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Counterfeit and substandard medicines: A systematic review of the literature

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ABSTRACT

Objective: To establish the extent of the problem of counterfeit and substandard medicines worldwide.

Design: Systematic review.

Data Sources: Databases used were Embase, Medline, PubMed and International Pharmaceutical Abstracts, including articles published till January 2013.

Eligibility criteria: Prevalence studies containing original data. WHO definitions (1992) used for counterfeit and substandard medicines.

Study appraisal and synthesis: Two reviewers independently scored study methodology against recommendations from the MEDQUARG Checklist. Studies were classified according to the World Bank classification of countries by income.

Data extraction: Data extracted for: place of the study; year of the study; type of drugs sampled; sample size; percentage of counterfeit/substandard medicines; dosage forms included; origin of the drugs and stated issues of counterfeit/substandard medicines.

Results: 44 prevalence studies identified, 15 found to have good methodological quality. These studies were conducted in 25 different countries; the majority (13) focussed on low-income countries (LIC) and/or lower-middle-income countries (LMIC). The median prevalence was similar in LIC and LMIC (24% and 38%). No individual data about the prevalence in upper-middle-income countries (UMIC) and high-income countries (HIC) was available. Antimicrobial drugs were the most extensively studied (13); antimalarials were the focus in two thirds (10). The majority of the studies contained samples with inadequate amount of active ingredients (93%), around half had samples with absence or excessive amounts of active ingredient. Only two studies included paediatric formulations and more than one third (77/210) of the samples tested were substandard.

Conclusion: There is a widespread use of counterfeit and substandard medicines throughout Africa and Asia in LIC and LMIC, more than a third of medicines available could be counterfeit and/or substandard. There are no published studies from UMIC and HIC countries.

Article summary

Article focus

- To systematically review the prevalence studies on counterfeit and substandard medicines published in the literature and to establish the extent of the problem worldwide.

Key messages

- There is a widespread use of counterfeit and/or substandard medicines throughout Africa and Asia in LIC and LMIC, a third of medicines available could be counterfeit and/or substandard.
- No evidence is available for UMIC and HIC countries.
- Antimicrobials are the most extensively studied group; little consideration has been given to other therapeutic classes or paediatric formulations.

Strengths and limitations of this study

- The article demonstrates a systematic review of prevalence studies on counterfeit and substandard medicines, with assessment of their quality before inclusion.
- This review is limited by searching only published work and methodology used in the included studies, such as sampling methods and assessment of single therapeutic classes.

INTRODUCTION

Counterfeiting in pharmaceutical products is an increasing problem worldwide, especially in lower income countries (LIC) and lower-middle-income countries (LMIC).[1] This kind of menace may affect patients in any part of the world in which drugs are used to treat life-threatening conditions. Even low-priced medicines simply taken to relieve pain are vulnerable to counterfeiting.[2]

Different organizations and agencies use a diverse range of definitions for counterfeiting; all of these definitions, however, imply that intent has been made to mislead the consumer.[3] The most widely used definition in the literature, in the last two decades, is that given in 1992 by the WHO.[4] The WHO defines a counterfeit medicine as a medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include any of the following: the correct ingredients, the wrong ingredients, no active ingredients, insufficient ingredients or fake packaging.[4] The WHO definition of substandard medicines states that these medicines are genuine medicines which have failed to pass the quality measurements and standards set for them. These quality standard tests have been derived from the official pharmacopoeias.[5]

The majority of the reviews, conducted during the last decade, comment on the lack of evidence available in the literature and the bias introduced into findings due to poor study methodology. Some focus on highlighting the major drug-quality surveys that have been conducted and their main findings,[6, 7] whilst others discuss the failure rate with respect to different quality tests or focus on specific drug groups such as antimalarials.[8, 9] The International Medical Products Anti-counterfeiting Taskforce (IMPACT) has estimated that the incidence of counterfeit medicines ranges from 1% in HIC to more than 30% in LIC and LMIC.[10] However, details on how these estimates were derived have not been provided. Thus, our objective is to explore and summarise the magnitude and the extent of the problem of counterfeit and substandard medicines by conducting a systematic review of prevalence studies published in the literature with assessment of their methodological quality before inclusion.

METHODS

A literature search has been carried out using the following medical databases: Embase (data range: 1974-January 2013), Medline (data range: 1948-January 2013), PubMed (data range: 1950- January 2013) and International Pharmaceutical Abstracts (data range: 1970- January 2013). The search terms used were 'fake', 'counterfeit', 'substandard' or 'falsified' and have been combined with 'drugs', 'medicines', 'pharmaceuticals', 'antimicrobials', 'antimalarials' or 'antibiotics' in order to retrieve any related articles. The search strategy is detailed in Table 1. The protocol was not registered. The review was performed in accordance with the PRISMA statement.[11]

The eligibility criteria were any studies that evaluated the prevalence of substandard or counterfeit medicines within a defined area. Studies which discussed analytical methods for the identification of these drugs as well as reviews, opinion papers, letters and comments were set as exclusion criteria.

Data collection process and data items

All abstracts were screened and evaluated against inclusion and exclusion criteria. Where there was a doubt or the abstract was not available, the full text was obtained to determine inclusion. Full articles were then retrieved for those considered suitable for inclusion and a manual search of the references was performed to identify additional relevant studies. The following data was extracted independently (TA) onto a data extraction form: place of the study; year of the study; type of drugs sampled; sample size; percentage of counterfeit/substandard medicines; dosage forms included; origin of the drugs and stated issues of counterfeit/substandard medicines. Study selection and data extraction were double-checked independently (HS) before inclusion. Studies were classified according to the World Bank classification of income level into the following: Low-income countries (LIC), Lower-middle-income countries (LMIC), Upper-middle-income countries (UMIC) and High-income countries (HIC).[12] Any study that contained information on more than one country was classified in the mixed group.

For studies that included paediatric formulations, the number of paediatric formulations and those that failed quality tests were extracted from the total number of formulations collected in each study. The number of medicines sampled and those that failed quality tests were also extracted from studies that included samples from licensed outlets (i.e. public and private sectors) and unlicensed outlets (i.e. informal markets).

Using the 1992 WHO definition of counterfeit drugs, the variation in the content of active ingredient is not necessarily indicative of counterfeiting. Therefore, forensic analysis of medicines has to be conducted to conclude whether they are substandard or counterfeit; and this involves comparing the suspected sample packaging and authenticity with genuine ones. Some authors did not attempt this step. Thus, it was unclear whether poor quality medications resulted from poor compliance with GMP or deliberate falsification of medicines. In this case, the terms substandard/counterfeit will be used whenever the reason for poor quality medications was unclear.

Quality evaluation assessment

Quality assessment of studies was conducted to try to minimise bias from the methodology used to collect data. The methodology of all identified studies were assessed against 12 criteria adapted from a previous published review (Box 1).[13] These criteria were given in the methodology section of the MEDQUARG (Medicine Quality Assessment Reporting Guidelines) Checklist of items to be addressed in reports of surveys of medicine quality. Two reviewers (TA and HS) independently performed the evaluation. If there was any disagreement level, an independent third person (IC) was consulted. As there has been no cut-off limit specified, all studies that scored 6 or more were included as a subset of the studies that have good methodological strength and therefore less chance of bias in their results.

Statistical analysis

The data was entered into Minitab (version 16). The median prevalence of these drugs was analysed for each income level group. Comparison of the prevalence in licensed (public and private sectors) and unlicensed (informal markets) outlets was

performed using the Fisher exact test for proportions. A significant difference was defined at P-value < 0.05.

RESULTS

A total of 44 studies of the prevalence of counterfeit and substandard medicines were identified. The number of articles screened and assessed is detailed in Figure 1. After independent assessment there was a 95% agreement level between the two assessors against the criteria specified for the quality assessment of study methodology (Box 1). No study fulfilled all 12 criteria. One study met 10 criteria whereas 29 studies met only 5 criteria or less (Figure 2). Fifteen studies fitted the pre specified criteria of scoring 6 or above[14-28] and were included in the analysis. They were conducted in 25 different countries and the majority, 13 studies (87%), assessed the quality of antimicrobial drugs. Antimalarial drugs were the most extensively studied group of medicines (10 studies). Two studies (13%) included other therapeutic agents, paracetamol, ranitidine, salbutamol, diazepam and analgesics, in their sampling process. Noteworthy, is that only two studies (13%) considered paediatric formulations (i.e. syrup and suspension) in their sampling process.

The studies were classified according to the income level of the country using the World Bank classification. Summaries of these studies are shown in Table 2. As some of these studies looked at prevalence in specific geographic areas, the prevalences are represented as a range, using the geographic region classifications of the World Bank (Table 3).

Study methodology

All studies were designed to select drug samples from a target geographical region. Five (33%) included public (i.e. pharmacy hospitals and primary health care centres), private and informal (i.e. market stalls and street sellers) sectors. Four (27%) studied both private and informal sectors, three (20%) private (i.e. community pharmacies) sector, two (13%) public and private sectors, and one (7%) study sampled just from the informal sector.

More than half of the studies used a convenience sampling method, in which investigators collected medicines from only accessible outlets. Only six studies used random sampling methods, in which investigators collected samples from outlets that were randomly chosen from a complete or registered list or outlets in a defined area.[15, 16, 18, 21, 25, 26] Information on the person collecting the samples was provided by 12 studies.[14, 16-22, 24-27] Samples in these studies were purchased by national collaborators, behaving as normal clients, in situations where the seller had no indication as to the purpose of the purchases.

Methods used for drugs analysis were variable according to the type of test, dosage form and drug analysed. Generally, analysis of these samples was carried out with regard to pharmacopoeia specifications. Non pharmacopoeial drugs were analysed in accordance with specifications and particular methods of their manufactures in order to evaluate the quality of these drugs.

Two studies only were designed to detect counterfeiting in the samples collected. One study was conducted in Africa [20] and one in Southeast Asia.[27] The prevalence of counterfeit drugs was 39% and 53%, respectively. The other studies were not designed to detect counterfeit medicines. However the possibility of counterfeiting was raised in five of these studies.[14, 16, 18, 21, 22]

The majority of the studies were conducted by investigators from different academic and research institutions (60%), 40% from multilateral organisations (e.g. WHO and UNICEF). The studies received their financial support from different recourses; namely: multilateral aid organisations (53%), national aid organisations (27%), academic and research institutions (13%), non-governmental organisations (7%).

Study location and prevalence of counterfeit and substandard medicines

The studies have been classified according to the World Bank classification of income level into three groups:

Studies in LIC in Asia and Africa: Four studies were conducted in four countries- Lao PDR, Cambodia, Tanzania and Uganda. The prevalence ranged from 12.2% to 44.5% (Median: 24%). Two studies attributed the poor quality medicines to substandard production (Table 4).

Studies in LMIC in Asia and Africa: Four studies have been identified (Table 5). Three studies were carried out in Africa and one in Asia. Reported prevalence in these studied ranged from 18% to 48 % (Median: 38%). One study reported poor quality medications to be a result of substandard manufacturing, whereas one study linked this issue to drug counterfeiting. The cause of this problem remained unclear in two studies.

Studies in mixed group: Seven studies discussed the problem of poorly compounded medications in 24 different Asian, African and Eastern European countries (11 LIC, 9 LMIC and 4 UMIC) (Table 6). The prevalence reported ranged from 11% to 44 % (Median: 28.5%). Substandard manufacturing was the reason for poorly compounded medications in five studies and one attributed to drug counterfeiting and substandard production. However, there was a doubt in one study regarding the reason behind low-quality medicines. No studies contained individual data from a high income country. Further statistical analysis was not performed due to the small number of studies in each group.

Stated issues of counterfeit and substandard medicines

The assessment of drugs was made through special procedures and methods derived from official pharmacopoeias. The most common issues with substandard and/or counterfeit drugs reported by these studies are shown in Table 7. Inadequate amount of active ingredients, as well as absent of active ingredients and excessive amount of active ingredients, were the most frequent problems reported.

Paediatric formulations tested

Two studies included syrup and suspension formulations in their sampling process (Table 8). More than one third of the 210 samples tested were substandard. Antimalarials were the only group of medicines studied. Both studies were conducted in Africa [21, 23] and their percentage failures were 19 and 48% respectively.

Prevalence according to where medicines are purchased

Where patients/parents purchase their medicines may affect the prevalence of substandard/counterfeit medicines. Five studies were identified in this review that sampled from licensed outlets (public and private sectors) and unlicensed outlets

(informal markets) (Table 9). The percentage of failed samples in unlicensed outlets was 51% whereas it was 24% in licensed outlets. The proportion of failed samples was significantly higher in the unlicensed markets (*p*=<0.000:95% CI 0.21-0.32). Further details on the individual failure rate in public and the private sectors were not given in these studies.

DISCUSSION

The aim of this systematic review was to summarise the current data in the literature regarding substandard/counterfeit medicines around the world. It has shown they are a significant problem, but most of the evidence is from Africa and Asia in LIC and LMIC. It is likely to be a problem in LIC and LMIC in other parts of the world, but there have been few studies outside these regions. The median prevalence reported in these studies was remarkably similar in both LIC and LMIC (24% and 38%). No individual data about the prevalence of these drugs in UMIC and HIC was available. Therefore the extent of the problem in these countries cannot be more clearly defined.

A recent commentary in the BMJ highlighted substandard medicines as a priority area in tropical diseases.[29] This review shows a high prevalence of substandard medicines in the countries affected by these diseases. Poor quality medicines may be highlighted by life threatening toxicities or high failure rates. Under-dosing of antimicrobials can enhance the survival of more resistant parasites and therefore emergence of drug resistance.[30, 31] There was strong evidence in our results of samples with an inadequate amount of active ingredient (93% of studies), absence of active ingredients (47%) and dissolution failure (33%), comparable with taking a medicine in low dose and therefore likely to cause treatment failure. In fact once 10% of patients fail treatment it is recommended by the WHO that there should be a change in malaria treatment policy.[32] The amount of substandard/counterfeit medicines in the supply chain needs to be considered prior to this happening. Studies to assess the direct link between counterfeit/substandard drugs and drug resistance however have not been documented.

There has been a growing concern regarding the safety of children's medications.[33, 34] Over the past few decades, over 300 children died as result of deliberate or inadvertent use of DEG, which is a potent nephrotoxic and neurotoxic poison, as a solvent in children's medications.[35] More than half of the patients who die of malaria in Africa are children under five years of age.[36] Poorly compounded paediatric formulations could have contributed, at least in part. Liquid formulations like syrups and suspensions are vulnerable to bacterial and fungal contaminations, if they are manufactured under poor GMP compliance.[37, 38] Our review of paediatric formulations shows that counterfeit and substandard medicines could be a serious problem for children, with more than a third failure rate in the small sample that has been tested. In some cases, laboratory investigation has revealed that counterfeit paediatric medicines have concentrations beyond all pharmacopeial limits.[21] More research is needed in this area.

Unofficial sale of drugs in LIC and LMIC is a common practice and considered a serious public health problem.[20, 39, 40] A survey carried out in Benin to explore different aspects of medicine purchasing behaviour was conducted on 600 randomly selected households.[39] The main outcome was that 86% of the individuals interviewed thought that drugs purchased from unauthorised markets were of a good quality.[39] Not unexpectedly, this review has shown that the prevalence of substandard and counterfeit drugs reported was significantly higher in the unauthorised market. This result might be clear for the majority of health care providers and drug regulatory authorities, but there is a need for an extensive campaign to educate people who do not understand the risk associated. The high cost of genuine drugs has been the main driving force for people to seek cheaper drugs from unauthorised markets.[20] Governments can play an important role in this matter by reducing taxes applied on medications as well as encouraging domestic manufacturing of good quality and affordable generic drugs.

A large proportion of the studies identified were found to have a poor methodological quality. Only 15 out of 44 studies identified met our quality inclusion criteria. "Convenience sampling" was often preferred and investigators collected samples haphazardly based on what outlets were accessible. This method is convenient and inexpensive, and gives an initial assessment of the problem faced (analogous to a case report), but is prone to bias and may not be representative of the target area

studied.[13] A more reliable and accurate measure involves an estimate of sample size and selection of a random number of outlets from a complete list from that area. Only six studies randomly selected from a complete list and only one calculated the sample size required.[15] Information on the person collecting the samples, what is said to retailers and the behaviour at collection sites is also very important, because if the seller realised the "customers" are a collection team for a drug quality survey (or linked to the drug regulatory authorities) this can affect their decision to offer counterfeit/substandard medicines for sale. "Mystery shoppers" are therefore the best sampling technique. Guidelines for survey of the quality of medicines have been published and give clear standards for future studies.[13]

Storage of medicines in inappropriate conditions, especially in tropical climates, may lead to early degradation of medicines.[41] Degraded medicines can be falsely attributed to substandard drug production and therefore may compound the prevalence. We have not found any study that tried to differentiate between these different types of quality defects. Attaran and colleagues have recently proposed a strengthened definition for substandard and counterfeit medicines, following a recent change in 2011 to the WHO definition.[3] This includes categories for substandard, unregistered and falsified medicines to more clearly define those that intentionally and unintentionally do not meet regulatory approval.[3] There are a number of international and national initiatives taking place, led by the WHO and its member states working group.[42 43]

Limitations and strengths

This review has a number of limitations including only searching published and accessible databases. Some reports were confidential, unpublished or published solely for limited distribution.[22] Some studies used different definitions and referred drug specifications to different pharmacopoeias. Furthermore, there have been inconsistencies in terms of drug sampling methods and the types of sector involved. All of these factors make direct comparison difficult. As antimicrobial drugs were the most extensively studied class of medicines, the prevalence of counterfeit and substandard drugs in other therapeutic classes remained unclear. In addition, data analysis and samples collected by investigators in some of these studies were not necessarily representative of a large target area, thus the prevalence obtained

cannot be extrapolated to the whole country studied. However, these studies give an insight into the problem, and following our assessment of methodology, give the best available evidence currently to assess the extent of the problem.

