessed for safety, quality and efficacy before they are released into the market. More importantly, they probably should complement drug registration with routine postmarketing surveillance to sustain the quality of drugs circulating in the market as well as maintain an updated published list of registered drugs.

Countries that rely heavily on imported drugs may consider opting for drugs that are WHO-prequalified. However, they should keep in mind that even among WHO-prequalified products, the quality of medicine may vary depending on the country of export.

The three-level testing approach developed by the PQM Program can offer regulators in limited resource settings with a "cost-effective high-throughput methodology" for quality monitoring of drugs that produces valid and reliable results.[53] The approach can strengthen drug quality assurance systems and ultimately reduce the prevalence of poor quality medicines.

While the evidence on licensing of drug outlets suggests it may not be effective by itself, policymakers may want to consider multifaceted interventions that include a mix of regulations, training of personnel, public-private collaborations and enforcement of legal actions.

Implications for research

There is still a dearth of methodologically rigorous studies to assess interventions to combat or prevent drug counterfeiting. Future research should produce effectiveness studies that address the methodological limitations of the available evidence. There should be more efforts made towards conducting well-designed randomised trials, quasi-experimental studies, and/or observational studies (eg, interrupted time series or pre–post studies with control groups). The latter should aim for proper assessment of exposures and outcomes, control for significant confounders and minimise selection biases.

Future studies should also evaluate other types of interventions such as packaging and traceability technologies, criminal enforcement laws, price control, as well as interventions that can improve the demand side. There is also a need to conduct cost-effectiveness studies on the different types of interventions at the country level.

Finally, there is a need to adopt a standard definition for what constitutes a counterfeit drug and develop standardised methodologies to minimise heterogeneity and allow comparison of interventions across different studies and settings.

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PROSPERO International prospective register of systematic reviews

Interventions to combat or prevent drug counterfeiting: a systematic review protocol

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Review question(s)

Primary question:

1.What is the effectiveness of interventions implemented to combat or prevent drug counterfeiting?

Secondary questions:

1.What interventions have been implemented or proposed to combat drug counterfeiting?

2.How do the interventions compare in terms of reliability, feasibility, efficiency or acceptability?

Searches

Search of electronic databases: MEDLINE, PubMed, EMBASE, Rx for change, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing & Allied Health Literature (CINAHL), Global Health Library, The Latin American Caribbean Health Sciences Literature (LILACS), Health Systems Evidence, Cab Direct, Academic Search Complete

Other search engines: Google Scholar, Mednar, GreylitNetwork, Opengrey

Search of websites of relevant organizations:, World Health Organization (WHO), Food and Drug Administration (FDA), Center for Disease Control (CDC), Ministries of Health (MOH)

Search of websites of pharmaceutical companies such as Pfizer, AstraZeneca, Cardinal, Purdue

Screening of references lists of included and relevant papers as well identified reviews

Contact of experts: We will contact content experts and the authors of relevant articles.

Forward searching of included papers (SCOPUS and Web of Science)

We will develop and validate the search strategy with the information specialist at the American University of Beirut. We will search the different databases using different search terms for the concept “counterfeit drug.” We will not introduce a concept for “interventions” since we are interested in the whole framework without limiting our search to any specific intervention.

We will identify the appropriate MeSH terms for each database. We will use no restriction for language or date.

We will include the following search terms for counterfeit: counterfeit* or anticounterfeit* or anti-counterfeit* or falsif* or fake* or substandard* or sub-standard* or spurious* or fraud* or kickback* or adulterat* or (fals* label*) or (incorrect* label*) or (inaccurate* label*)

We will include the following search terms for drug: drug* or medication* or medicine* or pharmaceutic* or pharmaceutical preparation* or tablet* or capsule* or suppositor* or vaccin* or pill* or antibiotic* or antimicrobial*

or antimalarial*

Types of study to be included

Types of study designs for the primary question on effectiveness:

• Randomized studies

• Non-randomized studies

Types of study designs for the secondary questions:

• Randomized studies

• Non-randomized studies

• Case studies

• Qualitative studies

• Economic studies

• Process evaluation studies

• Conceptual Papers (for proposed interventions)

Both published and unpublished research will be considered for use in this review.

Exclusion criteria:

•We will exclude commentaries, editorials, letters to the editor, and non-English studies.

•We will exclude studies that assess the prevalence of counterfeit drugs and/or quality of drugs in a particular area.

Condition or domain being studied

Condition being studies: Counterfeit medicines

Counterfeit medicine is defined by the World Health Organization as “one which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging” (WHO, 1999).

Drug counterfeiting has serious public health and safety implications (FDA, 2009). They can result in adverse clinical outcomes, development of drug resistance, and significant decline in confidence in health systems (Jackson et al, 2012).

Estimates show that counterfeit drugs can account for over 30% of all drugs in parts of the Middle East, Asia, and Africa (with variations between and within countries) in contrast to less than 1% in the US and Western Europe (WHO, 2006; Putze et al, n.d.). In a prioriy setting exercise held by the Alliance for Health Policy and Systems Research between 2010 and 2012 to identify priorities for access to medicine in low and middle income countries, the problem of drug counterfeiting was raised as one of the main policy concerns and priority issues by representatives from five different regions (Bigdeli et al, 2013).

Participants/ population

Problem:

Counterfeit/spurious/falsely-labelled/falsified/ medicines

Types of counterfeit:

• Products without active ingredients

• Products with the wrong active ingredients

• Products with insufficient active ingredients

• Products with fake packaging

• Products with high levels of impurities and contaminants

We will not limit the review to any specific class of therapeutic drug.

Exclusion criteria:

• We will exclude studies that focus on herbal medicines/cosmetics/food products.

• We will exclude studies that focus explicitly on substandard drugs (i.e. genuine medicines which have failed to pass the quality measurements and standards set for them). If however, the authors do not differentiate between substandard and counterfeit drugs, or use the term substandard drugs to refer to counterfeit drugs, then we will include the study.

Intervention(s), exposure(s)

We will include any intervention at the health system level to combat or prevent drug counterfeiting.

The interventions include (but are not limited to):

• National drug anti-counterfeiting laws and legislations

• Licensing of wholesalers and manufacturers

• Inspection and quality control

• Training of personnel

• Price control

• Technological interventions:

- Packaging technology

- Product Authentication technology

- Analytical technology

- Track and trace systems

• National counterfeit drug alertness systems

• Education and awareness campaigns

Exclusion criteria:

• We will exclude studies that focus on interventions at the hospital level to improve medication administration process or reduce medication errors.

• We will exclude studies that target internet/online drug counterfeiting.

Comparator(s)/ control
The comparator will be lack or absence of intervention.

Context
We will not limit the review to any specific type of setting.

Outcome(s)
Primary outcomes
• Changes in the prevalence of counterfeit/spurious/falsely-labelled/falsified/medicines.

• Number of seizures of counterfeited drugs/Closure of warehouses.

• Changes in quality of medicine on the market.

Secondary outcomes
These correspond to outcomes related to the secondary questions:

• Feasibility of intervention

• Failure rate of intervention

• Reliability

• Execution time

• Sensitivity

• Economic outcome (efficiency, cost-effectiveness)

• Barriers and facilitators to implementation

• Acceptability of intervention by end users

Data extraction, (selection and coding)
Selection Process:

Title and abstract Screening: Two reviewers will use the eligibility criteria to screen the full texts in duplicate and independently for eligibility. We will retrieve the full text for studies deemed relevant by at least one of the two reviewers.

Full text screening: Two reviewers will use the eligibility criteria to screen the full texts in duplicate and independently for eligibility. The teams of two reviewers will resolve disagreements by discussion or with the help of a third reviewer.

We will use standardized and pilot tested screening forms.

We will conduct calibration exercise to ensure validity of the selection process.

Data Abstraction Process:

Two reviewers will abstract data from eligible studies in duplicate and independently. They will resolve disagreement by discussion or with the help of a third reviewer.

We will use standardized and pilot tested data abstraction forms to collect core data on study design, setting, type of drug involved, level of intervention, characteristic of intervention, outcomes evaluated, statistical and non-statistical

results, funding, and reported conflicts of interests.

We will conduct calibration exercise to ensure the validity of the selection process.

Risk of bias (quality) assessment
Two reviewers will assess the risk of bias in each study in duplicate and independently. They will resolve disagreements by discussion or with the help of a third reviewer. We will use the Cochrane Risk of Bias tool to assess the risk of bias in randomized trials. We will use a modified version of the Cochrane Risk of Bias tool to assess the risk of bias in non-randomized studies. We will use the Critical Appraisal Skills Program (CASP) tool to assess the methodological limitations in qualitative studies. We will conduct calibration exercise to ensure the validity of the selection process.

Strategy for data synthesis
Quantitative analysis:

For categorical data, we will calculate the RR for each study. For continuous data, we will calculate the mean difference (or, when appropriate, the standardized mean difference) for each study. We will pool the results across studies using a random-effects model. We will test results for homogeneity across studies using the I-squared test and consider heterogeneity present if I-squared is greater than 50%. We will create inverted funnel plots of individual study results plotted against sample size in order to check for possible publication bias.We will also report the results narratively and stratified by type of intervention

Qualitative analysis:

We will report the results narratively, and stratified based on the type of interventions being considered (anti-counterfeiting laws and legislations, licensing, inspection and quality control, technological interventions, training of personnel, national counterfeit drug alertness systems, education and awareness campaigns). We will then conduct a meta-synthesis of these results.

Economic data analysis:

We will report the results narratively and stratified based on the type of interventions being considered (anti-counterfeiting laws and legislations, licensing, inspection and quality control, training of personnel, technological interventions, counterfeit drug alertness systems, education awareness campaigns).

Analysis of subgroups or subsets
None planned.

