May 2017 – SUPPORT Summary of a systematic review

Which interventions are effective in combatting or preventing drug counterfeiting?

Drug counterfeiting is widespread globally, including in low- and middle-income countries. Counterfeit medicines may include medicines with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging. Counterfeit drugs need to be distinguished from substandard drugs – the latter refers to genuine medicines that failed to meet certain quality specifications.

Interventions to combat drug counterfeiting can broadly be categorized into laws and regulations, technological innovations and quality control and vigilance.

Key messages

- **Certain regulatory measures, specifically drug registration, may decrease the prevalence of counterfeit and substandard drugs. It is uncertain whether licensing of drug outlets reduces the prevalence of counterfeit drugs or the failure rates of drugs undergoing quality testing.**
- **WHO prequalification of drugs may lead to a reduction in the failure rates of drugs undergoing quality testing.**
- **Multifaceted interventions (including a mix of regulations, training of inspectors, public-private collaborations and legal actions against counterfeiters) may be effective in decreasing the prevalence of counterfeit and substandard drugs.**
- **All studies identified were conducted in low- and middle-income countries.**
- **The transferability of the findings may be influenced by a country's existing pharmaceutical supply chain and infrastructure, the availability of routine data on drug quality, qualified and skilled personnel, and financial resources.**

Who is this summary for?

People making decisions concerning interventions to combat or prevent drug counterfeiting

! This summary includes:

- **Key findings** from research based on a systematic review
- **Considerations about the relevance of this research** for low-income countries

X Not included:

- Recommendations
- Additional evidence not included in the systematic review
- Detailed descriptions of interventions or their implementation

This summary is based on the following systematic review:

El-Jardali F, Akl E, Fadlallah R, Oliver S, Saleh N, El-Bawab L, Rizk R, Farha A, Hamra R. Interventions to Combat or Prevent Drug Counterfeiting: A Systematic Review. *BMJ Open.* 2015; 5:e006290.

What is a systematic review?

A summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise the relevant research, and to collect and analyse data from the included studies

SUPPORT was an international project to support the use of policy relevant reviews and trials to inform decisions about maternal and child health in low- and middle-income countries, funded by the European Commission (FP6) and the Canadian Institutes of Health Research.

Glossary of terms used in this report: www.supportsummaries.org/glossary-of-terms

Background references on this topic: See back page

Background

It is estimated that up to 10% of all drugs sold worldwide are counterfeit, with much higher prevalences reported in regions with weak drug regulatory and enforcement systems. Counterfeit drugs can lead to treatment failures and adverse health outcomes, the development of drug resistance, and a decline in confidence in health systems. Consequently, such drugs contribute to the burden of disease and to excess morbidity and mortality.

Policymakers from low- and middle-income countries have expressed the need for effective anti-counterfeit drug strategies to be identified. This is the first systematic review to assess the effectiveness of interventions to combat or prevent drug counterfeiting. Most of the included studies did not differentiate between counterfeit and substandard drugs; instead they used "failure rate" to measure changes in quality of medicine. "Failure" referred to drugs that did not meet the minimum requirements for basic testing, quality control laboratory testing, and/or packaging analysis.

How this summary was prepared

After searching widely for systematic reviews that can help inform decisions about health systems, we have selected ones that provide information that is relevant to low-income countries. The methods used to assess the reliability of the review and to make judgements about its relevance are described here: www.supportsummaries.org/how-support-summaries-are-prepared/

Knowing what's not known is important

A reliable review might not find any studies from low-income countries or might not find any well-designed studies. Although that is disappointing, it is important to know what is not known as well as what is known.

A lack of evidence does not mean a lack of effects. It means the effects are uncertain. When there is a lack of evidence, consideration should be given to monitoring and evaluating the effects of the intervention, if it is used.

About the systematic review underlying this summary

Review objective: To assess the evidence on the effectiveness of interventions implemented to combat or prevent drug counterfeiting, particularly in low- and middle-income countries

Types of	What the review authors searched for	What the review authors found
Study designs & Interventions	Randomised trials; non-randomised studies (e.g. cohort studies, retrospective studies, cross-sectional studies, before-after studies); and non-comparative studies. Any intervention at the health system level to combat or prevent drug counterfeiting. Studies that focused on internet/online drug counterfeiting, analytical techniques and medication errors were excluded. Studies that also considered substandard drugs were included only when they did not differentiate between substandard and counterfeit drugs, or where it was unclear if the poor quality medicine was counterfeit or substandard.	*Designs*: 21 studies with 25 comparisons: cross-sectional (17 studies); before-after (5); retrospective (1); non-comparative (1); randomised trial (1) *Interventions:* Drug registration (5 comparisons); WHO prequalification of drugs (3); licensing of drug outlets (8); multi-faceted interventions (6); deployment of handheld spectrometers at the point of sale (1); a public awareness campaign (1); an international model of collaboration (1)
Problem	"Counterfeit/spurious/falsely-labeled/falsified/medicines", as defined by WHO as medicines with the wrong ingredients, without active ingredients, with insufficient active ingredients or with fake packaging.	Most of the studies did not distinguish between counterfeit and substandard medicines
Settings	Any setting	Studies from low- and middle-income countries
Outcomes	Changes in failure rates of tested drugs; changes in the prevalence of counterfeit medicines; changes in quality of medicine; changes in consumer behaviour; seizures of counterfeit drugs; and closures of illegal outlets/warehouses.	Changes in failure rates of drugs (19 comparisons); changes in prevalence of counterfeit drugs (4); changes in purchasing behaviour of consumers (1); confiscation of counterfeit drugs (2); closure of illegal outlet(2) Some studies reported more than one outcome.