CONCLUSION

Counterfeit and substandard drugs represent a huge problem throughout Africa and Asia in LIC and LMIC, where the prevalence has been documented within studies. Antimicrobials, in their solid formulations, have been the most extensively studied group. Little consideration has been given to other therapeutic classes or paediatric formulations and this warrants further investigation. Well-designed prevalence studies, with adequate methodological details, are required to reflect the actual prevalence. The problem of counterfeit and substandard drugs in UMIC and HIC cannot be defined clearly as there are no relevant studies published in these countries.

Contributors:

TA and HS designed the search strategy. TA performed the literature search, screened the titles, abstracts and managed the references. HS independently double-checked the extracted data. TA and HS screened the retrieved papers against inclusion criteria and independently performed the quality evaluation assessment for the review. IC had the original idea for the study and interpreted the results. TA drafted the manuscript and IC and HS critically revised it. All authors approve of this final submitted version after their revision of the manuscript.

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Data sharing: No additional data available.

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Tables and Figures:

Table 1: Search strategy

No.	Searches	Results		
		Embase	Medline	International Pharmaceutical Abstract
1	Counterfeit*	477	296	301
2	Fake	631	491	22
3	Substandard	1017	874	78
4	Falsified	211	182	10
5	**1 or 2 or 3 or 4**	2230	1765	375
6	Drug*	2942573	1240863	248285
7	Medicine*	517065	379325	23766
8	Pharmaceutical*	62754	74697	47666
9	Antimicrobial*	61758	48954	7876
10	Antimalaria*	16651	14579	3147
11	Antibiotic*	311391	146476	24572
12	**6 or 7 or 8 or 9 or 10 or 11**	3520198	1708464	302874
13	**5 and 12**	833	522	346

Box 1. Quality assessment criteria

1. Timing and location of study clearly stated.
2. Definition of counterfeit or substandard medicines used mentioned.
3. Type of outlets sampled.
4. Sampling design and sample size calculation described.
5. Type and number of dosage units purchased per outlet.
6. Random sampling used.
7. Information on who collect the samples (Was mystery shoppers applied?)
8. Packaging assessment performed.
9. Statistical analysis described.
10. Chemical analysis clearly described.
11. Details on method validation.
12. Chemical analysis performed blinded to packaging.

Figure 1: Flow diagram of search and review process

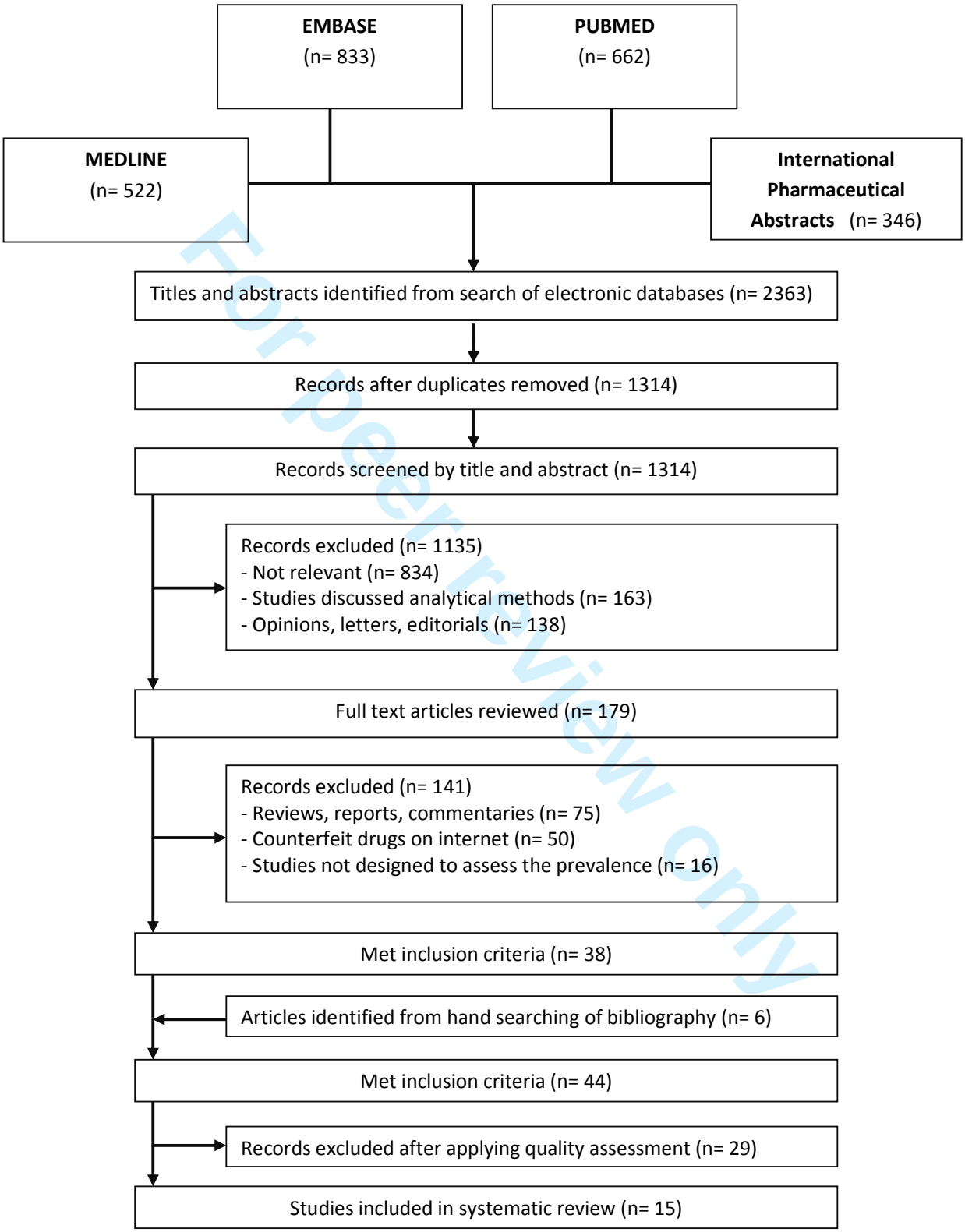

Figure 2: Quality assessment criteria for methodology of included studies

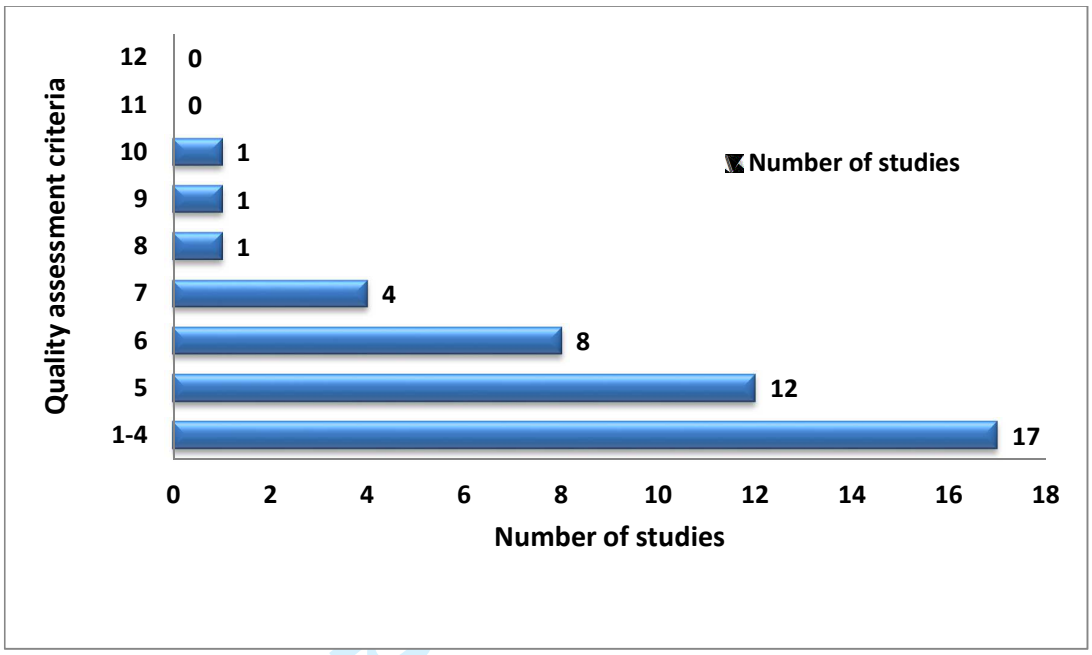

Table 2: The range of the prevalence of counterfeit and substandard medicines based on the World Bank classification of countries (by Income level)

Income Level Classification		Countries	Number of studies	Prevalence
				Range% (Median %)
Low-income countries		Lao PDR, Tanzania, Cambodia, Uganda	4	12.2 – 44.5 (24)
Lower-middle-income countries		Indonesia, Nigeria, Cameroon.	4	18 – 48 (38)
Upper-middle-income countries		0	0	----------
High-income countries		0	0	----------
Mixed group	LIC	Myanmar, Cambodia, Lao PDR, Ghana, Kenya, Tanzania, Uganda, Madagascar, Mali, Mozambique, Zimbabwe	7	11 – 44 (28.5)
	LMIC	Vietnam ,Thailand, Cameroon, Nigeria, Senegal, Sudan, Armenia, Ukraine, Uzbekistan		
	UMIC	Gabon, Azerbaijan, Belarus, Kazakhstan		
	HIC	0		

N.B: Mixed group represents the studies that have been carried out at more than one income level. **LIC**: low-income countries, **LMIC**: lower-middle-income countries, **UMIC**: upper-middle-income countries, **HIC**: high-income countries.

Table 3: The range of the prevalence of counterfeit and substandard medicines based on geographical regions

Geographic Region Classification	Countries	Number of studies	Prevalence
			Range% (Median %)
South Asia	Lao PDR, Cambodia, Indonesia, Myanmar, Vietnam, Thailand.	5	11 - 44 (22)
Europe and Central Asia	Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan	1	11.3
Latin America and the Caribbean	0	0	----------
Middle East	0	0	---------
Sub-Saharan Africa	Tanzania, Uganda, Nigeria, Cameroon, Ghana, Kenya, Madagascar, Senegal, Gabon, Mali, Mozambique, Sudan, Zimbabwe.	8	12.2 - 48 (34.5)
Mixed group	Nigeria, Thailand	1	36.5

N.B: Mixed group represents the studies that have been carried out in more than one geographic region.

Table 4: The prevalence of counterfeit and substandard medicines in low-income countries in Asia and Africa.

Country	Drugs (n=number of various products tested)	% substandard or counterfeit	Substandard/ counterfeit	Formulation studied	Labeled Origin	Stated problems	References	Methodological strength scoring (0-12)
Lao PDR	Ampicillin, tetracycline, Chloroquine and aspirin (n=300)	22	Substandard / counterfeit	Tablets and capsules	Laos, Thailand, France and unknown origin.	No active Ingredient, under/over concentration of active ingredient and weight variation outside approved limits	Syhakhang, Lundborg et al. 2004 [16]	10
Tanzania	Antimalarial drugs (sulfadoxine-pyrimethamine, sulfamethoxypyrazine-pyrimethamine, amodiaquine, quinine, artemisinin derivative (n=304)	12.2	Substandard	Tablets	Local and imported	Dissolution failure, Under concentration of active ingredient.	Kaur, Goodman et al. 2008[15]	9
Cambodia	Antimalarial drugs (Quinine, artesunate, mefloquine, chloroquine and tetracycline) (n=451)	27	Substandard / counterfeit	Tablets	16 countries	Failed in dissolution or under concentration of active ingredient ,no active ingredient, wrong active ingredient	Lon, Tsuyuoka et al. 2006[14]	6
Uganda	Chloroquine (n=92)	44.5	Substandard	Tablets, injection	Not stated	Under/over concentration of active ingredient.	Ogwal-Okeng, Owino et al. 2003[17]	6

Table 5: The prevalence of counterfeit and substandard medicines in low-middle-income countries in Asia and Africa.

Country	Drugs (n=number of various products tested)	% substandard or counterfeit	Substandard/ counterfeit	Formulation studied	Labelled Origin	Stated problems	References	Methodological strength scoring (0-12)
Indonesia	Amoxicillin, chloramphenicol, ciprofloxacin, cotrimoxazole, tetracycline. (n=104)	18	Substandard	Tablets, capsules	Indonesia	Under concentration of active ingredient	Hadi, van den Broek et al. 2010[19]	8
Nigeria	Artesunate, dihydroartemisinin, sulphadoxine-pyrimethamine, quinine and chloroquine (n=225)	37	Substandard / counterfeit	Tablets	Not stated	No active ingredient, wrong active ingredient, under concentration of active ingredient.	Onwujekwe, Kaur et al. 2009[18]	7
	Antimalarial drugs, antibacterials, antituberculosis, antihelmitics and antifungals (n = 581)	48	Substandard/ Counterfeit	Tablets, capsules, suspension and injection.	12 countries (Europe, Asia and Africa)	over/under concentration of active ingredient, no active ingredient	Taylor, Shakoor et al. 2001[21]	6
Cameroon	Antimalarial drugs (Antifolates, quinine, chloroquine) (n=284)	39.4	Counterfeit	Tablets, capsules	Not stated	No active ingredient, under concentration of active ingredient, wrong ingredient, unknown ingredien	Basco 2004[20]	6

Table 6: The prevalence of counterfeit and substandard medicines in the mixed group.

Country	Drugs (n=number of various products tested)	% substandard or counterfeit	Substandard/ counterfeit	Formulation studied	Labelled Origin	Stated problems	References	Methodological strength scoring (0-12)
Myanmar, Cambodia, Vietnam, Lao PDR, Thailand.	Artesunate and mefloquine (n=232)	44	Counterfeit (53%) and substandard (9%)	Tablets	China	Fake packaging, no active ingredient	Dondorp, Newton et al. 2004[27]	7
Cameroon, Ghana, Kenya, Nigeria, Tanzania	Antimalarial drugs (sulphadoxine-pyrimethamine, sulfamethoxypyrazine-pyrimethamine, artemisinin-based combination) (n=267)	28.5	Substandard	Tablets	Local and imported (India, USA, Bangladesh, China, Mauritius, Vietnam and the UK)	Over/under concentration of active ingredient, no active ingredient, tablet mass uniformity, impurity and dissolution failure	Sabartova, Toumi et al. 2011[25]	7
Uganda, Madagascar, Senegal	Antimalarial drugs (Artemisinin-based combination, sulphadoxine-pyrimethamine) (n=188)	32	Substandard	Tablets	Not stated	Dissolution failure, Impurity, Failure in the assay of active ingredient., uniformity test failure	USAID, DQI 2009[26]	7
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	Antimalarial drugs (chloroquine and sulphadoxine-pyrimethamine) (n = 278)	23% Range: 9% Sudan 41% Mali	Substandard	Tablets, syrup	Local and Imported	Under concentration	Maponga, Ondari 2003[23]	6
Myanmar (Burma) and Vietnam	Amoxicillin,ampicillin, metronidazole, paracetamol, salbutamol, tetracycline, chloroquine , chloramphenicol rifampicin and diazepam co-trimoxazole and ranitidine (n=500)	11	Substandard/ counterfeit	Tablets and capsules	More than 20 countries (Asia, Canada, Europe, USA and Australia)	Over/under concentration of active ingredient, wrong active ingredient	Wondemagegn-ehu 1999[22]	6

Table 6: continued

Country	Drugs (n=number of various products tested)	% substandard or counterfeit	Substandard/ counterfeit	Formulation studied	Labelled Origin	Stated problems	References	Methodological strength scoring (0-12)
Nigeria and Thailand	Chloroquine, amoxicillin, ampiclox cotrimoxazole, tetracycline, (n = 96)	36.5	Substandard	Tablets, capsules, suspension and injection.	Not stated	Over / under concentration of active ingredient	Shakoor, Taylor et al. 1997[24]	6
Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan	anti-tuberculosis medicines (n = 291)	11.3	Substandard	Tablets, capsules, injections	12 countries	Failure s in appearance, content, mass uniformity, dissolution and related substances tests	Sabartova, Nathanson et al. 2011[28]	6

Table 7: Frequency of six different issues reported concerning the quality of the medicines tested.

Stated Problem	Frequency of studies containing samples with stated problem	%
Inadequate amount of active ingredient	14	93
No active ingredient	7	47
Excessive amount of active ingredient	6	40
Dissolution failure	5	33
Wrong ingredient	4	27
Impurity	2	13

Table 8: Paediatric formulations tested

Country	Drugs (n=number of various products tested)	Formulation studied	Number of failed samples	% of failed samples	Substandard/ counterfeit	References
Nigeria	Antimicrobials (126)	syrups	61	48.4	Substandard/ Counterfeit	[21]
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	Chloroquine (n=84)	syrups	16	19	Substandard	[23]
Total	n= 210		77	36.6%		

Table 9: Percentage failure of samples collected at different sectors.