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Conflicts of interest
None known

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English

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Subject indexing assigned by CRD

Subject index terms
Counterfeit Drugs; Crime; Humans; Legislation, Drug; Pharmaceutical Preparations; Pharmaceutical Services; Pharmacists

Stage of review
Ongoing

Date of registration in PROSPERO
09 April 2014

Date of publication of this revision
09 April 2014

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Appendix 1

Search Strategy

Databases Searched:

Database	# of Hits	Date last searched
Medline	992	March 21, 2014
PubMed	2579	March 21, 2014
Embase	1434	March 21, 2014
CINAHL	483	February 18, 2014
Academic Search Complete	1753	February 19, 2014
Cab Direct	351	February 18, 2014
Google Scholar	100	February 19, 2014
Global Health Library	1432	February 17, 2014
Health System Evidence	1	February 17, 2014
Rx for Change	0	February 17, 2014
Opengrey	10	February 18, 2014
OPHLA	398	February 19, 2014
Mednar	656	February 19, 2014

Search Strategy for each database:

Database: Ovid Medline(R) <1946 to March Week 3 2014>

Search Strategy:

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1 exp Counterfeit Drugs/ (167)

2 exp Fraud/ (6382)

3 exp Pharmaceutical Preparations/ (621736)

4 2 and 3 (299)

5 ((counterfeit* or anticounterfeit* or anti-counterfeit* or falsif* or fake* or substandard* or sub-standard* or spurious* or fraud* or kickback* or adulterat* or ((fals* or incorrect* or inaccurate*) adj2 label*)) adj4 (drug* or medication* or medicine* or pharmaceutic* or tablet* or capsule* or suppositor* or vaccin* or pill* or antibiotic* or antimicrobial* or antimalarial*)).ti,ab. (775)

6 1 or 4 or 5 (992)

Database: PubMed <no restriction on date>

Last Searched: 21-March-2014

Search	Query	Items found
#10	Search #1 OR #4 OR #6 OR #9	2579
#9	Search #7 AND #8	2295
#8	Search (drug*[tiab] OR medication*[tiab] OR medicine*[tiab] OR pharmaceutic*[tiab] OR antibiotic*[tiab] OR antimicrobial*[tiab] OR antimalarial*[tiab] OR tablet*[tiab] OR pill*[tiab] OR capsule*[tiab] OR vaccin*[tiab])	2071782
#7	Search (counterfeit*[tiab] OR anticounterfeit*[tiab] OR anti-counterfeit*[tiab] OR falsif*[tiab] OR substandard*[tiab] OR sub-standard*[tiab] OR adulterat* [tiab] OR spurious*[tiab] OR fake*[tiab] OR fraud*[tiab])	15212
#6	Search #5 AND #3	69
#5	Search ((false*[tiab] OR incorrect[tiab] OR inaccurate*[tiab]) AND label*[tiab])	3060
#4	Search #2 AND #3	319
#3	Search "Pharmaceutical Preparations" OR "Pharmaceutical Preparations"[Mesh]	572506
#2	Search "Fraud" OR "Fraud"[Mesh]	6336
#1	Search "Counterfeit Drugs" OR "Counterfeit Drugs"[Mesh]	378

Database: Embase: <no restriction on date>

Last Searched: 21-March-2014

10. #1 OR #6 OR #8 OR #9 (1,434)

9. ((counterfeit* OR anticounterfeit* OR anti-counterfeit* OR falsif* OR fake OR substandard* OR spurious* OR fraud* OR adulterate*) NEAR/4 (drug* OR medication* OR medicine* OR pharmaceutical* OR tablet* OR pill* OR antibiotic* OR antimicrobial* OR antimalarial*)):ab,ti (1,188)

8. #5 AND #7 (18)

7. (false* NEAR/2 label*):ab,ti (110)

6. #2 AND #5 (85)

5. #3 OR #4 (2,776,421)

4. 'pharmaceutics'/exp (918, 802)

3. 'drug'/exp (2,138, 132)

2. 'fraud'/exp (834)

1. 'counterfeit drug'/exp (405)

Database: CINAHL <no restriction on date>
Last Searched: February 18 2014

#	Query	Results
S6	S1 OR S4 OR S5	483
S5	S2 AND S3	313
S4	(counterfeit* OR anticounterfeit* OR anti-counterfeit* OR falsif* OR fake OR substandard OR spurious OR fraud* OR fraudulent OR ((false* OR incorrect* OR inaccurate*) N4 label*)) N4 (drug* OR medication* OR medicine* OR pharmaceutical* OR pill* OR tablet* OR capsule* OR antibiotic* OR antimicrobial* OR antimalarial*)	276
S3	(MH "Fraud")	4,992
S2	(MH "Drugs+")	85,004
S1	(MH "Counterfeit Drugs")	89

Database: Academic Search Complete <no restriction on date>

Last Searched: February 19 2014

#	Query	Results
S9	Limit S8 to Academic Journal and Trades Publication	1753
S8	S1 OR S6 OR S7	3,402
S7	S4 AND S5	3,003
S6	S2 AND S3	1,171
S5	TI ((counterfeit* OR anticounterfeit* OR anti-counterfeit* OR falsif* OR fake OR substandard OR spurious OR fraud* OR fraudulent OR falsely-labelled)) OR AB ((counterfeit* OR anticounterfeit* OR anti-counterfeit* OR falsif* OR fake OR substandard OR spurious OR fraud* OR fraudulent OR falsely-labelled))	55,268
S4	TI ((drug* OR medication* OR medicine* OR pharmaceutical* OR tablet* OR capsule* OR pill* OR antibiotic* OR antimicrobial* OR antimalarial*)) OR AB ((drug* OR medication* OR medicine* OR pharmaceutical* OR tablet* OR capsule* OR pill* OR antibiotic* OR antimicrobial* OR antimalarial*))	972,455
S3	drugs	1,042,265
S2	fraud	42,600
S1	drug counterfeiting	151

Database: Cab direct: <no restriction on date>

Last Searched: February18 2014

Advanced Search:

((title:((drug* OR medication* OR medicine* OR pharmaceutical* OR antibiotic* OR antimicrobial* OR antimalarial*)) OR ab:((drug* OR medication* OR medicine* OR pharmaceutical* OR antibiotic* OR antimicrobial* OR antimalarial*)))) AND ((title:((counterfeit* OR falsif* OR fake OR substandard OR spurious OR fraud* OR fraudulent OR falsely-labelled)) OR ab:((counterfeit* OR falsif* OR fake OR substandard OR spurious OR fraud* OR fraudulent OR falsely-labelled)))) 351

Database: Google Scholar <no restriction on date>

Last Searched: February 19 2014

(counterfeit* OR anticounterfeit OR anti-counterfeit OR falsif* OR fake OR substandard OR spurious OR fraud* OR fraudulent OR falsely-labelled) AROUND(4) (drug* OR medication* OR medicine* OR pharmaceutical* OR pill* OR antibiotic* OR antimicrobial* OR antimalarial*)

The 1st 100 articles were retrieved

Database: Global Health Library<no restriction on date>

Last Searched: February 17 2014

Mesh term:
("Counterfeit Drugs" OR ("Fraud" AND "Pharmaceutical Preparations")

Keywords:
(counterfeit* OR anticounterfeit* OR anti-counterfeit* OR falsif* OR fake OR substandard OR spurious OR fraud* OR falsely-labeled) AND (drug* OR medication* OR medicine* OR pharmaceutical* OR pill* OR antibiotic* OR antimicrobial* OR antimalarial) - *by subject*

OR

(counterfeit* OR anticounterfeit* OR anti-counterfeit* OR falsif* OR fake OR substandard OR spurious OR fraud* OR falsely-labeled) AND (drug* OR medication* OR medicine* OR pharmaceutical* OR pill* OR antibiotic* OR antimicrobial* OR antimalarial) - *by title*

**Each search was run separately and duplicates removed*
Total number of articles retrieved:* ***1432*

Database: Health System Evidence: <no restriction on date>

Last Searched: February 17 2014

Keywords:

-Counterfeit

-substandard

-spurious

-falsified

Total number of articles retrieved:* ***1*

Database: Rx for Change <no restriction on date>

Last Searched: February 17 2014

Keywords:

(counterfeit OR substandard OR falsified OR fake) AND (drug OR drugs OR medicine OR medicines OR pharmaceutical OR pharmaceuticals)

-Counterfeit drug
-Counterfeit medicine
-Counterfeit pharmaceutical
-Substandard drug
-Substandard medicine
-Substandard pharmaceutical
-Falsified drug
-Falsified medicine
-Falsified pharmaceutical
-Fake drug
-Fake medicine
-Fake pharmaceutical

Total number of articles retrieved:* **0

Search for Grey Literature

Databases	Details of Search Strategy	Number of articles Retrieved	Date
Opengrey	Keywords: -Counterfeit drug -Counterfeit AND (drug OR drugs) -Counterfeit AND (medicine OR medicines) -Counterfeit AND (pharmaceutical OR pharmaceuticals) -Substandard AND (drug OR drugs) -Substandard AND (medicine OR medicines) -Substandard AND (pharmaceutical OR pharmaceuticals) -Falsified AND (drug OR drugs) -Falsified AND (medicine OR medicines) -Falsified AND (pharmaceutical OR pharmaceuticals) -Fake AND (drug OR drugs) -Fake AND (medicine OR medicines) -Fake AND (pharmaceutical OR pharmaceuticals)	10	February 18, 2014
OPHLA GreyLitNetwork-Science accelerator:	Counterfeit drug OR (counterfeit OR counterfeiting OR anti-counterfeit OR anticounterfeit) AND (drug OR drugs OR medication OR medications OR medicine OR medicines OR pharmaceutical OR pharmaceuticals) OR (fake OR substandard OR falsified) AND (drug OR drugs OR medication OR medications OR medicine OR medicines OR pharmaceutical OR pharmaceuticals)	398	February 19, 2014
Mednar	Mesh term: counterfeit drugs Keyword: counterfeit drug OR counterfeit drugs *(Limited to articles)	656	February 19, 2014

Hand-searching of Relevant Websites

Websites: **WHO** **CDC** **FDA** **INTERPOL** **USP**	Keywords used: (counterfeit OR substandard OR falsified OR fake) AND (drug OR drugs OR medicine OR medicines OR pharmaceutical OR pharmaceuticals) * -Counterfeit drug -Counterfeit medicine -Counterfeit pharmaceutical -Substandard drug -Substandard medicine -Substandard pharmaceutical -Falsified drug -Falsified medicine -Falsified pharmaceutical -Fake drug -Fake medicine -Fake pharmaceutical *Both the singular and plural forms of keywords were used	31	February 24, 2014