Country	Licensed outlets (Public and private sectors)			Unlicensed outlets (Informal market)			References
	Total number of Samples	Number of failed samples	% of failed samples	Total number of Samples	Number of failed samples	% of failed samples	
Cameroon, Ethiopia, Ghana, Kenya, Nigeria , Tanzania	240	64	26.6	27	12	44.4	[25]
Madagascar, Senegal, Uganda	144	41	28.4	53	23	43.4	[26]
Cambodia	38	22	58	133	100	75	[14]
Myanmar	215	34	16	23	20	87	[22]
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	229	52	23	136	37	27	[23]
Total	866	213	24	372	192	51	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 (not PRISMA registered)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table 1 & p5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5&6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6/ box 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6& 7

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency ($e.g., I^2$) for each meta-analysis.	5 & 6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6 & 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8,9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P 7/ figure 2, Methodological strength scoring was given for each study in tables 4-6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 4-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 2 and 3 & P 8&9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9/ table 8&9
DISCUSSION			

PRISMA 2009 Checklist

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10,11, 12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12, 13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Substandard and counterfeit medicines: A systematic review of the literature

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Secondary Subject Heading:	Infectious diseases, Health policy, Global health, Pharmacology and therapeutics
Keywords:	counterfeit drug, substandard drug, fake drug, anti-infective , drug counterfeiting

Substandard and counterfeit medicines: A systematic review of the literature

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Number of tables: 3 (4 online supplement)

Keywords: counterfeit drug, substandard drug, fake drug, anti-infective and drug counterfeiting.

ABSTRACT

Objective: To explore the evidence available of poor quality (counterfeit and substandard) medicines in the literature.

Design: Systematic review.

Data Sources: Databases used were Embase, Medline, PubMed and International Pharmaceutical Abstracts, including articles published till January 2013.

Eligibility criteria: Prevalence studies containing original data. WHO definitions (1992) used for counterfeit and substandard medicines.

Study appraisal and synthesis: Two reviewers independently scored study methodology against recommendations from the MEDQUARG Checklist. Studies were classified according to the World Bank classification of countries by income.

Data extraction: Data extracted : place of study; type of drugs sampled; sample size; percentage of substandard/counterfeit medicines; formulations included; origin of the drugs; chemical analysis and stated issues of counterfeit/substandard medicines.

Results: 44 prevalence studies were identified, 15 had good methodological quality. They were conducted in 25 different countries; the majority in low-income countries (11) and/or lower-middle-income countries (10). The median prevalence of substandard/counterfeit medicines was 28.5% (range: 11- 48%). Only 2 studies differentiated between substandard and counterfeit medicines. Prevalence data was limited to antimicrobial drugs (all 15 studies). Thirteen studies involved antimalarials, six antibiotics and two other medications. The majority of studies (93%) contained samples with inadequate amount of active ingredients. The prevalence of substandard/counterfeit antimicrobials was significantly higher when purchased from unlicensed outlets (p=<0.000:95% CI 0.21-0.32). No individual data about the prevalence in upper-middle-income countries and high-income countries was available.

Limitations: Studies with strong methodology were few. The majority did not differentiate between substandard and counterfeit medicines. Most studies assessed only a single therapeutic class, antimicrobials.

Conclusion: The prevalence of poor quality antimicrobial medicines is widespread throughout Africa and Asia in LIC and LMIC. Inadequate amount of the active ingredients was the main problem identified.

Article summary

Article focus

To systematically review prevalence studies on substandard and counterfeit medicines published in the literature.

Key messages

- The prevalence of substandard/counterfeit antimicrobials is high throughout Africa and Asia in LIC and LMIC.
- The prevalence of substandard/counterfeit medicines was significantly higher in the unlicensed markets.
- Inadequate amount of the active ingredients was the largest problem identified.

Strengths and limitations of this study

- The article demonstrates a systematic review of prevalence studies on substandard/counterfeit medicines, with assessment of their quality before inclusion.
- This review is limited by the methodology used in the included studies, such as sampling methods, the assessment of a single therapeutic class (antimicrobial drugs), as well as scarce packaging analysis data to differentiate between counterfeit and substandard medicines.

INTRODUCTION

Counterfeiting in pharmaceutical products is an increasing worldwide dilemma with a profound impact on lower income countries (LIC) and lower-middle-income countries (LMIC).[1, 2] It is also becoming an issue in high income countries (HIC).[3-5]

There is no clear, agreed international definition of counterfeit medicines.[6] The most widely used definition in the literature, in the last two decades, is that given in 1992 by the WHO.[7] This defines a counterfeit medicine as a medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include: the correct ingredients, the wrong ingredients, no active ingredients, insufficient ingredients or fake packaging (i.e. misleading about its origin or authenticity).[7] Substandard medicines are defined as genuine medicines which have failed to pass the quality measurements and standards set for them. These quality standard tests have been derived from the official pharmacopoeias.[8] In 2011, WHO member states chose to include counterfeit and substandard medicines under the new term "substandard/spurious/falsely-labeled/falsified/counterfeit medical products" (SSFFC). This new term however has been questioned recently [6] as it is felt not to distinguish sufficiently between the different illegitimate drugs categories (such as counterfeit and substandard) that require different monitoring and solutions.

According to The Pharmaceutical Security Institute data, the incidents of counterfeit medicines increased dramatically from 196 incidents in 2002 to 2018 incidents in 2012.[9] The data is, in part, a reflection of adequate law enforcement and regulatory oversight in countries where these reports came from.[10] However, this figure would be even higher if resource-poor countries had adequate surveillance systems. Drug regulatory authorities and pharmaceutical companies hold records on counterfeit medicines, yet most are inaccessible.[6, 10] More insight into the problem can be gained from prevalence studies published in the literature.[10] Thus our objective was to systematically review prevalence studies published in the literature.

METHODS

A literature search was carried out using the following medical databases: Embase (data range: 1974-January 2013), Medline (data range: 1948-January 2013), PubMed (data range: 1950- January 2013) and International Pharmaceutical Abstracts (data range: 1970- January 2013). A preliminary search for MeSH terms associated with published prevalence studies were conducted trying to choose the most specific and sensitive words for the search strategy. Specific therapeutic areas, such as antimalarials, were recognised and added as additional terms to increase sensitivity; the search however was not limited to these categories. The search terms included: 'fake', 'counterfeit', 'substandard' or 'falsified' and have been combined with 'drugs', 'medicines', 'pharmaceuticals', 'antimicrobials', 'antimalarials' or 'antibiotics'. The search strategy is detailed in supplementary table 1. The review was performed in accordance with the PRISMA statement.[11]

The eligibility criteria were any studies (irrespective of language) that evaluated the prevalence of substandard or counterfeit medicines within a defined area. Studies which discussed analytical methods for the identification of these drugs as well as reviews, opinion papers, letters and comments were set as exclusion criteria.

Data collection process and data items

All abstracts were screened and evaluated against the inclusion and exclusion criteria. Where there was a doubt or the abstract was not available, the full text was obtained to determine inclusion. Full articles were then retrieved and a manual search of the references was performed. The following data was extracted independently (TA): place of the study; type of drugs sampled; sample size; percentage of counterfeit/substandard medicines; dosage forms included; chemical analysis; origin of the drugs and stated issues of substandard/counterfeit medicines (defined in online supplementary table 2). The number of medicines sampled and those that failed quality tests were also extracted from studies that included samples from licensed outlets (i.e. public and private sectors) and unlicensed outlets (i.e. informal markets). Study selection and data extraction were double-checked independently (HS) before inclusion.

Studies were classified according to the World Bank classification of income level into the following: Low-income countries (LIC), Lower-middle-income countries (LMIC), Upper-middle-income countries (UMIC) and High-income countries (HIC).[12] Any study that contained information on more than one country was classified in the mixed group.

Substandard and counterfeit medicines are both recognised as poor-quality medicines. Chemical and packaging analysis is required to conclude if a medicine is substandard or counterfeit. This however is difficult and rarely reported.[13] Therefore, the term substandard/counterfeit medicine is used in this review unless studies formally assessed packaging to differentiate medicines into these two different categories.

Quality evaluation assessment

Quality assessment of studies was conducted to try to minimise bias from the methodology used to collect data. The methodology of all identified studies were assessed against 12 criteria adapted from a previous published review (Box 1).[14] These criteria were given in the methodology section of the MEDQUARG (Medicine Quality Assessment Reporting Guidelines) Checklist of items to be addressed in reports of surveys of medicine quality. Two reviewers (TA and HS) independently performed the evaluation. If there was any disagreement level, an independent third person (IC) was consulted. As there has been no cut-off limit specified, all studies that scored 6 or more were included as a subset of the studies that have good methodological strength and therefore less chance of bias in their results.

Statistical analysis

The median prevalence of substandard/counterfeit medicines was analysed for each income level group. Comparison of the prevalence in licensed (public and private sectors) and unlicensed (informal markets) outlets was performed using the Fisher exact test for proportions. A significant difference was defined at P-value < 0.05.

RESULTS

A total of 44 studies of the prevalence of substandard/counterfeit medicines were identified. The number of articles screened and assessed is detailed in Figure 1. After independent assessment there was a 95% agreement level between the two assessors against the criteria specified for the quality assessment of study methodology (Box 1). No study fulfilled all 12 criteria. One study met 10 criteria whereas 29 studies met only 5 criteria or less (Figure 2 and supplementary Table 3). Fifteen studies fitted the pre specified criteria of scoring 6 or above[15-29] and were included in the analysis.

Study methodology

All studies were designed to select drug samples from a target geographical region. These included drugs sampled from public (i.e. pharmacy hospitals and primary health care centres), private and/or informal (i.e. market stalls and street sellers) sectors (supplementary table 4).

More than half of the studies used a convenience sampling method, in which investigators collected medicines from only accessible outlets. Only four studies used random sampling methods, in which investigators collected samples from outlets that were randomly chosen from a complete or registered list or outlets in a defined area.[16, 17, 19, 22] Information on the person collecting the samples was provided by 12 studies.[15, 17-23, 25-28] Samples in these studies were purchased by national collaborators, behaving as normal clients, in situations where the seller had no indication as to the purpose of the purchases.

Methods used for drugs analysis were variable according to the type of test, dosage form and drug analysed. Generally, analysis of these samples was carried out with regard to pharmacopoeia specifications (supplementary table 4). Non pharmacopoeial drugs were analysed in accordance with specifications and particular methods of their manufactures in order to evaluate the quality of these drugs.

The majority of the studies were conducted by investigators from different academic and research institutions (60%), 40% from multilateral organisations (e.g. WHO and UNICEF).

Overview of the studies and prevalence of substandard/counterfeit medicines

The 15 studies were conducted in 25 different countries mainly from Africa and Asia. Twenty one were either LIC or LMIC. All 15 studies assessed the quality of antimicrobial drugs. Antimalarial drugs were the most extensively studied group of medicines (13 studies). Six studies included antibiotics and two studies included other therapeutic agents, paracetamol, ranitidine, salbutamol, diazepam and analgesics, in their sampling process.[17, 23] Only two studies considered paediatric formulations (i.e. syrup and suspension) in their sampling process. [22, 24]

The median prevalence of substandard/counterfeit medicines was 28.5% (range: 11-48%). The median prevalence of substandard/counterfeit medicines for each income level was similar in LIC (24%), LMIC (38%) and the mixed group (28.5%) (Table 1). The majority of the studies (8) were conducted in sub-Saharan Africa, where the prevalence of substandard/counterfeit medicines ranged from 12.2 to 48% (median 34%). This was similar in the five studies conducted in South Asia, range 11-44% (median 22%). This prevalence is mainly representative of antimicrobial drugs, as these accounted for the bulk of the tested samples. Details for each individual study are given in supplementary table 4.

Counterfeit medicines

Only two studies from Southeast Asia performed packaging analysis of the samples collected.[15, 28] The prevalence of counterfeit drugs was 16% and 43% of antimalarials, respectively. The other studies were not designed to detect counterfeit medicines. However the possibility of counterfeiting was raised in five of these studies as some of samples had the wrong or no active ingredients.[17, 19, 21-23]

Stated issues of substandard/counterfeit medicines

The assessment of drugs was made through special procedures and methods derived from official pharmacopoeias. The most common issues with substandard/counterfeit drugs reported by these studies are shown in Table 2. Inadequate amount of active ingredients was the most frequent problem reported.

Prevalence according to where medicines are purchased

Where patients purchase their medicines may affect the prevalence of substandard/counterfeit medicines. Five studies were identified in this review that sampled from licensed outlets (public and private sectors) and unlicensed outlets (informal markets) (Table 3). Four of these studies concerned antimalarials,[15, 24, 26, 27] and one antibiotics.[23] The percentage of failed samples in unlicensed outlets was 51% whereas it was 24% in licensed outlets. The proportion of failed samples was significantly higher in the unlicensed markets (*p*=<0.000:95% CI 0.21-0.32). Further details on the individual failure rate in public and the private sectors were not given in these studies.

DISCUSSION

The aim of this systematic review was to summarise the current data in the literature regarding substandard/counterfeit medicines around the world. The results have shown that there is a significant problem in Africa and Asia, in LIC and LMIC, regarding antimicrobial medicines. Our findings highlight the lack of studies that exist outside of these regions and therapeutic classes. It also shows the lack of evidence available that specifically differentiates between substandard and counterfeit medicines. No individual data about the prevalence of these drugs in UMIC and HIC was available.

Our review shows a high prevalence of poor quality antimicrobials. Most of the prevalence studies focused on antimicrobial medicines because of the considerable burden of infectious diseases in the study countries. This in keeping with a recent commentary in the BMJ that highlighted substandard medicines as a priority area in tropical diseases.[30] Under-dosing of antimicrobials can enhance the survival of more resistant parasites and therefore emergence of drug resistance.[31, 32] There was strong evidence in our results of samples with an inadequate amount of active ingredient (93% of studies), absence of active ingredients (47%) and dissolution failure (33%), comparable with taking a medicine in low dose and therefore likely to cause treatment failure. If 10% of patients fail treatment, it is recommended by the WHO that there should be a change in malaria treatment policy.[33] The amount of

substandard/counterfeit medicines in the supply chain needs to be considered prior to this happening. Studies to assess the direct link between substandard/counterfeit drugs and drug resistance however have not been documented.

This review has shown that the prevalence of substandard/counterfeit antimicrobials reported was significantly higher in the unauthorised market. Unofficial sale of drugs in LIC and LMIC is a common practice and considered a serious public health problem.[21, 34] A survey carried out in Benin found that 86% of individuals interviewed thought that drugs purchased from unauthorised markets were of a good quality.[(34)] The high cost of genuine drugs has been the main driving force for people to seek cheaper drugs from unauthorised markets.[21] Governments can play an important role in this matter by reducing taxes applied on medications as well as encouraging domestic manufacturing of good quality and affordable generic drugs.[35, 36]

A large proportion of the studies identified were found to have a poor methodological quality. Only 15 out of 44 studies identified met our quality inclusion criteria. “Convenience sampling” was often preferred and investigators collected samples haphazardly based on what outlets were accessible. This method is convenient and inexpensive, and gives an initial assessment of the problem faced (analogous to a case report), but is prone to bias and may not be representative of the target area studied.[14] A more reliable and accurate measure involves an estimate of sample size and selection of a random number of outlets from a complete list from that area. Only four studies randomly selected from a complete list and only one calculated the sample size required.[16] Information on the person collecting the samples, what is said to retailers and the behaviour at collection sites is also important, because if the seller realises the “customers” are performing a drug quality survey this can affect their decision to offer substandard/counterfeit medicines for sale. Guidelines for surveys of the quality of medicines have been published and give clear standards for future studies.[14]

There are a number of international and national initiatives taking place to combat the problem of counterfeit and substandard medicines. INTERPOL, in cooperation with the World Customs Organisation (WCO), International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and WHO, is working with national police forces in combating the illicit trade of medicines, targeting both illicit physical and online

outlets.[37, 38] The Container Control Programme (CCP) established by the United Nations Office on Drugs and Crime (UNDOC) and WCO, to enhance inspection of containers for counterfeit goods, has become an important tool to counteract the traffic of counterfeit drugs.[39] Recently, member states of the WHO have agreed on a new mechanism to tackle not only the problem of SSFFC but also to ensure the availability of quality, safe, efficacious and affordable medical products.[40, 41] However, more collaboration between different national and international organisations is needed to counteract this problem.

Limitations and strengths

This review has a number of limitations including only searching published and accessible databases. Some reports were confidential, unpublished or published solely for limited distribution.[23] Some studies used different definitions and referred drug specifications to different pharmacopoeias. Furthermore, there have been inconsistencies in terms of drug sampling methods and the types of sector involved. All of these factors make direct comparison difficult. Packaging analysis is important to confirm if a medicine is counterfeit or substandard. There is currently scarce data to measure the prevalence of each problem individually. This is important as the causes and remedies are different. All of the studies involved antimicrobials. The prevalence of counterfeit and substandard drugs in other therapeutic classes, therefore, remained unclear. In addition, data analysis and samples collected by investigators in some of these studies were not necessarily representative of a large target area, thus the prevalence obtained cannot be extrapolated to the whole country studied. However, these studies give an insight into the problem, and following our assessment of methodology, give the best available evidence currently in the literature.

CONCLUSION

Substandard/counterfeit antimicrobial drugs represent a huge problem throughout Africa and Asia in LIC and LMIC, where the prevalence has been documented within studies. Antimicrobials, in their solid formulations, have been the most extensively studied group. Inadequate amount of the active ingredients was the main problem

identified. Little consideration has been given to other therapeutic classes or paediatric formulations and this warrants further investigation. Well-designed prevalence studies, with adequate methodological details, are required indeed to reflect the actual prevalence.

Contributors:

TA and HS designed the search strategy. TA performed the literature search, screened the titles, abstracts and managed the references. HS independently double-checked the extracted data. TA and HS screened the retrieved papers against inclusion criteria and independently performed the quality evaluation assessment for the review. IC had the original idea for the study and interpreted the results. TA drafted the manuscript and IC and HS critically revised it. All authors approve of this final submitted version after their revision of the manuscript.

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Tables and Figures:

Box 1. Quality assessment criteria

1. Timing and location of study clearly stated.
2. Definition of counterfeit or substandard medicines used mentioned.
3. Type of outlets sampled.
4. Sampling design and sample size calculation described.
5. Type and number of dosage units purchased per outlet.
6. Random sampling used.
7. Information on who collected the samples (were mystery shoppers applied?)
8. Packaging assessment performed.
9. Statistical analysis described.
10. Chemical analysis clearly described.
11. Details on method validation.
12. Chemical analysis performed blinded to packaging.

Figure 1: Flow diagram of search and review process

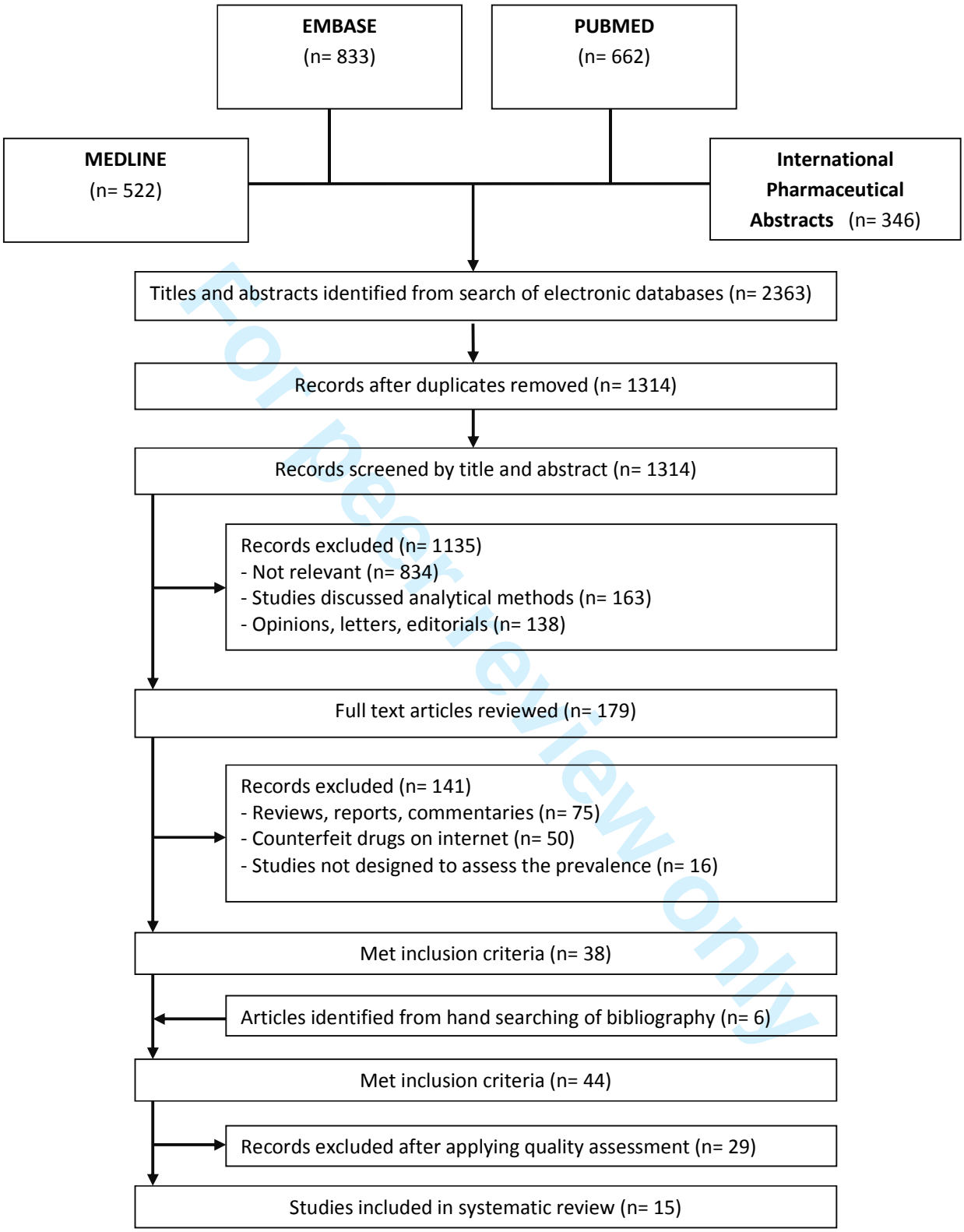

Figure 2: Quality assessment criteria for methodology of included studies

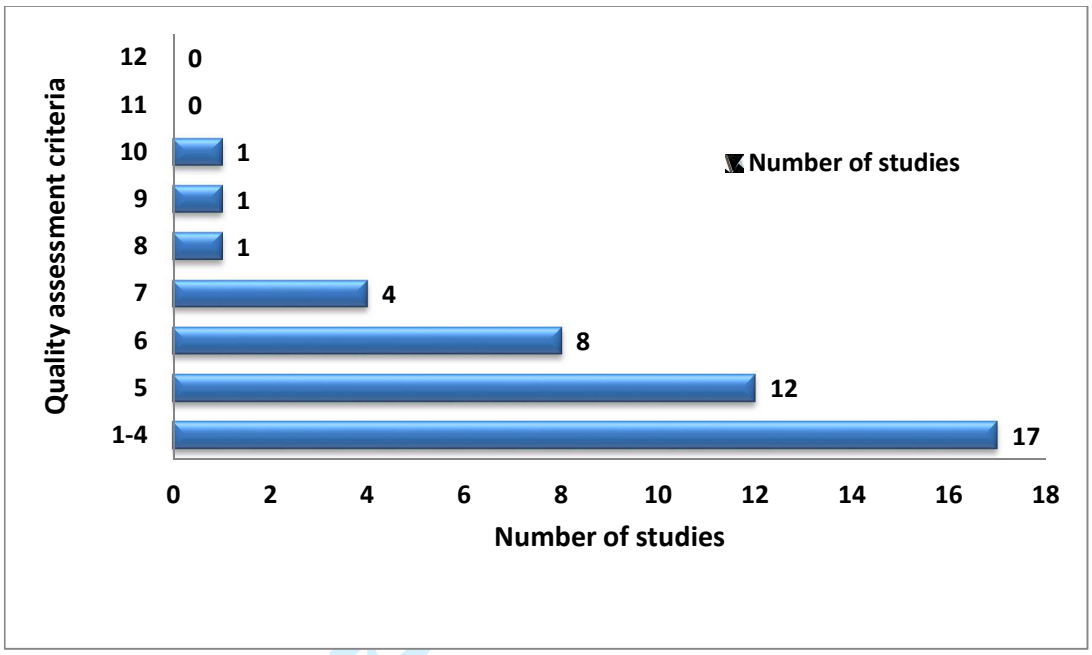

Table 1: The range of the prevalence of counterfeit and substandard medicines based on the World Bank classification of countries (by Income level)

Income Level Classification		Countries	Number of studies	Prevalence of substandard/counterfeit medicines
				Range% (Median %)
Low-income countries		Lao PDR, Tanzania, Cambodia, Uganda	4	12.2 – 44.5 (24)
Lower-middle-income countries		Indonesia, Nigeria, Cameroon.	4	18 – 48 (38)
Upper-middle-income countries		0	0	----------
High-income countries		0	0	----------
Mixed group	LIC	Myanmar, Cambodia, Lao PDR, Ghana, Kenya, Tanzania, Uganda, Madagascar, Mali, Mozambique, Zimbabwe	7	11 – 44 (28.5)
	LMIC	Vietnam ,Thailand, Cameroon, Nigeria, Senegal, Sudan, Armenia, Ukraine, Uzbekistan		
	UMIC	Gabon, Azerbaijan, Belarus, Kazakhstan		
	HIC	0		

N.B: Mixed group represents the studies that have been carried out at more than one income level. **LIC**: low-income countries, **LMIC**: lower-middle-income countries, **UMIC**: upper-middle-income countries, **HIC**: high-income countries.

Table 2: Frequency of six different issues reported concerning the quality of the medicines tested.

Stated Problem	Frequency of studies containing samples with stated problem	%
Inadequate amount of active ingredient	14	93
No active ingredient	7	47
Excessive amount of active ingredient	6	40
Dissolution failure	5	33
Wrong ingredient	4	27
Impurity	2	13

Table 3: Percentage failure of samples collected at different sectors.

Country	Licensed outlets (Public and private sectors)			Unlicensed outlets (Informal market)			References
	Total number of Samples	Number of failed samples	% of failed samples	Total number of Samples	Number of failed samples	% of failed samples	
Cameroon, Ethiopia, Ghana, Kenya, Nigeria , Tanzania	240	64	26.6	27	12	44.4	(26)
Madagascar, Senegal, Uganda	144	41	28.4	53	23	43.4	(27)
Cambodia	38	22	58	133	100	75	(15)
Myanmar	215	34	16	23	20	87	(23)
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	229	52	23	136	37	27	(24)
Total	866	213	24	372	192	51	

Substandard and counterfeit medicines: A systematic review of the literature

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ABSTRACT

Objective: To explore the evidence available of poor quality (counterfeit and substandard) medicines in the literature.

Design: Systematic review.

Data Sources: Databases used were Embase, Medline, PubMed and International Pharmaceutical Abstracts, including articles published till January 2013.

Eligibility criteria: Prevalence studies containing original data. WHO definitions (1992) used for counterfeit and substandard medicines.

Study appraisal and synthesis: Two reviewers independently scored study methodology against recommendations from the MEDQUARG Checklist. Studies were classified according to the World Bank classification of countries by income.

Data extraction: Data extracted : place of study; type of drugs sampled; sample size; percentage of substandard/counterfeit medicines; formulations included; origin of the drugs; chemical analysis and stated issues of counterfeit/substandard medicines.

Results: 44 prevalence studies were identified, 15 had good methodological quality. They were conducted in 25 different countries; the majority in low-income countries (11) and/or lower-middle-income countries (10). The median prevalence of substandard/counterfeit medicines was 28.5% (range: 11- 48%). Only 2 studies differentiated between substandard and counterfeit medicines. Prevalence data was limited to antimicrobial drugs (all 15 studies). Thirteen studies involved antimalarials, six antibiotics and two other medications. The majority of studies (93%) contained samples with inadequate amount of active ingredients. The prevalence of substandard/counterfeit antimicrobials was significantly higher when purchased from unlicensed outlets (*p*=<0.000:95% CI 0.21-0.32). No individual data about the prevalence in upper-middle-income countries and high-income countries was available.

Limitations: Studies with strong methodology were few. The majority did not differentiate between substandard and counterfeit medicines. Most studies assessed only a single therapeutic class, antimicrobials.

Conclusion: The prevalence of poor quality antimicrobial medicines is widespread throughout Africa and Asia in LIC and LMIC. Inadequate amount of the active ingredients was the main problem identified.

Article summary

Article focus

To systematically review prevalence studies on substandard and counterfeit medicines published in the literature.

Key messages

- The prevalence of substandard/counterfeit antimicrobials is high throughout Africa and Asia in LIC and LMIC.
- The prevalence of substandard/counterfeit medicines was significantly higher in the unlicensed markets.
- Inadequate amount of the active ingredients was the largest problem identified.

Strengths and limitations of this study

- The article demonstrates a systematic review of prevalence studies on substandard/counterfeit medicines, with assessment of their quality before inclusion.
- This review is limited by the methodology used in the included studies, such as sampling methods, the assessment of a single therapeutic class (antimicrobial drugs), as well as scarce packaging analysis data to differentiate between counterfeit and substandard medicines.

INTRODUCTION

Counterfeiting in pharmaceutical products is an increasing worldwide dilemma with a profound impact on lower income countries (LIC) and lower-middle-income countries (LMIC).[1, 2] It is also becoming an issue in high income countries (HIC).[3-5]

There is no clear, agreed international definition of counterfeit medicines.[6] The most widely used definition in the literature, in the last two decades, is that given in 1992 by the WHO.[7] This defines a counterfeit medicine as a medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include: the correct ingredients, the wrong ingredients, no active ingredients, insufficient ingredients or fake packaging (i.e. misleading about its origin or authenticity).[7] Substandard medicines are defined as genuine medicines which have failed to pass the quality measurements and standards set for them. These quality standard tests have been derived from the official pharmacopoeias.[8] In 2011, WHO member states chose to include counterfeit and substandard medicines under the new term "substandard/spurious/falsely-labeled/falsified/counterfeit medical products" (SSFFC). This new term however has been questioned recently [6] as it is felt not to distinguish sufficiently between the different illegitimate drugs categories (such as counterfeit and substandard) that require different monitoring and solutions.

According to The Pharmaceutical Security Institute data, the incidents of counterfeit medicines increased dramatically from 196 incidents in 2002 to 2018 incidents in 2012.[9] The data is, in part, a reflection of adequate law enforcement and regulatory oversight in countries where these reports came from.[10] However, this figure would be even higher if resource-poor countries had adequate surveillance systems. Drug regulatory authorities and pharmaceutical companies hold records on counterfeit medicines, yet most are inaccessible.[6, 10] More insight into the problem can be gained from prevalence studies published in the literature.[10] Thus our objective was to systematically review prevalence studies published in the literature.

METHODS

A literature search was carried out using the following medical databases: Embase (data range: 1974-January 2013), Medline (data range: 1948-January 2013), PubMed (data range: 1950- January 2013) and International Pharmaceutical Abstracts (data range: 1970- January 2013). A preliminary search for MeSH terms associated with published prevalence studies were conducted trying to choose the most specific and sensitive words for the search strategy. Specific therapeutic areas, such as antimalarials, were recognised and added as additional terms to increase sensitivity; the search however was not limited to these categories. The search terms included: 'fake', 'counterfeit', 'substandard' or 'falsified' and have been combined with 'drugs', 'medicines', 'pharmaceuticals', 'antimicrobials', 'antimalarials' or 'antibiotics'. The search strategy is detailed in supplementary table 1. The review was performed in accordance with the PRISMA statement.[11]

The eligibility criteria were any studies (irrespective of language) that evaluated the prevalence of substandard or counterfeit medicines within a defined area. Studies which discussed analytical methods for the identification of these drugs as well as reviews, opinion papers, letters and comments were set as exclusion criteria.

Data collection process and data items

All abstracts were screened and evaluated against the inclusion and exclusion criteria. Where there was a doubt or the abstract was not available, the full text was obtained to determine inclusion. Full articles were then retrieved and a manual search of the references was performed. The following data was extracted independently (TA): place of the study; type of drugs sampled; sample size; percentage of counterfeit/substandard medicines; dosage forms included; chemical analysis; origin of the drugs and stated issues of substandard/counterfeit medicines (defined in online supplementary table 2). The number of medicines sampled and those that failed quality tests were also extracted from studies that included samples from licensed outlets (i.e. public and private sectors) and unlicensed outlets (i.e. informal markets). Study selection and data extraction were double-checked independently (HS) before inclusion.

Studies were classified according to the World Bank classification of income level into the following: Low-income countries (LIC), Lower-middle-income countries (LMIC), Upper-middle-income countries (UMIC) and High-income countries (HIC).[12] Any study that contained information on more than one country was classified in the mixed group.

Substandard and counterfeit medicines are both recognised as poor-quality medicines. Chemical and packaging analysis is required to conclude if a medicine is substandard or counterfeit. This however is difficult and rarely reported.[13] Therefore, the term substandard/counterfeit medicine is used in this review unless studies formally assessed packaging to differentiate medicines into these two different categories.

Quality evaluation assessment

Quality assessment of studies was conducted to try to minimise bias from the methodology used to collect data. The methodology of all identified studies were assessed against 12 criteria adapted from a previous published review (Box 1).[14] These criteria were given in the methodology section of the MEDQUARG (Medicine Quality Assessment Reporting Guidelines) Checklist of items to be addressed in reports of surveys of medicine quality. Two reviewers (TA and HS) independently performed the evaluation. If there was any disagreement level, an independent third person (IC) was consulted. As there has been no cut-off limit specified, all studies that scored 6 or more were included as a subset of the studies that have good methodological strength and therefore less chance of bias in their results.

Statistical analysis

The median prevalence of substandard/counterfeit medicines was analysed for each income level group. Comparison of the prevalence in licensed (public and private sectors) and unlicensed (informal markets) outlets was performed using the Fisher exact test for proportions. A significant difference was defined at P-value < 0.05.

RESULTS

A total of 44 studies of the prevalence of substandard/counterfeit medicines were identified. The number of articles screened and assessed is detailed in Figure 1. After independent assessment there was a 95% agreement level between the two assessors against the criteria specified for the quality assessment of study methodology (Box 1). No study fulfilled all 12 criteria. One study met 10 criteria whereas 29 studies met only 5 criteria or less (Figure 2 and supplementary Table 3). Fifteen studies fitted the pre specified criteria of scoring 6 or above[15-29] and were included in the analysis.

Study methodology

All studies were designed to select drug samples from a target geographical region. These included drugs sampled from public (i.e. pharmacy hospitals and primary health care centres), private and/or informal (i.e. market stalls and street sellers) sectors (supplementary table 4).

More than half of the studies used a convenience sampling method, in which investigators collected medicines from only accessible outlets. Only four studies used random sampling methods, in which investigators collected samples from outlets that were randomly chosen from a complete or registered list or outlets in a defined area.[16, 17, 19, 22] Information on the person collecting the samples was provided by 12 studies.[15, 17-23, 25-28] Samples in these studies were purchased by national collaborators, behaving as normal clients, in situations where the seller had no indication as to the purpose of the purchases.

Methods used for drugs analysis were variable according to the type of test, dosage form and drug analysed. Generally, analysis of these samples was carried out with regard to pharmacopoeia specifications (supplementary table 4). Non pharmacopoeial drugs were analysed in accordance with specifications and particular methods of their manufactures in order to evaluate the quality of these drugs.