Appendix 2

Excluded Studies and Reasons for Exclusion

Total number of excluded studies (n=166)

1: Not in English, Arabic, or French (n=6)

2: Not a primary study (n= 40)

3: No full text available (n= 8)

4: Not about interventions to combat or prevent drug counterfeiting (n= 34)

5: Does not evaluate the effectiveness of intervention (n= 21)

6: Does not assess the outcomes of interest (n= 36)

7: No comparison group (n= 8)

8: No clear exposure (n= 7)

9: Duplicated data (n=5)

10: Not a therapeutic drug (n= 1)

Name of study	Reason for exclusion
Acierno, Carata, Maffia, et al, 2010[1]	5 (examines whether o exposure to RFID affects the molecular structure of drugs)
Affum, Lowor, Osae et al, 2013[2]	4 (prevalence study)
Agbaraji, Ochulor, and Ezeh, 2012[3]	2 (descriptive study)
Ali, 2010[4]	2 (narrative)
Ali, Ezika, Abdulraheem et al, 2011[5]	4 (prevalence study)
Almuzaini, Sammons, and Choonara, 2013[6]	2
Altunkan, Yasemin, Aykac et al, 2012[7]	6
Amin, Snow, and Kokwaro, 2005[8]	4 (prevalence study)
Assi, 2013[9]	6 (Analytical study)
Assi, 2012[10]	6
Assi, Watt, and Moffat, 2011[11]	6 (analytical study)
Assi, Watt, Moffat, 2011[12]	6 (analytical study)
Atemnkeng, De Cock, Plaizier-Vercammen, 2007[13]	8 (no enough information to compare registered and unregistered drugs
Audu, Taiwo, Saidu et al, 2012[14]	4
Barron, Zaman, Cole et al., 2010[15]	7
Bate, Coticelli, Tren et al,2008[16]	4 (prevalence study)
Bate, Tren, Mooney et al, 2009[17]	4 (prevalence study)
Bate, Tren, Hess et al, 2009[18]	6
Bate, and Hess 2010[19]	4
Bate, Hess, Mooney et al, 2010[20]	4 (prevalence study)
Bate, Mooney, and Hess, 2010[21]	9 (data is already present as part of another study) *Author conducted different studies using the same study population. Author was contacted and advised us which study to use to avoid duplication and overlap in data analysis
Bate, Putze, and Naoshy, 2010[22]	4 (does not investigate association between registration and quality of drug)
Bate, Mooney, Hess et al., 2012[23]	9 (data is already present as part of another study) * Author conducted different studies using the same study population. Author was contacted and advised us which study to use to avoid duplication and overlap in data analysis
Beckers, Riedl, and Schwerim , 2009[24]	6 (analytical study)
Binagwaho , Bate, Gasana et al, 2013[25]	5
Bobee, 2009[26]	2
Bockhorni and Schuberth, 2009[27]	6
Bridge, (n.d.)[28]	7
Broad, Dentinger, and Pasmore 2013[29]	2 (Review)
Catarinucci, Colella, De Blasi et al 2012[30]	
Chernetsova, Bochkov, Ovcharov et al., 2010[31]	6 (analytical study)
Christophe, 2010[32]	6 (analytical study)

Cohn, von Schoen-Angerer, Jambert et al 2013[33]	5
Coustasse, Arvidson, Rutsohn, 2010[34]	2
van Crevel, Burger,Nelwan , 2004[35]	4 (prevalence study)
Cuchet-Chosselet, Bocoum, Camara et al., 2011[36]	6 (only examines the efficacy of the campaign without linking it to any change in behavior related to poor quality drug)
Dekieffer, 2005[37]	2
De Peinder, Vredenbregt, Visser et al, 2008[38]	6 (analytical study)
Ding and Liu, 2009[39]	1 (not in English)
Dondorp, Newton, Mayxay et al., 2004[40]	4 (prevalence study)
Dooley and Sullivan, 2010[41]	2 (descriptive)
Eliasson and Matousek, 2007[42]	6 (analytical study)
Elisabeth, Alejandro, Louis et al, 2010[43]	5 (qualitative study that seeks opinions of stakeholder)
Elizarova, Shtyleva , Pleteneva, 2008[44]	6 (analytical study)
Enyinda and Tolliver, 2009[45]	2 (descriptive)
Ergin, Hai, Junyi et al, 2009[46]	5 (investigates the readability of RFID-tagged pharmaceutical Products)
Erhun, Babalola, and Erhun 2003[47]	5 (qualitative study on factors contributing to the preponderance of counterfeit drugs)
Exebio, Rodriguez, and Sayritupac , 2010[48]	1
Fotiou, Aravind, Wang et al, 2009[49]	4 (no any clear intervention- author compares smuggled drugs confiscated at airports to drugs from legal outlets)
Gaudiano, Di Maggio, Cocchieri et al., 2007[50]	4 (prevalence study)
Gimenez, Bruneton, and Narong 2001[51]	4
Gostin, Buckley, and Kelley 2013[52]	2 (viewpoint)
Green, Mount, Wirtz, 2000[53]	6 (analytical study)
Green, Nettey, Villalva et al, 2007[54]	6 (analytical study)
Guo, Cui, He et al 2013[55]	5
Hajjou, Qin, Bradby et al 2013[56]	6 (Analytical study)
Hall, Newton, Green et al, 2006[57]	4 (prevalence study)
Haneveld, 2004[58]	1
Havenstein, 2006[59]	2
Hollander 2006[60]	3 (powerpoint presentation)
Hosseini, Darbooy, Tehrani et al. 2011[60]	4 (prevalence study)
Howe, Goldner, and Fennig , 2007[61]	2 (outlines the technical solutions that are available)
Huang, Lucas, Vervaet et al, 2010[62]	5
Huff-Rousselle, Simooya, Kabwe et al, 2007[63]	5
Ilic, Michahelles, and Fleisch 2007[64]	5
Ioset and Kaur, 2009[65]	6 (analytical study)
Jackson, Patel, and Khan, 2012[66]	2
Jahnke, 2013[67]	2
Jahnke, 2004[68]	2 (descriptive)
Jahnke, Kusters, Fleischer 2001[69]	2 (descriptive)
Jameson, Chin, Peo et al, 2009[70]	1

Jehnkins, Barnett, and Mills, 2008[71]	7
Jehnkins, Mills, Maidment et al, 2007[72]	7
Jin, 2009[73]	7 (examines the reliability of the system itself)
Kalyanaraman, Dobler, and Ribick, 2010[74]	2 (review)
Kaur, Goodman, Thomson et al., 2008[75]	8 (authors observed drug quality at different level of distribution with no clear definition of what constitutes licensed and unlicensed drug outlets)
Kayumba, Risha, Shewiyo et al., 2004[76]	4 (prevalence study)
Kenyon, Kenyon, Kgarebe et al. , 1999[77]	4 (prevalence study)
Khan, Okumura, Sovannarith, et al., 2010[78]	9 (data is already present as part of a larger study done by the same author in 2011
Khan, Hatanaka, Sovannarith, et al, 2013[79]	4 (focuses on degradation of drug)
Klein, Luis, Jung et al, 2012[80]	4 (no intervention of interest)
Kristina, 2007[81]	2 (examines the different strategies firms may utilize in the battle against fake drugs)
Kubic, 2011[82]	2 (narrative study)
Ministry of Health of Vietnam, 2010[83]	9 (data is already present in the report by PQM, 2010)
Ofori-Kwakye, Asantewaa, and Gaye, 2008[84]	4 (prevalence study)
Kwok and Taylor, 2012[85]	6 (analytical study)
Kwok, Ting, Tsang et al, 2010[86]	5 (a proposed system)
Kyriacos, Mroueh, Chahine et al., 2008[87]	4 (prevalence study)
Labadie, 2012[88]	5
Laganga, 2011[89]	5
Lai and Chan, 2012[90]	2
Lanzarotta, Lakes, Marcott et al, 2011[91]	6 (analytical study)
Le Vaillant, Brenier, Grange et al, 2012[92]	2 (analytical study)
Lei, Luo, and Hu, 2008[93]	6 (analytical study)
Leng and Matsoso, 2008[94]	4
Liu, 2012[95]	2 (descriptive study)
Lopez and Wolff, 2009[96]	6 (analytical study)
Lukulay, Coignez, Pribluda, 2011[97]	2 (summary of the results of other studies)
Magdas, 2013[98]	6 (Analytical study)
Magnani and Vinther, 2012[99]	2 (descriptive study)
Maponga and ondari, 2003[100]	8 (author observed quality of drugs at different level of distribution with no clear definition of what constitutes licensed and unlicensed drug outlets)
Martino, Malet-Martino, Gilard, 2010[101]	2 (review of analytical techniques)
Maurin, Pluciński, Mazurek et al, 2007[102]	6 (analytical study)
Metheny et al, 2012[103]	3 (conference abstract not developed into a full-text article)
Ministry of Health_2010[104]	8 (No clearly defined pre-post interventions Summary of many interrelated interventions)
Ministry of Health, Kenya, 2007[105]	7 (only registration status of failed drugs provided)
Minzi, Moshi, Hipolite et al., 2003[106]	4 (prevalence study)
Nair, Strauch, Lauwo et al, 2011[107]	4 (prevalence study)