The majority of the studies were conducted by investigators from different academic and research institutions (60%), 40% from multilateral organisations (e.g. WHO and UNICEF).

Overview of the studies and prevalence of substandard/counterfeit medicines

The 15 studies were conducted in 25 different countries mainly from Africa and Asia. Twenty one were either LIC or LMIC. All 15 studies assessed the quality of antimicrobial drugs. Antimalarial drugs were the most extensively studied group of medicines (13 studies). Six studies included antibiotics and two studies included other therapeutic agents, paracetamol, ranitidine, salbutamol, diazepam and analgesics, in their sampling process.[17, 23] Only two studies considered paediatric formulations (i.e. syrup and suspension) in their sampling process. [22, 24]

The median prevalence of substandard/counterfeit medicines was 28.5% (range: 11-48%). The median prevalence of substandard/counterfeit medicines for each income level was similar in LIC (24%), LMIC (38%) and the mixed group (28.5%) (Table 1). The majority of the studies (8) were conducted in sub-Saharan Africa, where the prevalence of substandard/counterfeit medicines ranged from 12.2 to 48% (median 34%). This was similar in the five studies conducted in South Asia, range 11-44% (median 22%). This prevalence is mainly representative of antimicrobial drugs, as these accounted for the bulk of the tested samples. Details for each individual study are given in supplementary table 4.

Counterfeit medicines

Only two studies from Southeast Asia performed packaging analysis of the samples collected.[15, 28] The prevalence of counterfeit drugs was 16% and 43% of antimalarials, respectively. The other studies were not designed to detect counterfeit medicines. However the possibility of counterfeiting was raised in five of these studies as some of samples had the wrong or no active ingredients.[17, 19, 21-23]

Stated issues of substandard/counterfeit medicines

The assessment of drugs was made through special procedures and methods derived from official pharmacopoeias. The most common issues with substandard/counterfeit drugs reported by these studies are shown in Table 2. Inadequate amount of active ingredients was the most frequent problem reported.

Prevalence according to where medicines are purchased

Where patients purchase their medicines may affect the prevalence of substandard/counterfeit medicines. Five studies were identified in this review that sampled from licensed outlets (public and private sectors) and unlicensed outlets (informal markets) (Table 3). Four of these studies concerned antimalarials,[15, 24, 26, 27] and one antibiotics.[23] The percentage of failed samples in unlicensed outlets was 51% whereas it was 24% in licensed outlets. The proportion of failed samples was significantly higher in the unlicensed markets (*p*=<0.000:95% CI 0.21-0.32). Further details on the individual failure rate in public and the private sectors were not given in these studies.

DISCUSSION

The aim of this systematic review was to summarise the current data in the literature regarding substandard/counterfeit medicines around the world. The results have shown that there is a significant problem in Africa and Asia, in LIC and LMIC, regarding antimicrobial medicines. Our findings highlight the lack of studies that exist outside of these regions and therapeutic classes. It also shows the lack of evidence available that specifically differentiates between substandard and counterfeit medicines. No individual data about the prevalence of these drugs in UMIC and HIC was available.

Our review shows a high prevalence of poor quality antimicrobials. Most of the prevalence studies focused on antimicrobial medicines because of the considerable burden of infectious diseases in the study countries. This in keeping with a recent commentary in the BMJ that highlighted substandard medicines as a priority area in tropical diseases.[30] Under-dosing of antimicrobials can enhance the survival of more resistant parasites and therefore emergence of drug resistance.[31, 32] There was strong evidence in our results of samples with an inadequate amount of active ingredient (93% of studies), absence of active ingredients (47%) and dissolution failure (33%), comparable with taking a medicine in low dose and therefore likely to cause treatment failure. If 10% of patients fail treatment, it is recommended by the WHO that there should be a change in malaria treatment policy.[33] The amount of

substandard/counterfeit medicines in the supply chain needs to be considered prior to this happening. Studies to assess the direct link between substandard/counterfeit drugs and drug resistance however have not been documented.

This review has shown that the prevalence of substandard/counterfeit antimicrobials reported was significantly higher in the unauthorised market. Unofficial sale of drugs in LIC and LMIC is a common practice and considered a serious public health problem.[21, 34] A survey carried out in Benin found that 86% of individuals interviewed thought that drugs purchased from unauthorised markets were of a good quality.[(34)] The high cost of genuine drugs has been the main driving force for people to seek cheaper drugs from unauthorised markets.[21] Governments can play an important role in this matter by reducing taxes applied on medications as well as encouraging domestic manufacturing of good quality and affordable generic drugs.[35, 36]

A large proportion of the studies identified were found to have a poor methodological quality. Only 15 out of 44 studies identified met our quality inclusion criteria. “Convenience sampling” was often preferred and investigators collected samples haphazardly based on what outlets were accessible. This method is convenient and inexpensive, and gives an initial assessment of the problem faced (analogous to a case report), but is prone to bias and may not be representative of the target area studied.[14] A more reliable and accurate measure involves an estimate of sample size and selection of a random number of outlets from a complete list from that area. Only four studies randomly selected from a complete list and only one calculated the sample size required.[16] Information on the person collecting the samples, what is said to retailers and the behaviour at collection sites is also important, because if the seller realises the “customers” are performing a drug quality survey this can affect their decision to offer substandard/counterfeit medicines for sale. Guidelines for surveys of the quality of medicines have been published and give clear standards for future studies.[14]

There are a number of international and national initiatives taking place to combat the problem of counterfeit and substandard medicines. INTERPOL, in cooperation with the World Customs Organisation (WCO), International Medical Products Anti-Counterfeiting Taskforce (IMPACT) and WHO, is working with national police forces in combating the illicit trade of medicines, targeting both illicit physical and online

outlets.[37, 38] The Container Control Programme (CCP) established by the United Nations Office on Drugs and Crime (UNDOC) and WCO, to enhance inspection of containers for counterfeit goods, has become an important tool to counteract the traffic of counterfeit drugs.[39] Recently, member states of the WHO have agreed on a new mechanism to tackle not only the problem of SSFFC but also to ensure the availability of quality, safe, efficacious and affordable medical products.[40, 41] However, more collaboration between different national and international organisations is needed to counteract this problem.

Limitations and strengths

This review has a number of limitations including only searching published and accessible databases. Some reports were confidential, unpublished or published solely for limited distribution.[23] Some studies used different definitions and referred drug specifications to different pharmacopoeias. Furthermore, there have been inconsistencies in terms of drug sampling methods and the types of sector involved. All of these factors make direct comparison difficult. Packaging analysis is important to confirm if a medicine is counterfeit or substandard. There is currently scarce data to measure the prevalence of each problem individually. This is important as the causes and remedies are different. All of the studies involved antimicrobials. The prevalence of counterfeit and substandard drugs in other therapeutic classes, therefore, remained unclear. In addition, data analysis and samples collected by investigators in some of these studies were not necessarily representative of a large target area, thus the prevalence obtained cannot be extrapolated to the whole country studied. However, these studies give an insight into the problem, and following our assessment of methodology, give the best available evidence currently in the literature.

CONCLUSION

Substandard/counterfeit antimicrobial drugs represent a huge problem throughout Africa and Asia in LIC and LMIC, where the prevalence has been documented within studies. Antimicrobials, in their solid formulations, have been the most extensively studied group. Inadequate amount of the active ingredients was the main problem

identified. Little consideration has been given to other therapeutic classes or paediatric formulations and this warrants further investigation. Well-designed prevalence studies, with adequate methodological details, are required indeed to reflect the actual prevalence.

Contributors:

TA and HS designed the search strategy. TA performed the literature search, screened the titles, abstracts and managed the references. HS independently double-checked the extracted data. TA and HS screened the retrieved papers against inclusion criteria and independently performed the quality evaluation assessment for the review. IC had the original idea for the study and interpreted the results. TA drafted the manuscript and IC and HS critically revised it. All authors approve of this final submitted version after their revision of the manuscript.

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Tables and Figures:

Box 1. Quality assessment criteria

1. Timing and location of study clearly stated.
2. Definition of counterfeit or substandard medicines used mentioned.
3. Type of outlets sampled.
4. Sampling design and sample size calculation described.
5. Type and number of dosage units purchased per outlet.
6. Random sampling used.
7. Information on who collected the samples (were mystery shoppers applied?)
8. Packaging assessment performed.
9. Statistical analysis described.
10. Chemical analysis clearly described.
11. Details on method validation.
12. Chemical analysis performed blinded to packaging.

Figure 1: Flow diagram of search and review process

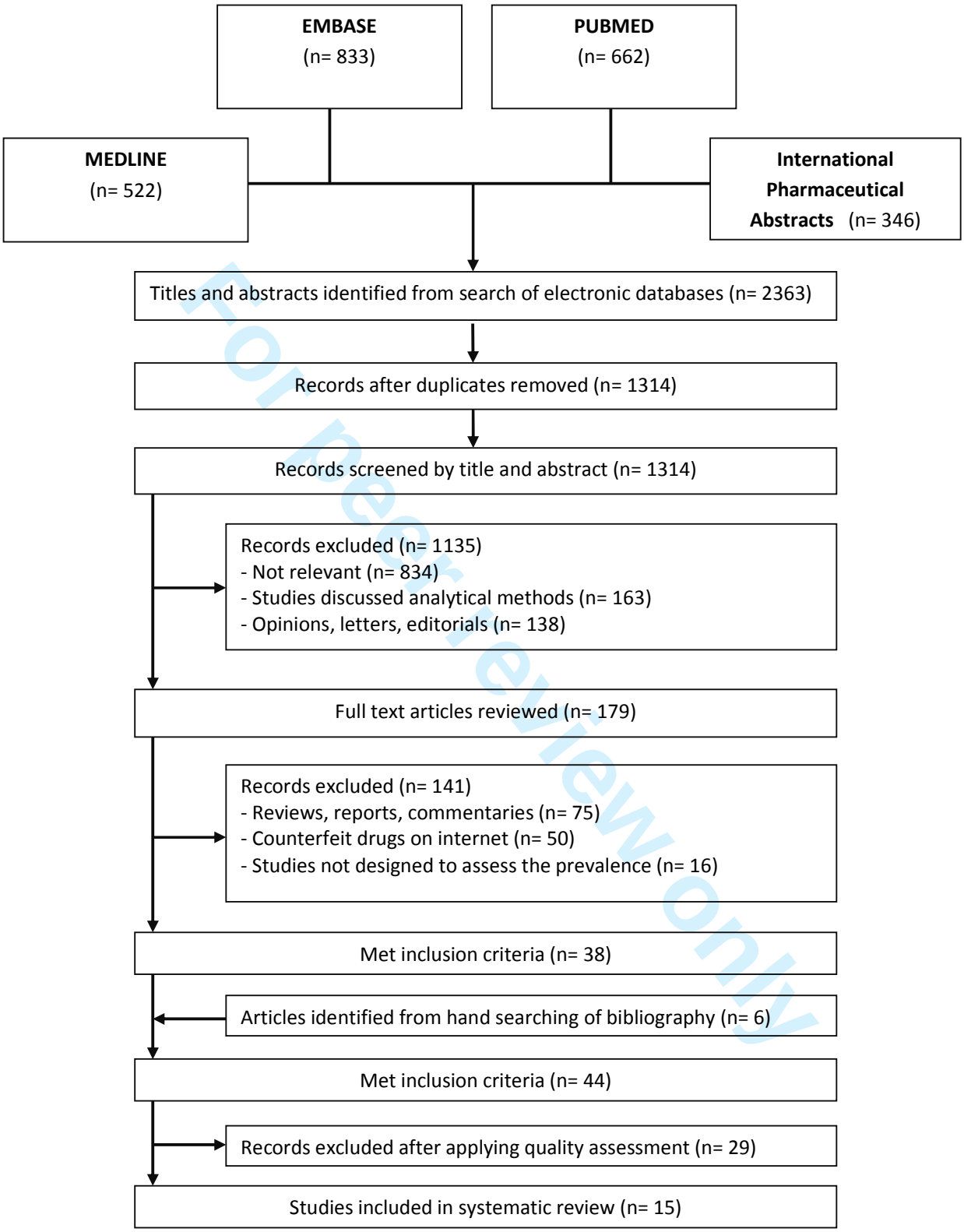

Figure 2: Quality assessment criteria for methodology of included studies

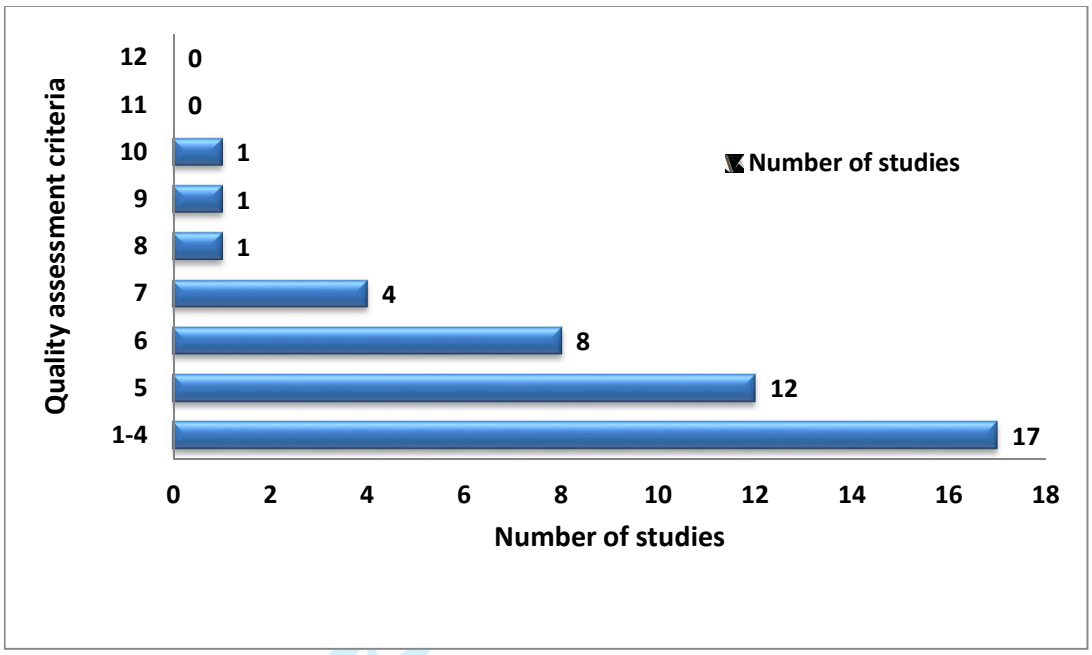

Table 1: The range of the prevalence of counterfeit and substandard medicines based on the World Bank classification of countries (by Income level)

Income Level Classification		Countries	Number of studies	Prevalence of substandard/counterfeit medicines
				Range% (Median %)
Low-income countries		Lao PDR, Tanzania, Cambodia, Uganda	4	12.2 – 44.5 (24)
Lower-middle-income countries		Indonesia, Nigeria, Cameroon.	4	18 – 48 (38)
Upper-middle-income countries		0	0	----------
High-income countries		0	0	----------
Mixed group	LIC	Myanmar, Cambodia, Lao PDR, Ghana, Kenya, Tanzania, Uganda, Madagascar, Mali, Mozambique, Zimbabwe	7	11 – 44 (28.5)
	LMIC	Vietnam ,Thailand, Cameroon, Nigeria, Senegal, Sudan, Armenia, Ukraine, Uzbekistan		
	UMIC	Gabon, Azerbaijan, Belarus, Kazakhstan		
	HIC	0		

N.B: Mixed group represents the studies that have been carried out at more than one income level. **LIC**: low-income countries, **LMIC**: lower-middle-income countries, **UMIC**: upper-middle-income countries, **HIC**: high-income countries.

Table 2: Frequency of six different issues reported concerning the quality of the medicines tested.

Stated Problem	Frequency of studies containing samples with stated problem	%
Inadequate amount of active ingredient	14	93
No active ingredient	7	47
Excessive amount of active ingredient	6	40
Dissolution failure	5	33
Wrong ingredient	4	27
Impurity	2	13

Table 3: Percentage failure of samples collected at different sectors.

Country	Licensed outlets (Public and private sectors)			Unlicensed outlets (Informal market)			References
	Total number of Samples	Number of failed samples	% of failed samples	Total number of Samples	Number of failed samples	% of failed samples	
Cameroon, Ethiopia, Ghana, Kenya, Nigeria , Tanzania	240	64	26.6	27	12	44.4	(26)
Madagascar, Senegal, Uganda	144	41	28.4	53	23	43.4	(27)
Cambodia	38	22	58	133	100	75	(15)
Myanmar	215	34	16	23	20	87	(23)
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	229	52	23	136	37	27	(24)
Total	866	213	24	372	192	51	

Supplementary data:

Table 1: Search strategy

No.	Searches	Results		
		Embase	Medline	International Pharmaceutical Abstract
1	Counterfeit*	477	296	301
2	Fake	631	491	22
3	Substandard	1017	874	78
4	Falsified	211	182	10
5	**1 or 2 or 3 or 4**	2230	1765	375
6	Drug*	2942573	1240863	248285
7	Medicine*	517065	379325	23766
8	Pharmaceutical*	62754	74697	47666
9	Antimicrobial*	61758	48954	7876
10	Antimalaria*	16651	14579	3147
11	Antibiotic*	311391	146476	24572
12	**6 or 7 or 8 or 9 or 10 or 11**	3520198	1708464	302874
13	**5 and 12**	833	522	346

Table 2: Categories of different issues of tested medicines

Stated problem	Description
Content assay of active ingredient: Inadequate active ingredient excessive active ingredient No active Ingredient	Quantification of the active ingredient content of a drug with regard to claim content declared on the packaging; the result should be within the specified range.
Wrong active ingredient	Detection of active ingredient in the drug that is not declared on the packaging
Dissolution failure	Solubility or release of active ingredients is not within the specified time range.
Presence of impurity	Coexistence of a substance with a drug, such as starting material, intermediates or that is formed as a result of any side reactions.
Fake packaging	Packaging has mislabelling information about a drug origin or authenticity
Mass uniformity test failure	The weight of a tablet or capsule is not within the average range specified
Unknown ingredient	Extraneous contaminants that should not present in a drug

Table 3: Studies excluded after applying quality assessment criteria

No.	Studies	Methodological strength scoring (0-12)
1	Stenson B, et al. The quality of drugs in private pharmacies in the Lao People's Democratic Republic. *Int J Risk Saf Med* 1998;**11**(4):243-9.	5
2	Atemnkeng MA, et al. Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and DR Congo.*Trop Med Int Health* 2007;**12**(1):68-74	5
3	Ogwal-Okeng J, et al. Quality of oral and parenteral chloroquine in Kampala. *East Afr Med J* 1998;**75**(12):692-4	5
4	Ofori-Kwakye K, et al. Quality of Artesunate Tablets Sold in Pharmacies in Kumasi, Ghana. *Trop J Pharm Res* 2008;**7**(4):1179-84	5
5	Minzi OMS, et al. Evaluation of the quality of amodiaquine and sulphadoxine/pyrimethamine tablets sold by private wholesale pharmacies in Dar Es Salaam Tanzania. *J Clin Pharm Ther* 2003;**28**(2):117-22	5
6	Tipke M, et al. Substandard anti-malarial drugs in Burkina Faso. *Malar J* 2008;**7**(1):95	5
7	Newton PN, et al. A Collaborative Epidemiological Investigation into the Criminal Fake Artesunate Trade in South East Asia. *PLoS Med* 2008;**5**(2):e32	5
8	Newton P, et al. Fake artesunate in southeast Asia. *Lancet* 2001;**357**(9272):1948-50	5
9	Laserson K, et al. Substandard tuberculosis drugs on the global market and their simple detection. *Int J Tuberc Lung Dis* 2001;**5**(5):448-54	5
10	ReMeD. La Qualite´ des me´dicaments sur le marche´ pharmaceutique africain: e´tude analytique dans trois pays: Cameroun, Madgascar, Tchad. Action Programme on Essential Drugs. In: WHO, ed. Geneva, 1995.	5
11	Baratta F, et al. Diffusion of counterfeit drugs in developing countries and stability of galenics stored for months under different conditions of temperature and relative humidity. *Croat Med J* 2012;**53**(2):173-84	5
12	Seear M, et al. The need for better data about counterfeit drugs in developing countries: a proposed standard research methodology tested in Chennai, India. *J Clin Pharm Ther* 2011;**36**(4):488-95	5
13	Amin AA, et al. The quality of sulphadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. *J Clin Pharm Ther* 2005;**30**(6):559-65	4
14	Odunfa O, et al. Pharmaceutical Equivalence of Some Commercial Samples of Artesunate and Amodiaquine Tablets Sold in Southwestern Nigeria. *Trop J Pharm Res* 2009;**8**(6):491-99	4
15	Kyriacos S, et al. Quality of amoxicillin formulations in some Arab countries. *J Clin Pharm Ther* 2008;**33**(4):375-79	4
16	Pribluda V, et al. Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005-2010 period. *Malar J* 2012;**11**(1):202	4
17	Obodozie OO, et al. A comparative study on the prevalence of substandard ampicillin/cloxacillin preparations in the	3

	Nigerian market: Mid 1990's and present. Journal of Phytomedicine and Therapeutics 2006;**11**(2006):1-8	
18	Prazuck T, et al. Quality Control of Antibiotics Before the Implementation of an STD Program in Northern Myanmar. *Sex Transm Dis* 2002;**29**(11):624-627.	3
19	Bate R, et al. Antimalarial drug quality in the most severely malarious parts of Africa - a six country study. *PLoS One* 2008;**3**:e2132	3
20	Atemnkeng MA, et al. Quality evaluation of chloroquine, quinine, sulfadoxine–pyrimethamine and proguanil formulations sold on the market in East Congo DR. *J Clin Pharm Ther* 2007;**32**(2):123-132.	3
21	Obaid A. Quality of ceftriaxone in Pakistan: reality and resonance. *Pak J Pharm Sci* 2009;**22**(2):220-9.	3
22	Abdo-Rabbo A, et al. The quality of antimalarials available in Yemen. *Malar J* 2005;**4**(1):28.	3
23	Roy J. The menace of substandard drugs. World Health Forum 1994;**15**:406-407.	2
24	Bate R, et al. Pilot Study of Essential Drug Quality in Two Major Cities in India. *PLoS One* 2009;**4**(6):e6003.	2
25	Iwuagwu MA, et al. In vitro assessment of ampicillin capsules marketed in Nigeria. International Journal of Pharmacy Practice 1992;**1**(3):167-171.	2
26	Abdullah M, et al. Report: in vitro dissolution studies of different brands of sustained release diclofenac sodium matrix tablet available in Bangladesh. *Pak J Pharm Sci* 2008;**21**(1):70-77.	1
27	Zaheer M, et al. In vitro Analysis and Data Comparison of Market Brands of Ciprofloxacin, Ofloxacin and Levofloxacin. *Pak J Sci Ind Res* 2009;**52**(4):186-190.	1
28	Alfadl A, et al. quality of antimalarial drugs in sudan: results of post-marketing surveillance. *Sudanese Journal of Public Health* 2006;**1**(2):108-111.	1
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Table 4: The prevalence of counterfeit/substandard medicines.

Country [Reference]	Drugs (n=number of various products tested)	Setting	Formulation studied	Labeled Origin	Method of testing/location*	Stated problems	% (substandard or counterfeit)	Methodological strength scoring (0-12)
The prevalence of counterfeit and substandard medicines in low-income countries in Asia and Africa.								
Lao PDR (17)	Ampicillin, tetracycline, Chloroquine and aspirin (n=300)	Private outlets	Tablets and capsules	Laos, Thailand, France and unknown origin.	HPLC, colorimetric test , ultraviolet spectrophotometry, thin-layer chromatography and mass uniformity analysis / National Food and Drug Quality Control Centre	No active Ingredient, Inadequate/ excessive active ingredient and mass uniformity failure	22% (Substandard / Counterfeit)	10
Tanzania (16)	Antimalarial drugs (sulfadoxine-pyrimethamine, sulfamethoxypyrazine-pyrimethamine, amodiaquine, quinine, artemisinin derivative (n=304)	Public and private outlets	Tablets	Local and imported	HPLC and dissolution test with US pharmacopeia standards/ Ifakara Health Research and Development Centre, Tanzania	Dissolution failure, Inadequate active ingredient.	12.2% (Substandard / Counterfeit)	9
Cambodia (15)	Antimalarial drugs (Quinine, artesunate, mefloquine, chloroquine and tetracycline) (n=451)	Public ,private and informal outlets	Tablets	16 countries	HPLC, disintegration test, thin-layer chromatography and packaging analysis/ National Laboratory for Drug Quality Control (NLDQC) in Cambodia	Failed in dissolution or inadequate active ingredient. ,no active ingredient, wrong active ingredient	27% (50/451 substandard and 72/451 counterfeit)	6
Uganda (18)	Chloroquine (n=92)	Private and informal outlets	Tablets, injection	Not stated	HPLC/ Makerere University laboratory	Inadequate/ excessive active ingredient	44.5 % (Substandard / Counterfeit)	6

The prevalence of counterfeit and substandard medicines in low-middle-income countries in Asia and Africa								
Indonesia (20)	Amoxicillin, chloramphenicol, ciprofloxacin, cotrimoxazole, tetracycline. (n=104)	Public ,private and informal outlets	Tablets, capsules	Indonesia	HPLC/ Farmalyse BV laboratories (certified laboratory registered in the European Union as a pharmaceutical control laboratory for chemical physical analyses)	Inadequate active ingredient	18% (Substandard / counterfeit)	8
Nigeria (19)	Artesunate, dihydroartemisinin, sulphadoxine-pyrimethamine, quinine and chloroquine (n=225)	Public ,private and informal outlets	Tablets	Not stated	HPLC and dissolution test, US pharmacopeia standards were used/ London School of Hygiene and Tropical Medicine laboratory	No active ingredient, wrong active ingredient, inadequate active ingredient.	37% (Substandard / Counterfeit)	7
Nigeria(22)	Antimalarial drugs, antibacterials, antituberculosis, antihelmitics and antifungals (n = 581)	Private outlet	Tablets, capsules, suspension and injection.	12 countries (Europe, Asia and Africa)	HPLC and dissolution test, British Pharmacopeia standards were used/ The Robert Gordon University School of Pharmacy laboratories	Inadequate/ excessive active ingredient, no active ingredient	48% (Substandard/ Counterfeit)	6
Cameroon (21)	Antimalarial drugs (Antifolates, quinine, chloroquine) (n=284)	Informal outlets	Tablets, capsules	Not stated	Thin-layer chromatography and Colorimetric test/ Unité de Recherche Paludologie Afro-tropicale, Institut de Recherche pour le Développement	No active ingredient, inadequate active ingredient, wrong ingredient, unknown ingredient	39.4% (Substandard/ Counterfeit)	6
The prevalence of counterfeit and substandard medicines in the mixed group								
Myanmar, Cambodia, Vietnam, Lao PDR, Thailand. (28)	Artesunate and mefloquine (n=232)	Public ,private and informal outlets	Tablets	China	HPLC, colorimetric testing (fast red dye) and packaging analysis/ Not stated	Fake packaging, no active ingredient	44% (4 /232 substandard and 99/232 counterfeit)	7

Cameroon, Ghana, Kenya, Nigeria, Tanzania (26)	Antimalarial drugs (sulphadoxine-pyrimethamine, sulfamethoxypyrazine-pyrimethamine, artemisinin-based combination) (n=267)	Public ,private and informal outlets	Tablets	Local and imported (India, USA, Bangladesh, China, Mauritius, Vietnam and the UK)	Compendial quality testing according to US pharmacopeia standards/ WHO collaborating laboratory in South Africa	Inadequate/ excessive active ingredient, no active ingredient, mass uniformity, impurity and dissolution test failure	28.5% (Substandard/ Counterfeit)	7
Uganda, Madagascar, Senegal (27)	Antimalarial drugs (Artemisinin-based combination, sulphadoxine-pyrimethamine) (n=188)	Public ,private and informal outlets	Tablets	Not stated	Compendial quality testing according to US pharmacopeia standards/ National Medicine Control Laboratory and laboratories at USP Headquarters	Dissolution failure, Impurity, Failure in the assay of active ingredient., mass uniformity test failure	32% (Substandard/ Counterfeit)	7
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe (24)	Antimalarial drugs (chloroquine and sulphadoxine-pyrimethamine) (n = 278)	Public ,private and informal outlets	Tablets, syrup	Local and Imported	HPLC, drug-specific c Assays and dissolution Test/ WHO collaborating laboratory in South Africa	inadequate active ingredient	23% Substandard/ Counterfeit	6
Myanmar (Burma) and Vietnam (23)	Amoxicillin,ampicillin, metronidazole, paracetamol, salbutamol, tetracycline, chloroquine , chloramphenicol rifampicin and diazepam co-trimoxazole and ranitidine (n=500)	Public ,private and informal outlets	Tablets and capsules	More than 20 countries (Asia, Canada, Europe, USA and Australia)	Compendial quality testing according to British pharmacopeia standards/ WHO collaborating laboratory in Thailand	Inadequate/ excessive active ingredient, wrong active ingredient	11% (Substandard/ counterfeit)	6
Nigeria and Thailand (25)	Chloroquine, amoxicillin, ampiclox cotrimoxazole, tetracycline, (n = 96)	Private and informal outlets	Tablets, capsules, suspension and injection.	Not stated	HPLC / Not stated	Inadequate/ excessive active ingredient	36.5% (Substandard/ counterfeit)	6

Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan (29)	anti-tuberculosis medicines (n = 291)	Public and private outlets	Tablets, capsules, injections	12 countries	HPLC, dissolution and mass uniformity test, US pharmacopeia standards were used/ Four WHO collaborating laboratories in Austria, Germany, Belgium and France	Content, mass uniformity, dissolution and related substances tests failures.	11.3% (Substandard/ counterfeit)	6

HPLC: High-performance liquid chromatography; **USP**: United state pharmacopeia; **location***: Location where is the analysis carried out.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 & 3 (not PRISMA registered)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary table 1 & p 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5&6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6/ box 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5 & 6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8,9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P 7/ figure 2, Methodological strength scoring was given for each study in Supplementary table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 1 & P 8&9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9/ Table 3
DISCUSSION			

PRISMA 2009 Checklist

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10, 11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11, 12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Substandard and counterfeit medicines: A systematic review of the literature

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Substandard and counterfeit medicines: A systematic review of the literature

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Number of tables: 3 (4 online supplement)

Keywords: counterfeit drug, substandard drug, fake drug, anti-infective and drug counterfeiting.

ABSTRACT

Objective: To explore the evidence available of poor quality (counterfeit and substandard) medicines in the literature.

Design: Systematic review.

Data Sources: Databases used were Embase, Medline, PubMed and International Pharmaceutical Abstracts, including articles published till January 2013.

Eligibility criteria: Prevalence studies containing original data. WHO definitions (1992) used for counterfeit and substandard medicines.

Study appraisal and synthesis: Two reviewers independently scored study methodology against recommendations from the MEDQUARG Checklist. Studies were classified according to the World Bank classification of countries by income.

Data extraction: Data extracted : place of study; type of drugs sampled; sample size; percentage of substandard/counterfeit medicines; formulations included; origin of the drugs; chemical analysis and stated issues of counterfeit/substandard medicines.

Results: 44 prevalence studies were identified, 15 had good methodological quality. They were conducted in 25 different countries; the majority in low-income countries (11) and/or lower-middle-income countries (10). The median prevalence of substandard/counterfeit medicines was 28.5% (range: 11- 48%). Only 2 studies differentiated between substandard and counterfeit medicines. Prevalence data was limited to antimicrobial drugs (all 15 studies). Thirteen studies involved antimalarials, six antibiotics and two other medications. The majority of studies (93%) contained samples with inadequate amount of active ingredients. The prevalence of substandard/counterfeit antimicrobials was significantly higher when purchased from unlicensed outlets (p=<0.000:95% CI 0.21-0.32). No individual data about the prevalence in upper-middle-income countries and high-income countries was available.

Limitations: Studies with strong methodology were few. The majority did not differentiate between substandard and counterfeit medicines. Most studies assessed only a single therapeutic class, antimicrobials.

Conclusion: The prevalence of poor quality antimicrobial medicines is widespread throughout Africa and Asia in LIC and LMIC. Inadequate amount of the active ingredients was the main problem identified.

Article summary

Article focus

To systematically review prevalence studies on substandard and counterfeit medicines published in the literature.

Key messages

- The prevalence of substandard/counterfeit antimicrobials is high throughout Africa and Asia in LIC and LMIC.
- The prevalence of substandard/counterfeit medicines was significantly higher in the unlicensed markets.
- Inadequate amount of the active ingredients was the largest problem identified.

Strengths and limitations of this study

- The article demonstrates a systematic review of prevalence studies on substandard/counterfeit medicines, with assessment of their quality before inclusion.
- This review is limited by the methodology used in the included studies, such as sampling methods, the assessment of a single therapeutic class (antimicrobial drugs), as well as scarce packaging analysis data to differentiate between counterfeit and substandard medicines.

INTRODUCTION

Counterfeiting in pharmaceutical products is an increasing worldwide dilemma with a profound impact on lower income countries (LIC) and lower-middle-income countries (LMIC).[1, 2] It is also becoming an issue in high income countries (HIC).[3-5]

There is no clear, agreed international definition of counterfeit medicines.[6] The most widely used definition in the literature, in the last two decades, is that given in 1992 by the WHO.[7] This defines a counterfeit medicine as a medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products. Counterfeit products may include: the correct ingredients, the wrong ingredients, no active ingredients, insufficient ingredients or fake packaging (i.e. misleading about its origin or authenticity).[7] Substandard medicines are defined as genuine medicines which have failed to pass the quality measurements and standards set for them. These quality standard tests have been derived from the official pharmacopoeias.[8] In 2011, WHO member states chose to include counterfeit and substandard medicines under the new term "substandard/spurious/falsely-labeled/falsified/counterfeit medical products" (SSFFC). This new term however has been questioned recently [6] as it is felt not to distinguish sufficiently between the different illegitimate drugs categories (such as counterfeit and substandard) that require different monitoring and solutions.

According to The Pharmaceutical Security Institute data, the incidents of counterfeit medicines increased dramatically from 196 incidents in 2002 to 2018 incidents in 2012.[9] The data is, in part, a reflection of adequate law enforcement and regulatory oversight in countries where these reports came from.[10] However, this figure would be even higher if resource-poor countries had adequate surveillance systems. Drug regulatory authorities and pharmaceutical companies hold records on counterfeit medicines, yet most are inaccessible.[6, 10] More insight into the problem can be gained from prevalence studies published in the literature.[10] Thus our objective was to systematically review prevalence studies published in the literature.