Nemes, Hoover, and Keire, 2013[108]	6 (Analytical study
Newton, Green, Mildenhall et al, 2011[109]	4 (prevalence study)
Newton, Green, Fernandez et al, 2006[110]	2 (review)
Obodizie, Mustapha, Ebeshi et al, 2003[111]	8 (no any clear intervention)
Okumara, Taga, Tei et al, 2010[112]	5
Olsen, Borrer, Perry et al, 2002[113]	6 (analytical study)
Opuni, Darko, Sabblah et al, 2010 [114]	3 (article not developed into full text, only abstract)
Ortiz, Mariotti, Schwab et al,2012[115]	6 (Analytical study)
Ortiz, Mariotti, Holzschuh et al, 2013[116]	4
Peter, John and Barde, 2013[117]	2 (1-pg commentary)
Phanouvong, 2010[118]	3 (conference Report - author contacted but no response)
Phanouvong, Dijiiba, Vijaykadga et al, 2013[119]	4 (prevalence study)
Pierson, 2010[120]	2 (press release summary report)
Philip and Hellstrom, 2011[121]	3
Polli, Hoag, and Flank, 2009[122]	6 (analytical study)
Pribluda, Barojas, Coignez et al, 2014[123]	2 (review)
Pribluda, Evans, Barillas et al, 2014[124]	9
Purdue Pharma, 2009[125]	6
Rehman, Rasool, Ayub et al, 2011[126]	5
Rfid, 2007[127]	6
Ricci , Nyadong, Yang et al, 2008[128]	6 (analytical study)
Risha, Msuya, Ndomondo-Sigonda et al, 2006[129]	4
Risha, Msuya, Clark et al, 2008[130]	7
Rodomonte, Gaudiano, Antoniella et al, 2010[131]	6 (analytical study)
Rosenfield, 2005[132]	2 (1-pg commentary)
Sacre, Deconinck, De Beer et al, 2010[133]	6 (analytical study)
Sacre, Deconinck, Daszykowski et al, 2011[134]	6 (analytical study)
Salawu and Adeyemo, 2005[135]	3
Sanofi, 2013[136]	2 (factsheet)
Santamaria-Fernandez, Hearn, and Wolff, 2008[137]	6 (analytical study)
santini et al, 2008[138]	3
Scafi and Pasquini, 2001[139]	6 (analytical study)
Schutz, 2007[140]	2
Sengaloundeth, Green, Fernandez et al., 2009[141]	4 (prevalence study)
Shakoor, Taylor and Behrens, 1997[142]	4 (prevalence study)
Sharma, Subramanian, and Brewer, 2008[143]	2 (proposed study)
Sherma, 2008[144]	2 (literature review)
Simoens, 2009[145]	7 (examines the reliability and efficacy of the system itself)
Song, Weng, and Lu et al, 2010[146]	1 (Chinese)
Staake and Fleisch, 2008[147]	2
Stanton, Koski, Cofie et al., 2011[148]	8 (no clarity regarding registration status of drugs)
Stenson, Syhakhang, Lundborg et al, 2001[149]	8 (focuses on the practice of pharmacies without linking it to drug quality)

Storme, Rebiere, Matoga et al, 2010[150]	6 (analytical study)
Syhakhang, 2002[151]	5
Taher and Setiawati, 2013[152]	10
Taylor and Craig, 2009[153]	2 (perspective)
Vijaykadga, Cholpol, Sitthimongkol et al, 2006[154]	4 (prevalence study)
Wadman, 2008[155]	2 (news)
Wallstabe and Pohl, 2008[156]	5
Wesch and Malik, 2003[157]	1
WHO, 2002[158]	5 (describes the regulatory system in different countries without linking it to changes in drug quality)
WHO, 2010[159]	3
WHO, WRPO/pharmaceuticals[160]	2
WHO, [161]	2 (news)
Yang, Shen, Huang et al, 2012[162]	4 (prevalence study)
Yoshida, Tanimoto, Kimura et al, 2014[163]	4 (prevalence study)
Zebra, 2008[164]	5 (an overview of the capabilities of track-and-trace technologies and applications)
2011[165]	2 (news)
2013[166]	5

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Figure S1: Risk of bias summary reflecting review authors' judgments about each risk of bias item for included observational studies

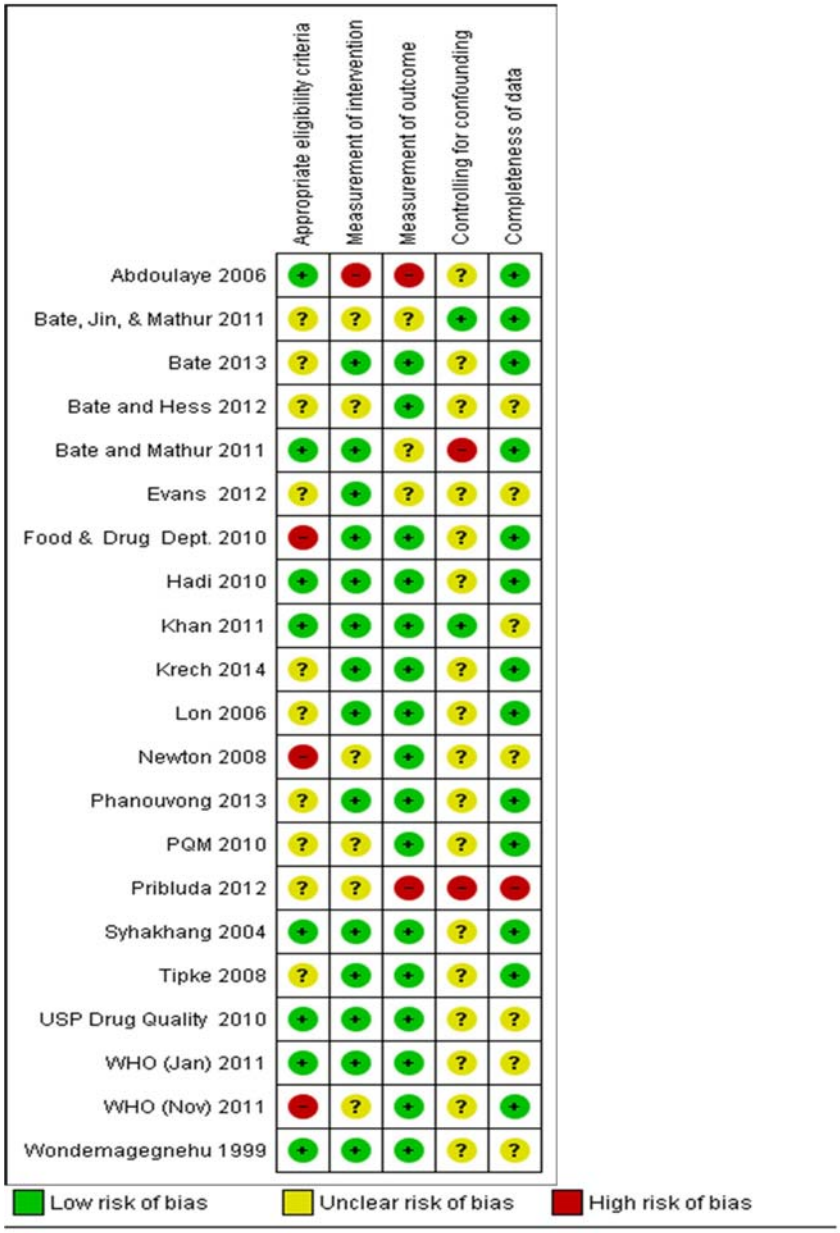

Figure S2: Risk of bias summary reflecting review authors' judgments about each risk of bias item for the single randomized trial.

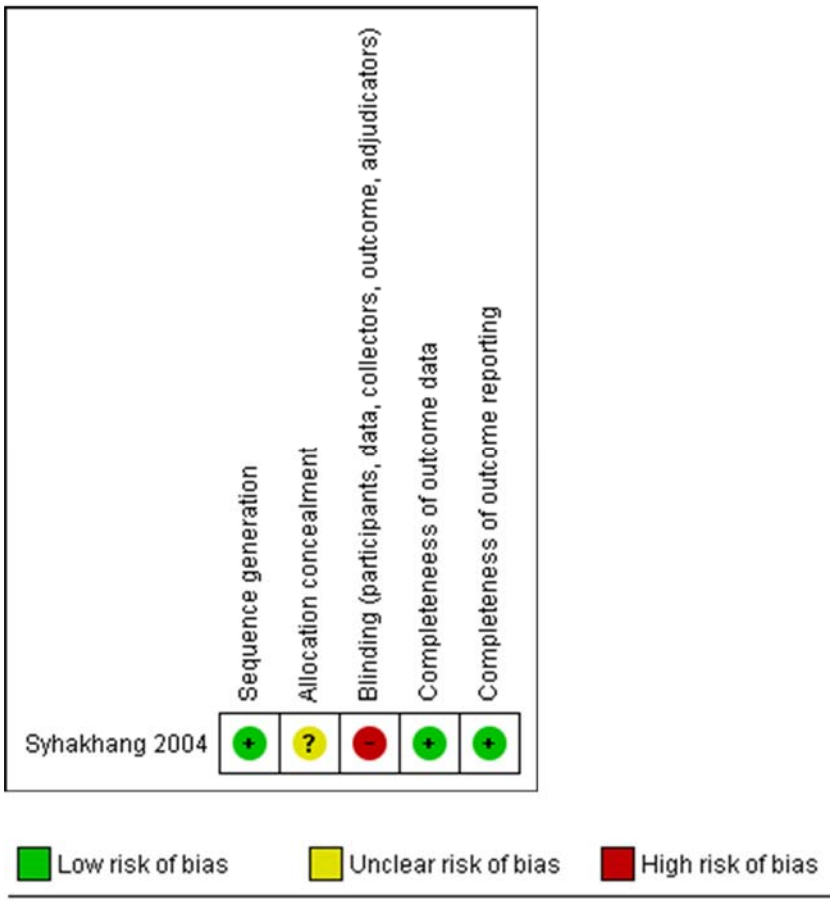

Figure S3: Forest plot for registration of drug intervention, outcome: changes in failure rates and prevalence of counterfeit drugs

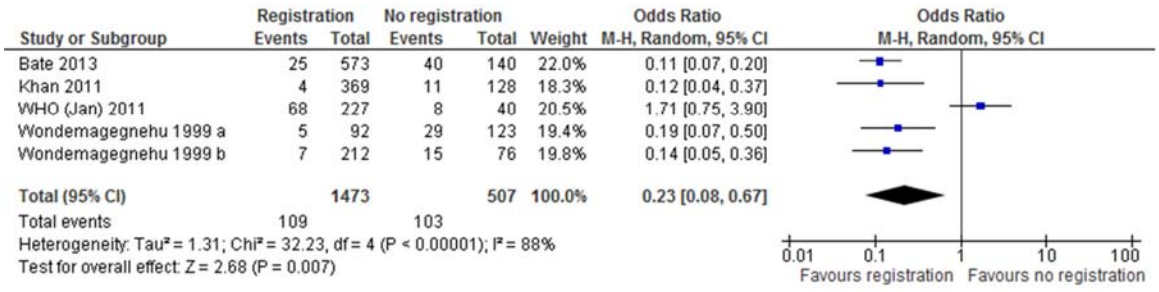

Figure S4: Forest plot for WHO-prequalification of drug intervention, outcome: changes in failure rates of tested drugs