METHODS

A literature search was carried out using the following medical databases: Embase (data range: 1974-January 2013), Medline (data range: 1948-January 2013), PubMed (data range: 1950- January 2013) and International Pharmaceutical Abstracts (data range: 1970- January 2013). A preliminary search for MeSH terms associated with published prevalence studies were conducted trying to choose the most specific and sensitive words for the search strategy. Specific therapeutic areas, such as antimalarials, were recognised and added as additional terms to increase sensitivity; the search however was not limited to these categories. The search terms included: 'fake', 'counterfeit', 'substandard' or 'falsified' and have been combined with 'drugs', 'medicines', 'pharmaceuticals', 'antimicrobials', 'antimalarials' or 'antibiotics'. The search strategy is detailed in supplementary table 1. The review was performed in accordance with the PRISMA statement.[11]

The eligibility criteria were any studies (irrespective of language) that evaluated the prevalence of substandard or counterfeit medicines within a defined area. Studies which discussed analytical methods for the identification of these drugs as well as reviews, opinion papers, letters and comments were set as exclusion criteria.

Data collection process and data items

All abstracts were screened and evaluated against the inclusion and exclusion criteria. Where there was a doubt or the abstract was not available, the full text was obtained to determine inclusion. Full articles were then retrieved and a manual search of the references was performed. The following data was extracted independently (TA): place of the study; type of drugs sampled; sample size; percentage of counterfeit/substandard medicines; dosage forms included; chemical analysis; origin of the drugs and stated issues of substandard/counterfeit medicines (defined in online supplementary table 2). The number of medicines sampled and those that failed quality tests were also extracted from studies that included samples from licensed outlets (i.e. public and private sectors) and unlicensed outlets (i.e. informal markets). Study selection and data extraction were double-checked independently (HS) before inclusion.

Studies were classified according to the World Bank classification of income level into the following: Low-income countries (LIC), Lower-middle-income countries (LMIC), Upper-middle-income countries (UMIC) and High-income countries (HIC).[12] Any study that contained information on more than one country was classified in the mixed group.

Substandard and counterfeit medicines are both recognised as poor-quality medicines. Chemical and packaging analysis is required to conclude if a medicine is substandard or counterfeit. This however is difficult and rarely reported.[13] Therefore, the term substandard/counterfeit medicine is used in this review unless studies formally assessed packaging to differentiate medicines into these two different categories.

Quality evaluation assessment

Quality assessment of studies was conducted to try to minimise bias from the methodology used to collect data. The methodology of all identified studies were assessed against 12 criteria adapted from a previous published review (Box 1).[14] These criteria were given in the methodology section of the MEDQUARG (Medicine Quality Assessment Reporting Guidelines) Checklist of items to be addressed in reports of surveys of medicine quality. Two reviewers (TA and HS) independently performed the evaluation. If there was any disagreement level, an independent third person (IC) was consulted. As there has been no cut-off limit specified, all studies that scored 6 or more were included as a subset of the studies that have good methodological strength and therefore less chance of bias in their results.

Statistical analysis

The median prevalence of substandard/counterfeit medicines was analysed for each income level group. Comparison of the prevalence in licensed (public and private sectors) and unlicensed (informal markets) outlets was performed using the Fisher exact test for proportions. A significant difference was defined at P-value < 0.05.

RESULTS

A total of 44 studies of the prevalence of substandard/counterfeit medicines were identified. The number of articles screened and assessed is detailed in Figure 1. After independent assessment there was a 95% agreement level between the two assessors against the criteria specified for the quality assessment of study methodology (Box 1). No study fulfilled all 12 criteria. One study met 10 criteria whereas 29 studies met only 5 criteria or less (Figure 2 and supplementary Table 3). Fifteen studies fitted the pre specified criteria of scoring 6 or above[15-29] and were included in the analysis.

Study methodology

All studies were designed to select drug samples from a target geographical region. These included drugs sampled from public (i.e. pharmacy hospitals and primary health care centres), private and/or informal (i.e. market stalls and street sellers) sectors (supplementary table 4).

More than half of the studies used a convenience sampling method, in which investigators collected medicines from only accessible outlets. Only four studies used random sampling methods, in which investigators collected samples from outlets that were randomly chosen from a complete or registered list or outlets in a defined area.[16, 17, 19, 22] Information on the person collecting the samples was provided by 12 studies.[15, 17-23, 25-28] Samples in these studies were purchased by national collaborators, behaving as normal clients, in situations where the seller had no indication as to the purpose of the purchases.

Methods used for drugs analysis were variable according to the type of test, dosage form and drug analysed. Generally, analysis of these samples was carried out with regard to pharmacopoeia specifications (supplementary table 4). Non pharmacopoeial drugs were analysed in accordance with specifications and particular methods of their manufactures in order to evaluate the quality of these drugs.

The majority of the studies were conducted by investigators from different academic and research institutions (60%), 40% from multilateral organisations (e.g. WHO and UNICEF).

Overview of the studies and prevalence of substandard/counterfeit medicines

The 15 studies were conducted in 25 different countries mainly from Africa and Asia. Twenty one were either LIC or LMIC. All 15 studies assessed the quality of antimicrobial drugs. Antimalarial drugs were the most extensively studied group of medicines (13 studies). Six studies included antibiotics and two studies included other therapeutic agents, paracetamol, ranitidine, salbutamol, diazepam and analgesics, in their sampling process.[17, 23] Only two studies considered paediatric formulations (i.e. syrup and suspension) in their sampling process. [22, 24]

The median prevalence of substandard/counterfeit medicines was 28.5% (range: 11-48%). The median prevalence of substandard/counterfeit medicines for each income level was similar in LIC (24%), LMIC (38%) and the mixed group (28.5%) (Table 1). The majority of the studies (8) were conducted in sub-Saharan Africa, where the prevalence of substandard/counterfeit medicines ranged from 12.2 to 48% (median 34%). This was similar in the five studies conducted in South Asia, range 11-44% (median 22%). This prevalence is mainly representative of antimicrobial drugs, as these accounted for the bulk of the tested samples. Details for each individual study are given in supplementary table 4.

Only two studies from Southeast Asia performed packaging analysis of the samples collected.[15, 28] The prevalence of counterfeit drugs was 16% and 43% of antimalarials, respectively. The other studies were not designed to detect counterfeit medicines. However the possibility of counterfeiting was raised in five of these studies as some of samples had the wrong or no active ingredients.[17, 19, 21-23]

Stated issues of substandard/counterfeit medicines

The assessment of drugs was made through special procedures and methods derived from official pharmacopoeias. The most common issues with substandard/counterfeit drugs reported by these studies are shown in Table 2. Inadequate amount of active ingredients was the most frequent problem reported.

Prevalence according to where medicines are purchased

Where patients purchase their medicines may affect the prevalence of substandard/counterfeit medicines. Five studies were identified in this review that sampled from licensed outlets (public and private sectors) and unlicensed outlets (informal markets) (Table 3). Four of these studies concerned antimalarials,[15, 24, 26, 27] and one antibiotics.[23] The percentage of failed samples in unlicensed outlets was 51% whereas it was 24% in licensed outlets. The proportion of failed samples was significantly higher in the unlicensed markets (*p*=<0.000:95% CI 0.21-0.32). Further details on the individual failure rate in public and the private sectors were not given in these studies.

DISCUSSION

The aim of this systematic review was to summarise the current data in the literature regarding substandard/counterfeit medicines around the world. The results have shown that there is a significant problem in Africa and Asia, in LIC and LMIC, regarding antimicrobial medicines. Our findings highlight the lack of studies that exist outside of these regions and therapeutic classes. It also shows the lack of evidence available that specifically differentiates between substandard and counterfeit medicines. No individual data about the prevalence of these drugs in UMIC and HIC was available.

Our review shows a high prevalence of poor quality antimicrobials. Most of the prevalence studies focused on antimicrobial medicines because of the considerable burden of infectious diseases in the study countries. This in keeping with a recent commentary in the BMJ that highlighted substandard medicines as a priority area in tropical diseases.[30] Under-dosing of antimicrobials can enhance the survival of more resistant parasites and therefore emergence of drug resistance.[31, 32] There was strong evidence in our results of samples with an inadequate amount of active ingredient (93% of studies), absence of active ingredients (47%) and dissolution failure (33%), comparable with taking a medicine in low dose and therefore likely to cause treatment failure. If 10% of patients fail treatment, it is recommended by the WHO that there should be a change in malaria treatment policy.[33] The amount of

substandard/counterfeit medicines in the supply chain needs to be considered prior to this happening. Studies to assess the direct link between substandard/counterfeit drugs and drug resistance however have not been documented.

This review has shown that the prevalence of substandard/counterfeit antimicrobials reported was significantly higher in the unauthorised market. Unofficial sale of drugs in LIC and LMIC is a common practice and considered a serious public health problem.[21, 34] A survey carried out in Benin found that 86% of individuals interviewed thought that drugs purchased from unauthorised markets were of a good quality.[(34)] The high cost of genuine drugs has been the main driving force for people to seek cheaper drugs from unauthorised markets.[21] Governments can play an important role in this matter by reducing taxes applied on medications. It has also to encourage domestic manufacturing of good quality and affordable generic drugs and to implement robust policies to ensure domestic market utilisation of these drugs.[35,36]

A large proportion of the studies identified were found to have a poor methodological quality. Only 15 out of 44 studies identified met our quality inclusion criteria. “Convenience sampling” was often preferred and investigators collected samples haphazardly based on what outlets were accessible. This method is convenient and inexpensive, and gives an initial assessment of the problem faced (analogous to a case report), but is prone to bias and may not be representative of the target area studied.[14] A more reliable and accurate measure involves an estimate of sample size and selection of a random number of outlets from a complete list from that area. Only four studies randomly selected from a complete list and only one calculated the sample size required.[16] Information on the person collecting the samples, what is said to retailers and the behaviour at collection sites is also important, because if the seller realises the “customers” are performing a drug quality survey this can affect their decision to offer substandard/counterfeit medicines for sale. Guidelines for surveys of the quality of medicines have been published and give clear standards for future studies.[14]

There are a number of international and national initiatives taking place to combat the problem of counterfeit and substandard medicines. INTERPOL, in cooperation with the World Customs Organisation (WCO) and WHO, is working with national police forces in combating the illicit trade of medicines, targeting both illicit physical

and online outlets.[37, 38] The Container Control Programme (CCP) established by the United Nations Office on Drugs and Crime (UNDOC) and WCO, to enhance inspection of containers for counterfeit goods, has become an important tool to counteract the traffic of counterfeit drugs.[39] Recently, member states of the WHO have agreed on a new mechanism to tackle not only the problem of SSFFC but also to ensure the availability of quality, safe, efficacious and affordable medical products.[40, 41] However, more collaboration between different national and international organisations is needed to counteract this problem.

Limitations and strengths

This review has a number of limitations including only searching published and accessible databases. Some reports were confidential, unpublished or published solely for limited distribution.[23] Some studies used different definitions and referred drug specifications to different pharmacopoeias. Furthermore, there have been inconsistencies in terms of drug sampling methods and the types of sector involved. All of these factors make direct comparison difficult. Packaging analysis is important to confirm if a medicine is counterfeit or substandard. There is currently scarce data to measure the prevalence of each problem individually. This is important as the causes and remedies are different. All of the studies involved antimicrobials. The prevalence of counterfeit and substandard drugs in other therapeutic classes, therefore, remained unclear. In addition, data analysis and samples collected by investigators in some of these studies were not necessarily representative of a large target area, thus the prevalence obtained cannot be extrapolated to the whole country studied. However, these studies give an insight into the problem, and following our assessment of methodology, give the best available evidence currently in the literature.

CONCLUSION

Substandard/counterfeit antimicrobial drugs represent a huge problem throughout Africa and Asia in LIC and LMIC, where the prevalence has been documented within studies. Antimicrobials, in their solid formulations, have been the most extensively studied group. Inadequate amount of the active ingredients was the main problem

identified. Little consideration has been given to other therapeutic classes or paediatric formulations and this warrants further investigation. Well-designed prevalence studies, with adequate methodological details, are required indeed to reflect the actual prevalence.

Contributors:

TA and HS designed the search strategy. TA performed the literature search, screened the titles, abstracts and managed the references. HS independently double-checked the extracted data. TA and HS screened the retrieved papers against inclusion criteria and independently performed the quality evaluation assessment for the review. IC had the original idea for the study and interpreted the results. TA drafted the manuscript and IC and HS critically revised it. All authors approve of this final submitted version after their revision of the manuscript.

Competing interests: None.

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Data sharing: No additional data available.

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Tables and Figures:

Box 1. Quality assessment criteria

1. Timing and location of study clearly stated.
2. Definition of counterfeit or substandard medicines used mentioned.
3. Type of outlets sampled.
4. Sampling design and sample size calculation described.
5. Type and number of dosage units purchased per outlet.
6. Random sampling used.
7. Information on who collected the samples (were mystery shoppers applied?)
8. Packaging assessment performed.
9. Statistical analysis described.
10. Chemical analysis clearly described.
11. Details on method validation.
12. Chemical analysis performed blinded to packaging.

Figure 1: Flow diagram of search and review process

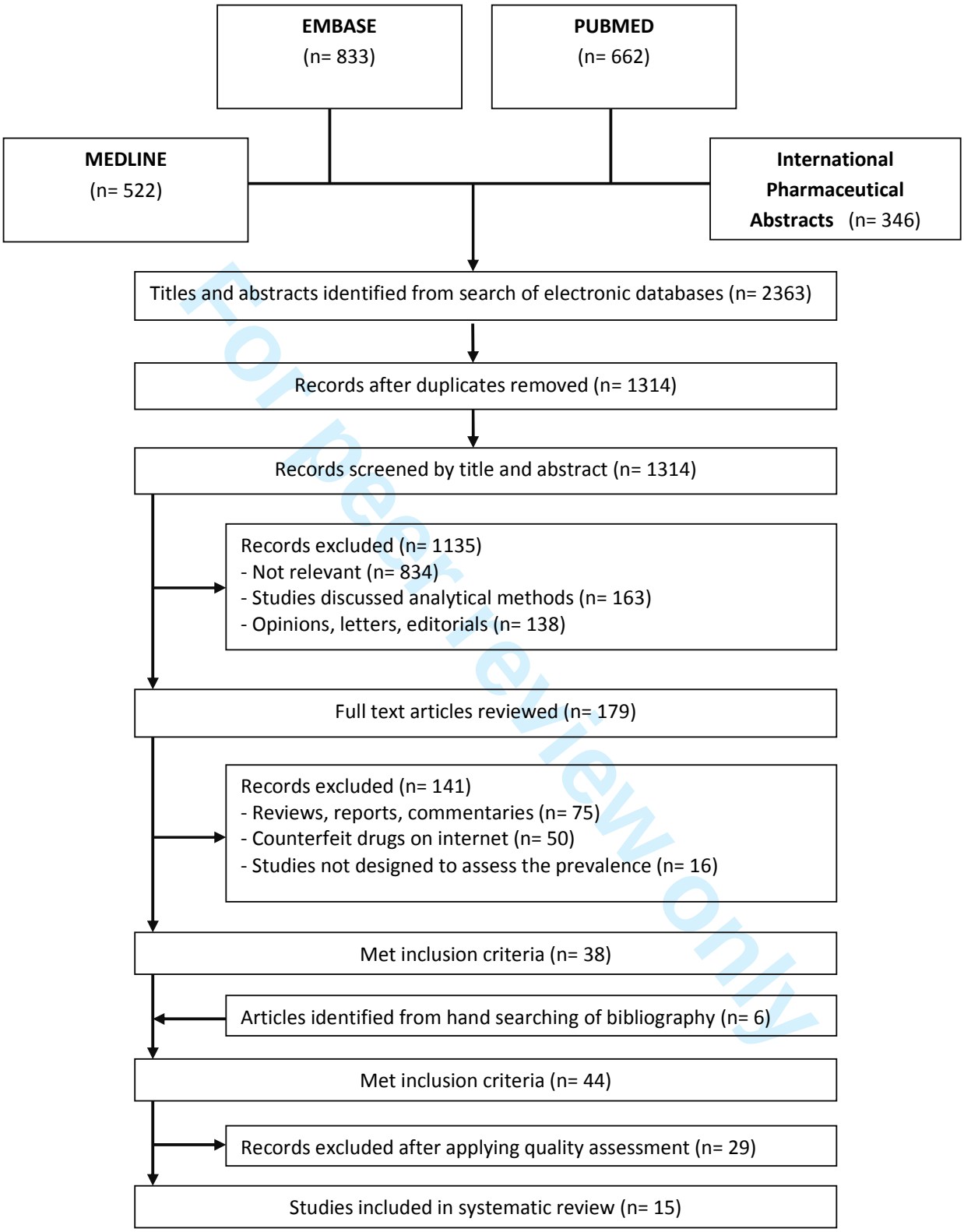

Figure 2: Quality assessment criteria for methodology of included studies

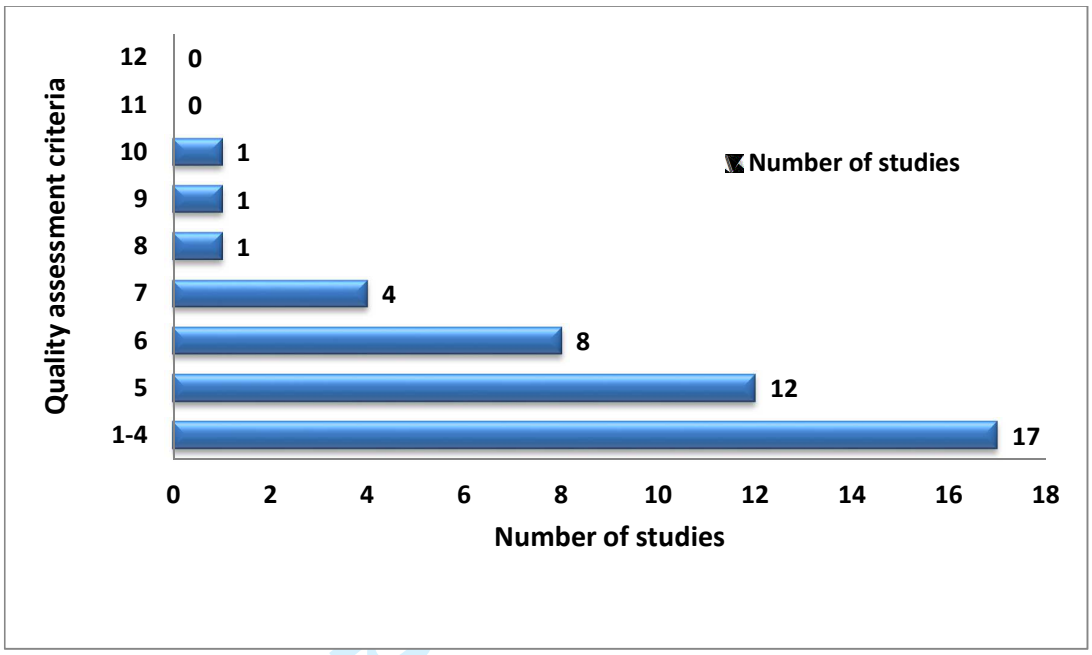

Table 1: The range of the prevalence of counterfeit and substandard medicines based on the World Bank classification of countries (by Income level)

Income Level Classification		Countries	Number of studies	Prevalence of substandard/counterfeit medicines
				Range% (Median %)
Low-income countries		Lao PDR, Tanzania, Cambodia, Uganda	4	12.2 – 44.5 (24)
Lower-middle-income countries		Indonesia, Nigeria, Cameroon.	4	18 – 48 (38)
Upper-middle-income countries		0	0	----------
High-income countries		0	0	----------
Mixed group	LIC	Myanmar, Cambodia, Lao PDR, Ghana, Kenya, Tanzania, Uganda, Madagascar, Mali, Mozambique, Zimbabwe	7	11 – 44 (28.5)
	LMIC	Vietnam ,Thailand, Cameroon, Nigeria, Senegal, Sudan, Armenia, Ukraine, Uzbekistan		
	UMIC	Gabon, Azerbaijan, Belarus, Kazakhstan		
	HIC	0		

N.B: Mixed group represents the studies that have been carried out at more than one income level. **LIC**: low-income countries, **LMIC**: lower-middle-income countries, **UMIC**: upper-middle-income countries, **HIC**: high-income countries.