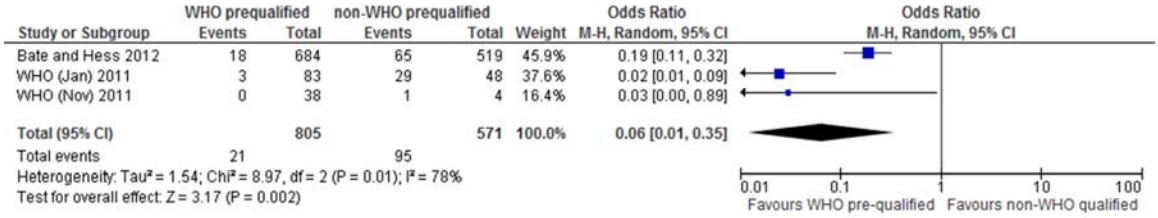

Figure S5: Forest plot for licensing of drug outlet intervention, outcome: changes in failure rates of tested drugs

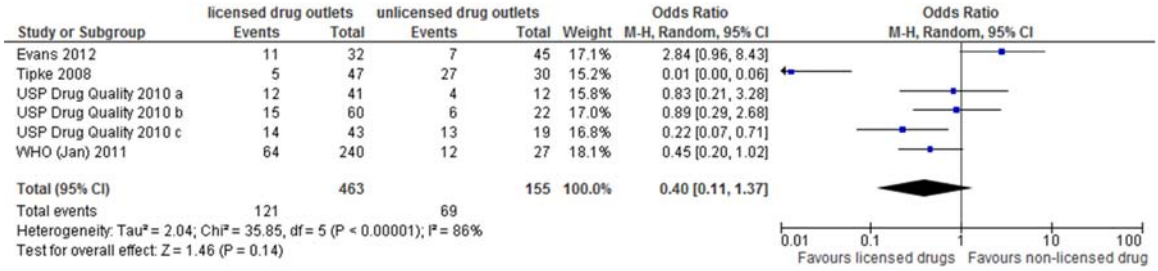

Table S1: Characteristics of the included observational studies

Study Name, Funding	Study Design	Definition of counterfeit	Setting and type of drugs collected	Strategies/Interventions	Control/Comparison Group	Outcomes
Abdoulaye, Chastanier,Azondekon et al, 2006[24]	Cross-sectional study	No clear definition provided for the term illicit medicine used in the study	Cotonue, Benin Households (mother or father) Not limited to any specific type of drug	A public awareness campaign (TV and radio announcements) to promote public awareness of the dangers of counterfeit medicines from illicit markets The campaign was designed based on a previous survey data collected to evaluate the purchasing practices of consumers	Individuals not exposed to the public awareness campaign	Changes in behaviors (or purchasing practices) of households towards illicit medicines markets
Bate and Mathur, 2011[38] Funded by The Legatum funded all of the research	Retrospective study Samples collected between mid-2007 and mid-2010	Authors referred to counterfeits and substandard drug as poor-quality drug	Lagos, Nigeria Samples of anti-malarial tablet formulations, namely: sulphadoxine–pyrimethamine (SP), artemisinin monotherapies and artemisinin combination therapies) Samplings from pharmacies	Deployment of six hand-held laser Trsucan (Raman) spectrometers at various inspection points by the Nigerian Government at the end of 2009	Period prior to deployment of technology	Changes in prevalence of poor quality drugs, measured in terms of failure rate
Bate, Jin, and Mathur, 2011 [27] Funded by Legatum Foundation and Legatum Institute	Cross-sectional study Samples collected over the past three years (2008 - 2010)	Authors referred to counterfeit and substandard drugs as poor-quality drugs “ Poor-quality drugs may be wrongly labeled, contain the wrong type of ingredient, formulate	Eleven African cities, three Indian cities, and five cities from mid-income countries 899 drug samples (8 drug types) from the World Health Organization’s essential medicines list,	Registration of drugs with local authority	Drugs not registered with local authorities	Quality of drugs, measured in terms of failure rate Failure is defined as failing any of the three tests (visual inspection, minilab, and spectrometry test)

		the active ingredients incorrectly, or be contaminated with pathogens"	including antimalarials, antibiotics and anti-mycobacterials Drugs procured from 185 private pharmacies			
Bate and Hess, 2012[30] Funded by Legatum Institute and the Social Sciences and Humanities Research Council of Canada	Cross-sectional study Samples were collected over the past 5 years	WHO definition used Counterfeit refers to "drugs that appeared to be deliberately and fraudulently mislabeled with regard to identity or source" Substandard refers to drugs that appeared to be poorly manufactured or degraded	11 African cities (Accra, Addis Ababa, Cairo, Dar es Salaam, Kampala, Kigali, Lagos, Luanda, Lubumbashi, Lusaka, Nairobi), three Indian cities (Delhi, Chennai and Kolkata), and 2 mid-income cities, Bangkok and Beijing 1203 samples of artemisinin-based combination therapies (ACTs) (co-blisters and fixed-dose combinations) Sampling from private pharmacies and drug stores	Approval of drugs by the WHO Prequalification Program, (i.e. WHO-approved manufacturer)	Non-WHO prequalified drugs	Quality of ACTs, assessed in terms of failure rate Failure is defined as a medicine failing quality control test for API concentration The authors did not contact manufacturers to confirm whether the drugs were substandard versus counterfeit
Bate, Jensen, Hess, Mooney et al., 2013[26] The Legatum Institute, London, UK, and the Social Sciences and Humanities Research Council of Canada funded the research	Cross-sectional study Sample collection period not mentioned	'Falsified' reflected the term counterfeit and is defined as "drugs that appeared to be deliberately and fraudulently mislabeled with regard to identity" "Samples that appeared to be poorly manufactured or degraded were	19 cities in Angola, Brazil, China, Democratic Republic of Congo, Egypt, Ethiopia, Ghana, India (n=3), Kenya, Nigeria, Russia, Rwanda, Thailand, Turkey, Uganda, United Republic of Tanzania and Zambia 713 samples of 2 main first-line anti-tuberculosis	Registration of drugs by the country of collection national drug authority (Registration means that drug is authorized by the relevant drug regulatory authority in the country in which the drug was sold)	Non-registered drugs	Quality of drugs, assessed in terms of failure rate Failures referred to drugs that did not pass the most basic requirements of API concentration and solubility. It was not always feasible to compare drug packaging with reference samples (drugs with low API levels

		considered substandard"	medicines, isoniazid and rifampicin Sampling from private sector pharmacies			may have been falsified)
Evans, Coignez, Barojas et al., 2012[32] Funded by USAID	Cross-sectional study Samples collected in 2009	Authors did not provide definitions for the terms counterfeit and substandard used in the study Authors stated that according to legislation in Guyana, "when a medicine contains no active ingredient it is considered as substandard unless there is other incriminating evidence that proves the drug is counterfeit"	Guyana and Suriname 77 anti-malarial medicines (primaquine, quinine and chloroquine soli dosage form, mefloquine tablets, and ACTs) Sampling from private and informal sectors	Licensed drug outlets (pharmacies, wholesalers and distributors)	Unlicensed drug outlets (shops and conveniences stores)	Quality of medicine, assessed in terms of failure rate Failure was defined as a medicine failing any single quality control test and/or visual and physical inspection. A sample failing both was considered a single failure
Ministry of Health, Food and Drug Department (MOH, FDD)[43] Funding not reported	Pre-post study Report Samples collected from 2005-2009	No clear definition provided for the terms counterfeit and substandard used in the study	The Lao People's Democratic Republic (Lao PDR) 1567 samples of anti-malarial, anti-TB, HIV/AIDS, antibiotics and AI combined Sampling from both public and private sectors	Medicine quality monitoring (MQM) project supported by the Promoting Quality of Medicine (PQM) program From 2005-2009 the program extended to cover law enforcement, procurements and good manufacturing practice	Pre- expansion of program	-Changes in prevalence of counterfeit drugs -Changes in prevalence of substandard drugs, measured in terms of failure rate Failure was defined as a medicine failing confirmatory testing -Arrests and seizures of counterfeits
Hadi, van den Broek, Kolopaking	Cross-sectional study	WHO definition used	Indonesia (the city of Surabaya, East Java)	Licensed drug outlets (pharmacies and drug stores)	Unlicensed drug outlets	Prevalence of substandard drugs

et al, 2010[33] Main sponsor: The Royal Netherlands Academy of Arts and Sciences (KNAW) Additional sponsors: Leiden University Medical Centre (LUMC), Gilead/UCB Pharma, The Netherlands, Merck Sharp & Dohme bv, The Netherlands, and Bristol Myers Squibb bv, The Netherlands	Samples collected between 7 and 15 April 2006	"Counterfeit drug is one that is deliberately and fraudulently mislabeled with respect to identity, source, or both. Counterfeit products can contain the correct amount, too little or too much of the active ingredient" A substandard drug is a drug that "fails to meet the specifications upon laboratory testing in accordance with the specifications it claims to comply with"	104 samples of antibiotics (amoxicillin, chloramphenicol, tetracycline, cotrimoxazole, or ciprofloxacin) Sampling from pharmacies, drug stores and kiosks		(Kiosks or roadside stalls)	Authors had no indication that any of the drug samples were counterfeit
Khan, Okumura, Sovannarith et al., 2011[28] Financial support from the Japan Pharmaceutical Manufacturers Association(JPMA)	Cross-sectional study Samples collected from 2006 to 2008	No clear definition provided for the term counterfeit used in the study	Cambodia (seven districts of the capital, Phnom Penh, and three provinces: Kandal, Takeo and Kampong Spue) 710 samples collected 2006: amoxicillin, ampicillin, cephalexin, paracetamol, artesunate and chloroquine 2007: amoxicillin, ampicillin, cephalexin, paracetamol 2008: anti-helminthics	-Licensed drug outlets -Registration of drugs by the Department of Drugs and Food (DDF), Cambodia	-Unlicensed drug outlet -Non-registered drugs	Prevalence of counterfeit drugs