Table 2: Frequency of six different issues reported concerning the quality of the medicines tested.

Stated Problem	Frequency of studies containing samples with stated problem	%
Inadequate amount of active ingredient	14	93
No active ingredient	7	47
Excessive amount of active ingredient	6	40
Dissolution failure	5	33
Wrong ingredient	4	27
Impurity	2	13

Table 3: Percentage failure of samples collected at different sectors.

Country	Licensed outlets (Public and private sectors)			Unlicensed outlets (Informal market)			References
	Total number of Samples	Number of failed samples	% of failed samples	Total number of Samples	Number of failed samples	% of failed samples	
Cameroon, Ethiopia, Ghana, Kenya, Nigeria , Tanzania	240	64	26.6	27	12	44.4	(26)
Madagascar, Senegal, Uganda	144	41	28.4	53	23	43.4	(27)
Cambodia	38	22	58	133	100	75	(15)
Myanmar	215	34	16	23	20	87	(23)
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe	229	52	23	136	37	27	(24)
Total	866	213	24	372	192	51	

Supplementary data:

Table 1: Search strategy

No.	Searches	Results		
		Embase	Medline	International Pharmaceutical Abstract
1	Counterfeit*	477	296	301
2	Fake	631	491	22
3	Substandard	1017	874	78
4	Falsified	211	182	10
5	**1 or 2 or 3 or 4**	2230	1765	375
6	Drug*	2942573	1240863	248285
7	Medicine*	517065	379325	23766
8	Pharmaceutical*	62754	74697	47666
9	Antimicrobial*	61758	48954	7876
10	Antimalaria*	16651	14579	3147
11	Antibiotic*	311391	146476	24572
12	**6 or 7 or 8 or 9 or 10 or 11**	3520198	1708464	302874
13	**5 and 12**	833	522	346

Table 2: Categories of different issues of tested medicines

Stated problem	Description
Content assay of active ingredient: Inadequate active ingredient excessive active ingredient No active Ingredient	Quantification of the active ingredient content of a drug with regard to claim content declared on the packaging; the result should be within the specified range.
Wrong active ingredient	Detection of active ingredient in the drug that is not declared on the packaging
Dissolution failure	Solubility or release of active ingredients is not within the specified time range.
Presence of impurity	Coexistence of a substance with a drug, such as starting material, intermediates or that is formed as a result of any side reactions.
Fake packaging	Packaging has mislabelling information about a drug origin or authenticity
Mass uniformity test failure	The weight of a tablet or capsule is not within the average range specified
Unknown ingredient	Extraneous contaminants that should not present in a drug

Table 3: Studies excluded after applying quality assessment criteria

No.	Studies	Methodological strength scoring (0-12)
1	Stenson B, et al. The quality of drugs in private pharmacies in the Lao People's Democratic Republic. *Int J Risk Saf Med* 1998;**11**(4):243-9.	5
2	Atemnkeng MA, et al. Quality control of active ingredients in artemisinin-derivative antimalarials within Kenya and DR Congo.*Trop Med Int Health* 2007;**12**(1):68-74	5
3	Ogwal-Okeng J, et al. Quality of oral and parenteral chloroquine in Kampala. *East Afr Med J* 1998;**75**(12):692-4	5
4	Ofori-Kwakye K, et al. Quality of Artesunate Tablets Sold in Pharmacies in Kumasi, Ghana. *Trop J Pharm Res* 2008;**7**(4):1179-84	5
5	Minzi OMS, et al. Evaluation of the quality of amodiaquine and sulphadoxine/pyrimethamine tablets sold by private wholesale pharmacies in Dar Es Salaam Tanzania. *J Clin Pharm Ther* 2003;**28**(2):117-22	5
6	Tipke M, et al. Substandard anti-malarial drugs in Burkina Faso. *Malar J* 2008;**7**(1):95	5
7	Newton PN, et al. A Collaborative Epidemiological Investigation into the Criminal Fake Artesunate Trade in South East Asia. *PLoS Med* 2008;**5**(2):e32	5
8	Newton P, et al. Fake artesunate in southeast Asia. *Lancet* 2001;**357**(9272):1948-50	5
9	Laserson K, et al. Substandard tuberculosis drugs on the global market and their simple detection. *Int J Tuberc Lung Dis* 2001;**5**(5):448-54	5
10	ReMeD. La Qualite´ des me´dicaments sur le marche´ pharmaceutique africain: e´tude analytique dans trois pays: Cameroun, Madgascar, Tchad. Action Programme on Essential Drugs. In: WHO, ed. Geneva, 1995.	5
11	Baratta F, et al. Diffusion of counterfeit drugs in developing countries and stability of galenics stored for months under different conditions of temperature and relative humidity. *Croat Med J* 2012;**53**(2):173-84	5
12	Seear M, et al. The need for better data about counterfeit drugs in developing countries: a proposed standard research methodology tested in Chennai, India. *J Clin Pharm Ther* 2011;**36**(4):488-95	5
13	Amin AA, et al. The quality of sulphadoxine-pyrimethamine and amodiaquine products in the Kenyan retail sector. *J Clin Pharm Ther* 2005;**30**(6):559-65	4
14	Odunfa O, et al. Pharmaceutical Equivalence of Some Commercial Samples of Artesunate and Amodiaquine Tablets Sold in Southwestern Nigeria. *Trop J Pharm Res* 2009;**8**(6):491-99	4
15	Kyriacos S, et al. Quality of amoxicillin formulations in some Arab countries. *J Clin Pharm Ther* 2008;**33**(4):375-79	4
16	Pribluda V, et al. Implementation of basic quality control tests for malaria medicines in Amazon Basin countries: results for the 2005-2010 period. *Malar J* 2012;**11**(1):202	4
17	Obodozie OO, et al. A comparative study on the prevalence of substandard ampicillin/cloxacillin preparations in the	3

	Nigerian market: Mid 1990's and present. Journal of Phytomedicine and Therapeutics 2006;**11**(2006):1-8	
18	Prazuck T, et al. Quality Control of Antibiotics Before the Implementation of an STD Program in Northern Myanmar. *Sex Transm Dis* 2002;**29**(11):624-627.	3
19	Bate R, et al. Antimalarial drug quality in the most severely malarious parts of Africa - a six country study. *PLoS One* 2008;**3**:e2132	3
20	Atemnkeng MA, et al. Quality evaluation of chloroquine, quinine, sulfadoxine–pyrimethamine and proguanil formulations sold on the market in East Congo DR. *J Clin Pharm Ther* 2007;**32**(2):123-132.	3
21	Obaid A. Quality of ceftriaxone in Pakistan: reality and resonance. *Pak J Pharm Sci* 2009;**22**(2):220-9.	3
22	Abdo-Rabbo A, et al. The quality of antimalarials available in Yemen. *Malar J* 2005;**4**(1):28.	3
23	Roy J. The menace of substandard drugs. World Health Forum 1994;**15**:406-407.	2
24	Bate R, et al. Pilot Study of Essential Drug Quality in Two Major Cities in India. *PLoS One* 2009;**4**(6):e6003.	2
25	Iwuagwu MA, et al. In vitro assessment of ampicillin capsules marketed in Nigeria. International Journal of Pharmacy Practice 1992;**1**(3):167-171.	2
26	Abdullah M, et al. Report: in vitro dissolution studies of different brands of sustained release diclofenac sodium matrix tablet available in Bangladesh. *Pak J Pharm Sci* 2008;**21**(1):70-77.	1
27	Zaheer M, et al. In vitro Analysis and Data Comparison of Market Brands of Ciprofloxacin, Ofloxacin and Levofloxacin. *Pak J Sci Ind Res* 2009;**52**(4):186-190.	1
28	Alfadl A, et al. quality of antimalarial drugs in sudan: results of post-marketing surveillance. *Sudanese Journal of Public Health* 2006;**1**(2):108-111.	1
29	Kibwage IO, et al. Drug quality control work in Daru: observations during 1983-1986. *East Afr Med J* 1992;**69**(10):577-80.	1

Table 4: The prevalence of counterfeit/substandard medicines.

Country [Reference]	Drugs (n=number of various products tested)	Setting	Formulation studied	Labeled Origin	Method of testing/location*	Stated problems	% (substandard or counterfeit)	Methodological strength scoring (0-12)
The prevalence of counterfeit and substandard medicines in low-income countries in Asia and Africa.								
Lao PDR (17)	Ampicillin, tetracycline, Chloroquine and aspirin (n=300)	Private outlets	Tablets and capsules	Laos, Thailand, France and unknown origin.	HPLC, colorimetric test , ultraviolet spectrophotometry, thin-layer chromatography and mass uniformity analysis / National Food and Drug Quality Control Centre	No active Ingredient, Inadequate/ excessive active ingredient and mass uniformity failure	22% (Substandard / Counterfeit)	10
Tanzania (16)	Antimalarial drugs (sulfadoxine-pyrimethamine, sulfamethoxypyrazine-pyrimethamine, amodiaquine, quinine, artemisinin derivative (n=304)	Public and private outlets	Tablets	Local and imported	HPLC and dissolution test with US pharmacopeia standards/ Ifakara Health Research and Development Centre, Tanzania	Dissolution failure, Inadequate active ingredient.	12.2% (Substandard / Counterfeit)	9
Cambodia (15)	Antimalarial drugs (Quinine, artesunate, mefloquine, chloroquine and tetracycline) (n=451)	Public ,private and informal outlets	Tablets	16 countries	HPLC, disintegration test, thin-layer chromatography and packaging analysis/ National Laboratory for Drug Quality Control (NLDQC) in Cambodia	Failed in dissolution or inadequate active ingredient. ,no active ingredient, wrong active ingredient	27% (50/451 substandard and 72/451 counterfeit)	6
Uganda (18)	Chloroquine (n=92)	Private and informal outlets	Tablets, injection	Not stated	HPLC/ Makerere University laboratory	Inadequate/ excessive active ingredient	44.5 % (Substandard / Counterfeit)	6

The prevalence of counterfeit and substandard medicines in low-middle-income countries in Asia and Africa								
Indonesia (20)	Amoxicillin, chloramphenicol, ciprofloxacin, cotrimoxazole, tetracycline. (n=104)	Public ,private and informal outlets	Tablets, capsules	Indonesia	HPLC/ Farmalyse BV laboratories (certified laboratory registered in the European Union as a pharmaceutical control laboratory for chemical physical analyses)	Inadequate active ingredient	18% (Substandard / counterfeit)	8
Nigeria (19)	Artesunate, dihydroartemisinin, sulphadoxine-pyrimethamine, quinine and chloroquine (n=225)	Public ,private and informal outlets	Tablets	Not stated	HPLC and dissolution test, US pharmacopeia standards were used/ London School of Hygiene and Tropical Medicine laboratory	No active ingredient, wrong active ingredient, inadequate active ingredient.	37% (Substandard / Counterfeit)	7
Nigeria(22)	Antimalarial drugs, antibacterials, antituberculosis, antihelmitics and antifungals (n = 581)	Private outlet	Tablets, capsules, suspension and injection.	12 countries (Europe, Asia and Africa)	HPLC and dissolution test, British Pharmacopeia standards were used/ The Robert Gordon University School of Pharmacy laboratories	Inadequate/ excessive active ingredient, no active ingredient	48% (Substandard/ Counterfeit)	6
Cameroon (21)	Antimalarial drugs (Antifolates, quinine, chloroquine) (n=284)	Informal outlets	Tablets, capsules	Not stated	Thin-layer chromatography and Colorimetric test/ Unité de Recherche Paludologie Afro-tropicale, Institut de Recherche pour le Développement	No active ingredient, inadequate active ingredient, wrong ingredient, unknown ingredient	39.4% (Substandard/ Counterfeit)	6
The prevalence of counterfeit and substandard medicines in the mixed group								
Myanmar, Cambodia, Vietnam, Lao PDR, Thailand. (28)	Artesunate and mefloquine (n=232)	Public ,private and informal outlets	Tablets	China	HPLC, colorimetric testing (fast red dye) and packaging analysis/ Not stated	Fake packaging, no active ingredient	44% (4 /232 substandard and 99/232 counterfeit)	7

Cameroon, Ghana, Kenya, Nigeria, Tanzania (26)	Antimalarial drugs (sulphadoxine-pyrimethamine, sulfamethoxypyrazine-pyrimethamine, artemisinin-based combination) (n=267)	Public ,private and informal outlets	Tablets	Local and imported (India, USA, Bangladesh, China, Mauritius, Vietnam and the UK)	Compendial quality testing according to US pharmacopeia standards/ WHO collaborating laboratory in South Africa	Inadequate/ excessive active ingredient, no active ingredient, mass uniformity, impurity and dissolution test failure	28.5% (Substandard/ Counterfeit)	7
Uganda, Madagascar, Senegal (27)	Antimalarial drugs (Artemisinin-based combination, sulphadoxine-pyrimethamine) (n=188)	Public ,private and informal outlets	Tablets	Not stated	Compendial quality testing according to US pharmacopeia standards/ National Medicine Control Laboratory and laboratories at USP Headquarters	Dissolution failure, Impurity, Failure in the assay of active ingredient., mass uniformity test failure	32% (Substandard/ Counterfeit)	7
Gabon, Ghana, Kenya, Mali, Mozambique, Sudan, Zimbabwe (24)	Antimalarial drugs (chloroquine and sulphadoxine-pyrimethamine) (n = 278)	Public ,private and informal outlets	Tablets, syrup	Local and Imported	HPLC, drug-specific c Assays and dissolution Test/ WHO collaborating laboratory in South Africa	inadequate active ingredient	23% Substandard/ Counterfeit	6
Myanmar (Burma) and Vietnam (23)	Amoxicillin,ampicillin, metronidazole, paracetamol, salbutamol, tetracycline, chloroquine , chloramphenicol rifampicin and diazepam co-trimoxazole and ranitidine (n=500)	Public ,private and informal outlets	Tablets and capsules	More than 20 countries (Asia, Canada, Europe, USA and Australia)	Compendial quality testing according to British pharmacopeia standards/ WHO collaborating laboratory in Thailand	Inadequate/ excessive active ingredient, wrong active ingredient	11% (Substandard/ counterfeit)	6
Nigeria and Thailand (25)	Chloroquine, amoxicillin, ampiclox cotrimoxazole, tetracycline, (n = 96)	Private and informal outlets	Tablets, capsules, suspension and injection.	Not stated	HPLC / Not stated	Inadequate/ excessive active ingredient	36.5% (Substandard/ counterfeit)	6

Armenia, Azerbaijan, Belarus, Kazakhstan, Ukraine, and Uzbekistan (29)	anti-tuberculosis medicines (n = 291)	Public and private outlets	Tablets, capsules, injections	12 countries	HPLC, dissolution and mass uniformity test, US pharmacopeia standards were used/ Four WHO collaborating laboratories in Austria, Germany, Belgium and France	Content, mass uniformity, dissolution and related substances tests failures.	11.3% (Substandard/ counterfeit)	6

HPLC: High-performance liquid chromatography; **USP**: United state pharmacopeia; **location***: Location where is the analysis carried out.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2 & 3 (not PRISMA registered)
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary table 1 & p 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5&6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6/ box 1
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5 & 6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7,8,9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	P 7/ figure 2, Methodological strength scoring was given for each study in Supplementary table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables 1 & P 8&9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9/ Table 3
DISCUSSION			

PRISMA 2009 Checklist

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9,10, 11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11, 12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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