			albendazole, mebendazole and metronidazole Sampling from urban and rural private drug outlets (Pharmacy, Depot-A, Depot-B, and non-licensed outlets)			
Krech, Barlow, Siv et al., 2014[41] Funding not reported	Pre-post study Samples collected from 2005-2012	The article used the term "poor quality" to cover all substandard/ spurious/falsely labeled/falsified/ counterfeit (SSFFC) medical products.	Twelve Cambodian provinces 4,381 samples of anti-infective medicines, the majority of which were antimalarial and antibiotics Sampling from legal private sector facilities and illegal outlets	The Promoting the Quality of Medicines (PQM) program which was initiated in 2009 Key features: - Early detection of poor-quality drugs (using a three-level approach to testing) -Collaborations with the country's medicine regulatory authorities and international partners (WHO, INTERPOL) for enforcement actions based on evidence obtained from the field -Technical support to the Inter-Ministerial Committee to Fight against Counterfeit & Substandard Medicines (IMC)	Pre-implementation and expansion of the PQM's medicine quality monitoring (MQM program	-Changes in the prevalence of substandard drugs, measured in terms of failure rate Failure was defined as a medicine failing verification testing -Changes in prevalence of counterfeit drugs -Closure of illegal outlets
Lon, Tsuyuoka, Phanouvong et al., 2006[36] Financial support provided by the United States Agency for International Development	Cross-sectional study Study initiated in May 2003	No clear definition provided for the term counterfeit used in the study	Four provinces in Cambodia (Pursat, Battambong, Pailin and Preah Vihea) 451 antimalarial drug samples Sampling from public and private health sector	Licensed drug outlet (legal drug outlets are licensed)	Unlicensed drug outlets (illegal drug outlets are unlicensed) Illegal drug trade refers to "practices of production, sale and distribution of	-Prevalence of counterfeit drugs -Changes in failure rate of tested drugs Failure was defined as sample that "did not pass any tests including identity of active pharmaceutical

through the U.S. Pharmacopeia Drug Quality and Information Program and the WHO					drugs without formal authorization of the Ministry of Health's Drug Regulatory Agency"	ingredient, disintegration, assay for content of API, and any major physical deficiencies such as improper labeling"
Newton, Fernandez, Plancon et al., 2008[39] Funded by: Wellcome Trust of Great Britain; USAID; Western Pacific Regional Office (WPRO) of WHO; United States National Science Foundation	Case study Samples collected from 1999–2006	Not explicitly stated but may include products with "fake packaging, no API, wrong API or sub-therapeutic quantities of API"	Samples collected in Vietnam (75), Cambodia (48), Lao PDR (115), Myanmar (Burma) (137) and the Thai/Myanmar border (16) 391 samples of genuine and counterfeit artesunate Samples collected by the Wellcome Trust-Oxford SE Asian Tropical Medicine Research Program	A model of International cross-disciplinary collaborations between WHO officials, physicians, pharmacists, and scientists (criminal analysts, chemists, palynologists) working in the region with the INTERPOL	Relatively little action and collaborations	Quantification and identification of source of counterfeit artesunate in South-East Asia

Phanouvong, Raymond, Krech et al, 2013[34] Funded by the United States Agency for International Development Regional Development Mission for Asia and the United States Pharmacopeia, and by the Bill and Melinda Gates Foundation through the World Health Organization	Cross-sectional study Project Implemented from January 2009 to October 2011	Cambodia's definition used. "Counterfeit medicines are those that are deliberately produced with an incorrect quantity, wrong active ingredients, without active ingredients or unregistered products; deliberately or fraudulently mislabeled with respect to identity, source or with fake packaging or repacked or produced by an unauthorized agent" Substandard medicines are those "produced by a legitimate manufacturer but do not meet quality specifications set for them"	Six provinces in western Cambodia along the border with Thailand 377 antimalarial drugs Sampling from both public and private sectors	Licensed sector (public sector and legal private sector)	Unlicensed sector (illegal private sector)	Quality of medicine, measured in terms of failure rate A failed sample was one that did not conform to the "recognized standard specifications for identity of API, disintegration, dissolution, and assay for content of API, or any major physical deficiencies."
Pribluda, Barojas, Anez et al 2012[42]	Pre-post study Samples collected from 2005-2010	Authors cited another article for definitions and distinctions between counterfeit, substandard and degraded products.	Amazon Basin countries (Bolivia, Brazil, Colombia, Ecuador, Guyana, Peru, and Surinam and selected countries in Central America) 1,663 malaria medicines Sampling from public sector	The Promoting the Quality of Medicine (PQM) program's monitoring quality of medicine (MQM activities Key feature: Technical assistance to implement the use of basic tests as a key screening mechanism and ensure the quality of malaria medicines	Pre-implementation of PQM's MQM assessments (2005)	Changes in quality of medicine, measured in terms of failure rate Failure was defined as a sample that "did not comply with V&P inspection and/or basic tests requirements" Confirmatory and/or other forensic testing and follow up with manufacturers would have been necessary

						to determine if the failures were due to counterfeits
PQM Program, 2010[40] Funded by the USAID	Pre-post study Report Samples collected from 2005-2010	No clear definition provided for the terms counterfeit and substandard used in the report	Samples collected from Southeast Asia (Cambodia, Lao PDR, Thailand, Vietnam) and Philippine Samples include 3021 antibiotic, 6176 antimalarial, 625 anti-tuberculosis, and 234 antiretroviral medicines Sampling from public, private, and unlicensed sectors at wholesalers, health care facilities, retail pharmacies, and non-pharmacy outlets	Initiation and expansion of the Promoting the Quality of Medicine (PQM) Program In 2006-2007 the program expanded to include other drug types and classes in both the public and private sectors with increased cooperation and collaboration with country's MOH, drug regulatory authorities, national priority disease control programs, national medicine quality control laboratory, surveillance site staffs, and community healthcare workers	Pre-expansion of the PQM program	Changes in prevalence of counterfeit and substandard medicines, measured in terms of failure rate
WHO, Jan 2011[25] This document has been produced with the financial assistance of the European Union, the Bill and Melinda Gates Foundation and UNITAID	Cross-sectional study Report Samples collected in the period April - June 2008	No clear definition provided for the terms counterfeit and substandard drugs used in the study Authors stated that "confirmation of substandard products as counterfeits is a very complex activity going beyond the scope of quality testing and therefore could not be fully executed."	Six countries of sub-Saharan Africa (Cameroon, Ethiopia, Ghana, Kenya, Nigeria and the United Republic of Tanzania). 935 samples of selected antimalarials (artemisinin-based combination therapy (ACT) products and sulfadoxine/pyrimethamine (SP) products) Sampling from different distribution levels including the informal market in at least three geographical regions of	-Registration of drugs (authorization for use in the country of collection by the National Medicines Regulatory Authority) -WHO-prequalified drugs -Licensed drug outlets	-Non-registered drugs -Non-WHO prequalified drugs -Unlicensed drugs outlets	Changes in quality of medicine, assessed in terms of failure rate

			high malaria prevalence			
Syhakhang, Lundborg, Lindgren et al, 2004[23] Funded by the Swedish International Development Cooperation Agency (Sida)	Retrospective study Samples collected in 1997 and 1999	No clear definition provided for the terms counterfeit and substandard used in the study	Lao PDR, Savannakhet province Essential drugs ampicillin, tetracycline, chloroquine and acetyl salicylic acid In 1997, 366 samples were analysed and 300 in 1999 Sampling from private licensed pharmacies .	Implementation of the National Drug Policy Programme (NDPP) between 1997–1999 Key features: (i) The development of regulations, e.g., improvement of the drug registration system and increased requirement for imported products (ii) Training of drug inspectors in good manufacturing and pharmacy practice (iii) Appropriate legal actions, e.g., fines and product recall	Pre-implementation of Program	Changes in prevalence of substandard drugs, measured in terms of failure rate *Substandard drugs included drugs with no active ingredients
Tipke, Diallo, Coulibaly et al, 2008[35] Funding from the Deutsche Forschungsgemeinschaft	Cross-sectional study Study carried out in 2006	No clear definition provided for the terms substandard drug used in the study Authors acknowledge that it would be difficult to distinguish if failed samples with substandard active ingredients during manufacture were deliberately or unintentionally performed	Nouna Health District in north-western Burkina Faso 88 samples of anti-malarial medications (tablets and capsules of chloroquine, amodiaquine, sulphadoxine/pyrimethamine, quinine, artesunate and, artemether-lumefantrine) Sampling from licensed and illicit drug outlets	Licensed drug outlets (public and private pharmacies, community health workers)	Unlicensed drug outlets (market and street vendors, shops)	Quality of drug assessed in terms of failure rates Failure was defined as a medicine failing any single quality control test (including physical and visual inspections) *Failed drugs were referred to as substandard (one sample contained none of the stated active ingredient)
USP Drug Quality and Information Program, 2010[37] Funding source not clearly mentioned but	Cross-sectional study Report Samples collected over the period of	No definition provided for the terms counterfeit and substandard medicine used in the study	Three African countries: Madagascar, Uganda. Senegal 491 artemisinin-based combination therapy (ACT) and sulfadoxine-pyrimethamine (SP) products	Licensed sectors (regulated public and private sector)	Unlicensed sector (informal market)	Prevalence of substandard and counterfeit drugs, measured in terms of failure rate

most probably involves WHO and USP	April–June 2008		Sampling from both wholesale and retail outlets, in the regulated private and public sectors and informal market			
Wondemagegnehu, 1999[29] Financed by The Government of Japan	Cross-sectional study Report Field visits made in 1996 and 1997	WHO definition used "Counterfeit products may include products with correct ingredients, wrong ingredients, without active ingredients, with the incorrect quantity of active ingredient or with fake packaging" Author acknowledges the absence of a universal definition of counterfeit drugs	Two Asian countries: Myanmar and Viet Nam 503 samples of Amoxicillin, ampicillin, chloramphenicol, chloroquine, co-trimoxazole, diazepam, metronidazole, paracetamol, ranitidine, rifampicin, salbutamol and tetracycline Sampling from public and private drug outlets and market places	Registration of drugs by Drug Regulatory Authorities (DRAs)	Non-registered drugs	Prevalence of counterfeit and substandard drugs Outcome assessed in terms of authentication and quality testing for API
WHO, Nov. 2011[31] The document has been produced with the financial assistance of the Bill & Melinda Gates Foundation and UNITAID.	Cross-sectional study Report Samples collected between September 2009 and February 2010	Substandard, spurious, falsely-labelled, falsified or counterfeit medicines may include those with "the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging."	Six countries: Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan 291 samples of first and second-line anti-Tuberculosis medicines Sampling from 84 discrete sites from public and private sector procurement and treatment centres	WHO pre-qualification of drugs WHO Pre-qualification is a "service provided by WHO to facilitate access to medicines that meet unified standards of quality, safety and efficacy primarily for HIV/AIDS, malaria, TB, and reproductive health"	Non-WHO pre-qualified drugs	Quality of selected medicines assessed in terms of failure rate Samples were considered to be in compliance with standards if they met the specifications as outlined in the quality control tests

Table S2: Characteristics of the included RCT

Study Name	Study Design	Participants, setting	Exposure	Control	Outcomes
Syhakhang, Lundborg, Lindgren et al 2004[23] Funded by the Swedish International Development Cooperation Agency (Sida)	Cluster randomized trial	The 214 licensed private pharmacies in Savannakhet province, Lao P.D.R., constituted the target population. Each pharmacy constituted a study unit. Sampling of essential drugs such as ampicillin, tetracycline, chloroquine and acetyl salicylic acid	Pharmacies in the active intervention package received, in addition to what the control group received, two extra inspections which focused on improving pharmacy services: 1. Intensified supervision and 2. Additional training for the district drug inspectors	The regular intervention packages included: 1. Four high-quality annual inspections 2. Sanctions for any violation 3. Distribution of regulation documents to the private pharmacies (documents); 4. Provision of information to the drug sellers about particular points needing improvement (information) It was implemented in the way and at the speed that would have taken place in the absence of this study.	Percentage changes in quality of drugs

Table S3: Risk of bias in the included observational studies

Study Name, Funding	Developing and applying appropriate eligibility criteria	Measurement of Strategy	Measurement of outcome	Controlling for confounding	Completeness of data
Abdoulaye, Chastanier,Azondekon et al, 2006[24]	Low risk Cluster random sampling was used Appropriate sample size (sample size calculation)	High risk Subjective measurement of exposure where participants reported if they watched or heard the campaign messages	High risk Subjective measurement of outcome using self-reported questionnaire Authors did not mention if questionnaire is validated. Also, the identity of the investigator was unclear	Unclear risk The authors only controlled for having a TV and being in a monogamy or polygamy house	Low risk The author did not report on missing data
Bate and Mathur, 2011[38]	Low risk Random selection of samples from private pharmacies Study agents posed as customers and were blinded to the purpose of sample collection 114 samples collected prior- and 137 post- introduction of spectrometry .	Low risk Date of deployment of intervention was confirmed by NAFDAC general director and through review of press reports. “This provides us a clear cutoff date in our sample period to study any changes in trend that may have occurred in the sale and use of “counterfeit” medicines”	Unclear risk The validity and/or reliability of portable Raman spectrometer not reported Compendia procedures (QC laboratory testing), not performed on a subset of samples The Global Pharma Health Fund e.V. Minilab® protocol was used for visual inspection and to run semi-quantitative thin-layer chromatography and disintegration tests on each sample in duplicate Samples were also tested using a portable Raman spectrometer (TruScan) to reflect all contents of the sample including the active pharmaceutical ingredients	High risk “Sample size is too small to conduct any rigorous regression analysis”	Low risk 251 samples were collected and tested

Bate, Jin, and Mathur, 2011 [27]	Unclear risk It is not clear whether and how random sampling was conducted "covert shoppers helped identify non-slum, middle class areas of their city and then took a random walk through those areas collecting samples" 899 drug samples were collected	Unclear risk Authors generated a dummy variable equal to one if a drug has been registered in the purchase country at the time of purchase using drug registration data collected in the study by Bate et al. (2010 a,b)	Unclear risk Basic testing followed by Raman spectrometry tests for drug authentication The validity and/or reliability of Raman spectrometer not reported Three-level approach: 1st level: visual inspection of packaging and pills for correctness 2nd level: Minilab tests (disintegration and thin-layer chromatography using the Global Pharma Health Fund e.V. Minilab® protocol.) 3rd level: Raman spectrometry test for product authentication	Low risk Regression was performed to control for city-specific effects such as literacy rate, maximum penalty, taxes and price regulations Same sampling protocol used across countries to provide comparable results	Low risk Authors controlled for missing data by using dummy cells and re-running the analysis
Bate and Hess, 2012[30]	Unclear risk Although covert shoppers were blinded to the purpose for which they were collecting samples, sampling was not done randomly 1203 samples of ACTs were procured	Unclear risk No information was provided on how the WHO pre-qualification status of drugs was assessed and/or verified	Low risk Basic testing was complemented by confirmatory testing in laboratories using acceptable pharmacopeial specifications Two-stage testing approach: Samples were assessed via visual inspection, disintegration and semi-quantitative thin-layer chromatograph using the Global Pharma Health Fund e.V. Minilab protocol. A subset of suspicious drugs were then analyzed using high-performance liquid	Unclear risk Control for confounding not reported Drugs were properly stored (ambient temperature, low humidity, no sunlight) until testing	Unclear risk Study is mainly a re-analysis of data collected in other studies

			chromatography (HPLC) for deviances from API standards in accordance with WHO International Pharmacopoeia		
Bate, Jensen, Hess, Mooney et al., 2013[26]	Unclear risk Although covert shoppers were not informed about the purpose of the collection, convenient sampling was used 713 treatment packs were procured	Low risk "Each drug brand was checked against the official list of authorized products in the country in which it was purchased"	Low risk Validated methods were used to test drug samples "In previous studies, TLC testing using the Minilab protocol yielded broadly similar results to high-performance liquid chromatography when used to analyze pharmaceuticals." "Laserson et al. showed that TLC is an effective method of detecting substandard anti tuberculosis drugs"	Unclear risk control for confounding not reported The purchased drugs were properly stored (ambient temperature, low humidity, no sunlight) until testing.	Low risk 713 samples were collected and tested
Evans, Coignez, Barojas et al., 2012[32]	Unclear risk Local workers implemented both overt and covert shopping techniques to procure samples It was not reported whether random sampling of drugs was used 77 anti-malarial medicine samples were collected	Low risk Private sectors were considered as licensed whereas informal sectors were unlicensed	Low risk Samples were analyzed using validated methods All samples underwent visual and physical inspection followed by quality control testing for identity, content, dissolution, impurities, and weight variation according to pharmacopeial, manufacturer, or other validated methods.	Unclear risk Controlling for confounding factors not reported All samples were properly stored to ensure sample integrity and avoid adulteration	Unclear risk "Due to limited sample availability, not all specified tests could be conducted on a sample therefore the type of tests performed depended on the number of units collected"
Ministry of Health, Food and Drug Department (MOH, FDD)[43]	High risk Convenient sampling was used for sample collection Drug sellers were aware that the data collector is a drug inspector or regulator	Low risk Cut-off date for baseline measurement of intervention taken as 2005 "From 2005-2009 the	Low risk Basic tests performed at 6 Mini-Labs followed by verification and confirmation tests at the National and reference laboratory Testing procedures and assay method	Unclear risk Controlling for confounding not reported Samples were properly stored until testing	Low risk 1567 samples were collected and tested

	1567 samples were collected	program has been extended to cover the issues on law enforcement, procurements and good manufacturing practice"	were carried out according to "the latest edition of International Pharmacopoeia (IP), and/or USP/NF and/or other leading pharmacopeias"		
Hadi, van den Broek, Kolopaking et al, 2010[33]	Low risk Simulated clients were used Although random sampling was not used authors stated that their "field survey approach should exclude major bias."	Low risk Categorization of drug outlets into licensed and unlicensed outlets in accordance with Indonesia's law	Low risk Sample testing was conducted in certified control laboratories using validated methods. Drugs were subjected to high performance liquid chromatography in duplicate and in conformity with GMP-GCLP guidelines Testing was carried according to the British Pharmacopoeia BP2005 monographs and the United States Pharmacopeia USP 29	Unclear risk Controlling for confounding variables not reported Samples were properly stored in air-conditioned room until testing	Low risk All samples collected were used for analysis
Khan, Okumura, Sovannarith et al., 2011[28]	Low risk Clear eligibility and sample selection criteria Stratified random sampling was used Locally recruited members purchased medicines as average customers 710 samples were collected	Low risk The method for registration verification was adopted from the WHO. Registration status was also verified with the Medicine Regulatory Authorities (MRAs) and manufacturers of the drug samples Drug outlets were categorized into licensed (Pharmacy, Depot-A and Depot-B) and unlicensed	Low risk The method for authenticity investigation verification was adopted from the WHO. Samples were also assessed by high performance liquid chromatography (HPLC) and dissolution test at quality control labs according to standard Pharmacopoeia	Low risk Logistic regression analysis was performed to identify significant factors responsible for the dependent variable. Samples were transported taking temperature controlled measures and preserved at 20–25°C until analyzed	Unclear risk Of the 710 collected samples, 513 samples underwent authenticity investigation and 487 were subjected to quality testing.

		outlets in accordance Cambodia's law			
Krech, Barlow, Siv et al., 2014[41]	Unclear risk Although samples were collected using covert clients, it was not clear whether sampling was done randomly 4,381 medicines were collected and tested	Low risk The Promoting the Quality of Medicines (PQM) program was initiated in 2009, thus cut-off date for baseline measurement of intervention is taken as pre-2009	Low risk Basic testing was complemented by confirmatory testing in laboratories Three-level approach Level 1: Visual inspection of the package and label Level 2: Global Pharma Health Fund (GPHF) Minilabs® to determine identity, content, impurities and disintegration Level 3: Verification of subset of sample samples at the National Health Product Quality Control Center according to the pharmacopeia utilized	Unclear risk Controlling for confounding variables not reported	Low risk 4,381 medicines were collected and tested
Lon, Tsuyuoka, Phanouvong et al., 2006[36]	Unclear risk Convenient sampling was used Sampling team primarily disguised as ordinary customers, but at times dressed up as a formal mission 451 drug samples were collected	Low risk Licensure status was determined based on a list of Pharmacies and Depot of Pharmacies A and B by the Cambodia Department of Drugs and Food at 31 December 2002	Low risk Samples were analyzed at three levels according to established guidelines for antimalarial drug sampling 1st level: basic testing at the sentinel sites (physical/visual inspections, simple disintegration and TLC) using the German Pharma Health Fund Minilab kits. 2nd level: verification testing by the National Laboratory for Drug Quality Control in Cambodia using TLC	Unclear risk Controlling for confounding factors not reported	Low risk All 451 samples collected were analyzed using the basic testing methods

			3rd level: confirmation of a subset of samples at selected reference laboratories in accordance with pharmacopeial monographs in International Pharmacopoeia		
Newton, Fernandez, Plancon et al., 2008[39]	High risk 391 samples were collected using convenient sampling and random sampling (in Laos only) and ad hoc at the demand of non-governmental organizations and individuals in the region	Unclear risk Authors did not report how the collaborative model was measured. The strategy involved a complex model of "International cross-disciplinary collaborations"	Low risk Samples underwent high performance liquid chromatography (HPLC), X-ray diffraction, organic mass spectrometry, stable isotope ratio mass spectrometry, gas chromatographic 'head space' analysis, pollen analysis, and packaging inspection. All laboratories conducted the analyses blinded to the results obtained from other laboratories	Unclear risk Control for confounding variables not reported	Unclear risk Only a small subset of the 391 samples collected could be analyzed due to financial constraints
Phanouvong, Raymond, Krech et al, 2013[34]	Unclear risk The authors did not report whether random sampling and simulated clients were used "PQM has designed country-specific sampling protocols"	Unclear risk No clear pre-post cut-off date for baseline measurement of intervention The PQM was initiated in 2003 and expanded in 2006-2007	Low risk Basic testing using Minilabs followed by confirmatory testing for a proportion of samples at the national medicine quality control laboratories according to defined protocols	Unclear risk Control for confounding not reported	Low risk The authors did not report on missing data
Pribluda, Barojas, Anez et al 2012[42]	Unclear risk Samples were collected using formal announced technique in public sector and "mystery shopper" in private sector	Low risk Clear distinction between the two types of sector: Licensed: Pharmacy Depot A and B sites, "consultation rooms," private pharmacies	Low risk Basic testing using GPHF Minilab techniques followed by confirmatory testing for a subset of samples in quality control laboratories in accordance with latest edition of the US Pharmacopeia and other internationally-acceptable pharmacopoeias	Unclear risk Control for confounding not reported Samples stored properly to prevent any deterioration or adulteration	Low risk Of 377 samples collected (3 were expired at time of collection) so 374 were screened

		Unlicensed: illegal drug retailers or unregistered grocery stores.			
PQM Program, 2010[40]	Unclear risk Convenience sampling was used 1,663 malaria medicines	Unclear risk No clear pre-post cut-off date for baseline measurement of intervention across countries Discontinuation of program in various countries	High risk Confirmatory testing was done for only a subset of samples from Brazil and Guyana. "the lack of consistent confirmatory tests in the quality control (QC) laboratory" "Doxycycline medicines in Brazil and more than 50% of the samples from Suriname could not be assessed by TLC due to the lack, at the time, of a validated TLC methodology"	High risk Most of the failure were due to performing basic tests on expired medicines	High risk Several countries ceased participation before the end of the study period
WHO, Jan 2011[25]	Low risk Clear eligibility and sample selection criteria Survey protocol was uniformly applied in all participating countries. Sampling sites were randomly selected according to predefined criteria. Mystery clients were used to collect samples 935 samples were collected and 306 underwent lab testing	Low risk The registration status of the sampled drugs as recorded on the sample collection forms at the time of collection and later verified with country focal points Sampled drugs were classified as prequalified if they were "of the same dosage form and strength, in the same immediate packaging and from the same manufacturing site as listed by WHO"	Low risk Basic testing followed by confirmatory testing for a subset of samples in quality control laboratories -GPHF-Minilab procedures: visual inspection, TLC identification, simple disintegration - Quality control laboratory testing was performed on a subset of samples by reliable quality control laboratories in accordance with recognized pharmacopoeias	Unclear risk Control for confounding factors not reported Drugs were stored properly to avoid deterioration or degradation	Unclear risk Out of 306 samples, 267 were fully tested with conclusive results. Authors calculated failure rates as percentages of non-compliant samples out of the total number of samples with conclusive results
Syhakhang, Lundborg,	Low risk	Low risk	Low risk	Unclear risk	Low risk

Lindgren et al, 2004[23]	Clear eligibility and sample selection criteria Random selection of pharmacies from all 214 licensed private pharmacies in the districts in Savannakhet Covert shoppers used 366 drug samples were collected in June 1997 and 300 in February 1999	Clear cut-off point for implementation of program	Drug samples were analyzed at the Food and Drug Quality Control Centre with the quality of the laboratory's work examined in an inter-laboratory test using high-performance liquid chromatography, potentiometric titration, and ultraviolet spectrophotometry. Identity, assay and measurement of weight variation tests were performed Drug quality were compared according to the standards of the British and United States' pharmacopoeias	Although controlling for confounding variables was not reported, samples were collected from the same pharmacies as pre-intervention	No missing data reported
Tipke, Diallo, Coulibaly et al, 2008[35]	Unclear risk For artemisinin and ACT, convenience sample was taken from market places and private pharmacies in randomly selected quarters A representative sample of 86 anti-malarial medicines was collected .	Low risk "For analysis, private pharmacies, community health workers, and the health centre and hospital pharmacies were defined as licensed market, while markets, street vendors, and shops were summarized as illicit market"	Low risk Basic testing followed by confirmatory testing for a subset of samples in reference laboratories: All samples underwent visual inspection, disintegration test, qualitative color reaction test and semi-quantitative thin-layer chromatography with the standard procedures of the German Pharma Health Fund-Minilab. Any failing sample was re-examined by a second investigator for validation Suspected drugs were re-tested in a reference laboratory for disintegration in accordance with the European Pharmacopoeia standards. The investigators were blinded to the origin of samples	Unclear risk Control for confounding not reported Drug samples were properly stored (dark, dry & air conditioned place) until testing	Low risk Only 9 samples were missing from analysis "A total of 86 anti-malarial drug samples have been collected, of which 77 were included in the final analysis"

USP Drug Quality and Information Program, 2010[37]	Low risk Clear eligibility and sample selection criteria Random selection of sampling sites Mystery client technique used 491 samples were collected	Low risk Regulated private and public were considered as licensed and informal market as unlicensed Samples were collected from selected sites of the regulated private and public sector as well as from the informal market based on a national sampling plan	Low risk Basic testing using the minilab kits followed by confirmatory testing using compendia procedures (QC laboratory testing), on a sub-sample for each country	Unclear risk Control for confounding not reported All samples were stored properly (under ambient conditions) until testing	Unclear risk Of the 491 samples collected, 444 were tested using minilab and 197 were tested in QC laboratory testing
Wondemagegnehu, 1999[29]	Low risk Clear eligibility and sample selection criteria Random selection of drug outlets Mystery client technique used A total of 503 samples were collected from both countries	Low risk Drug samples were confirmed as registered and genuine by the responsible staff of the drug regulatory authorities (DRAs) of Myanmar and Vietnam The samples of unregistered products were sent to the DRAs of the countries of manufacture to confirm their registration and authenticity	Low risk Authentication of suspect samples was investigated by contacting the drug regulatory authority of the country of manufacture and the drug manufacturer Laboratory testing was done in the WHO collaborating laboratory to check the identity and content of the active pharmaceutical ingredients. Tests were carried out in accordance with the British and the United States pharmacopoeias.	Unclear risk Control for confounding factors not reported	Unclear risk The registration status of 45 (out of 214) drug samples could not be confirmed, hence were excluded from analysis
WHO, Nov. 2011[31]	High risk Limited laboratory capacity and funding for testing did not allow the use of “a standardized, randomized sampling procedure for	Unclear risk No information was provided on how the WHO-prequalification status of drugs was assessed	Low risk Drug samples were tested using standardized laboratory testing methods and specifications in accordance with established pharmacopoeias	Unclear risk Control for confounding variables not reported Samples were properly stored and transported to	Low risk 291 samples were collected and tested

	selection of sample collection sites or the selection of samples” A total of 291 samples were collected and tested.		The reliability of results was ensured by testing at reliable quality control laboratories Samples were tested for appearance, identity assay, related substances, dissolution, uniformity of mass, pH value, sterility, bacterial endotoxins	avoid quality deterioration before testing.	

Table S4: Risk of bias in the included RCT

Study Name	Sequence generation	Allocation concealment	Blinding (participants, data collectors, outcome adjudicators)	Completeness of outcome data	Completeness of outcome reporting
Syhakhang, Lundborg, Lindgren et al 2004[23]	Low risk "The names of the two districts in each pair were written on identical squares of paper, and one was drawn to give the active intervention district." "Sampling was made by numbering the pharmacies in the district and drawing numbered squares of paper from a box under the immediate supervision of the researchers."	Unclear risk Not reported	High risk "It was not possible to make the study blinded with regard to the main intervention vehicle, the district pharmacists." The research assistants were also "aware of the scope of the intervention. It could not be established to which extent the drug sellers had any active knowledge of the study objectives"	Low risk The baseline study reached 92% and the post-intervention study was 80% of the pharmacies in the original sample	Low risk No evidence of selective outcome reporting