Date of most recent search: April 2014

Limitations: This was a well-conducted systematic review with only minor limitations. However, the included studies used largely observational designs.

El-Jardali F, Akl E, Fadlallah R, Oliver S, Saleh N, El-Bawab L, Rizk R, Farha A, Hamra R. Interventions to Combat or Prevent Drug Counterfeiting: A Systematic Review. *BMJ Open.* 2015; 5:e006290.

Summary of findings

Twenty-one studies reporting on 25 comparisons met the inclusion criteria for this review. All of the studies were conducted in low- and middle-income countries.

1) Regulatory measures

Ten studies with 13 comparisons examined the association between regulatory measures and changes in the prevalence of counterfeit and substandard drugs.

Drug registration

Five comparisons focused on drug registration. This involves assessments by drug regulatory authorities of manufacturers of all components of drugs to ensure they meet international standards for good manufacturing practice before authorising drugs for sale.

➔ **Drug registration may decrease the prevalence of counterfeit and substandard drugs. The certainty of this evidence is low.**

➔ **No studies were found on the impact of regulatory measures on the price of drugs or access to medication, particularly among marginalized groups.**

About the certainty of the evidence (GRADE) *

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This is sometimes referred to as 'quality of evidence' or 'confidence in the estimate'.

† Substantially different = a large enough difference that it might affect a decision

See last page for more information.

Drug registration compared with no intervention

Target Antimalarial drugs, antibiotics, first-line anti-tuberculosis medicines, anti-mycobacterial medicines
Settings Low- and middle-income countries
Intervention Registration of drugs
Comparison No registration of drugs

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Without drug registration	**With drug registration**		
Prevalence of counterfeit and substandard drugs	285 per 1000	74 per 1000 (28 to 202)	RR 0.26 (0.1 to 0.71) (4 studies) (5 comparisons)	⊕⊕◯◯ Low
	Difference: 211 fewer counterfeit and substandard drugs per 1000 drugs tested (Margin of error: 83 fewer to 257 fewer)			
Impact on price of drugs	No evidence identified			
Access to generic medications	No evidence identified			

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)
* The risk WITHOUT the intervention is based on the median control group risk (28.5%) across studies from a systematic review on the prevalence of counterfeit and substandard drugs in low-and middle- income countries (Almuzaini et al, 2013). The corresponding risk WITH the intervention (and the 95% confidence interval for the difference) is based on the overall relative effect (and its 95% confidence interval).

Licensing of drug outlets

Eight comparisons focused on licensing of drug outlets. This intervention involves the authorization of pharmaceutical establishments with the aim of ensuring that the supply and sale of drugs are carried under conditions that meet regulatory requirements.

➔ **It is uncertain whether the licensing of drug outlets reduces the prevalence of counterfeit drugs or the failure rates of drugs undergoing quality testing as the certainty of this evidence is very low.**

2) WHO prequalification of drugs

Three studies examined the association between drugs purchased from manufacturers with World Health Organization (WHO) approved certificates of Good Manufacturing Practices and the failure rates of tested drugs. WHO prequalification programmes refer to services provided by the WHO to "facilitate access to medicines that meet unified standards of quality, safety and efficacy primarily for HIV/AIDS, malaria, Tuberculosis, and reproductive health".

➔ **WHO prequalification of drugs may lead to a reduction in the failure rates of drugs undergoing quality testing. The certainty of this evidence is low.**

➔ **No studies were found on the impact of WHO prequalification on the price of drugs or access to medication, particularly among marginalized groups.**

WHO prequalification of drugs compared with no prequalification

Target Antimalarial drugs and first and second-line anti-Tuberculosis medicines
Settings Low- and middle-income countries
Intervention WHO prequalified drugs
Comparison Drugs that have not met WHO prequalification

Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Without WHO prequalification	**With WHO prequalification**		
Prevalence of counterfeit and substandard drugs	285 per 1000	31 per 1000	RR 0.11 (0.04 to 0.33)	⨁⨁◯◯ Low
	Difference: 254 fewer counterfeit and substandard drugs per 1000 drugs tested (Margin of error: 191 fewer to 274 fewer)		(3 studies)	
Impact on price of drugs	No evidence identified			
Access to generic medications, particulalry among marginalized groups	No evidence identified			

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

* The risk WITHOUT the intervention is based on the median control group risk (28.5%) across studies from a systematic review on the prevalence of counterfeit and substandard drugs in low-and middle- income countries (Almuzaini et al, 2013). The corresponding risk WITH the intervention (and the 95% confidence interval for the difference) is based on the overall relative effect (and its 95% confidence interval).

3) Multi-faceted interventions

Five studies reporting on 6 comparisons examined the effects of multi-faceted interventions on the prevalence of counterfeit and substandard drugs. Four of the studies focused on the 'Promoting Quality of Medicine' (PQM) programme which combined quality drug-testing, collaborations with regulatory authorities, and capacity building. The remaining study focused on the 'Quality Assurance System' (QAS) which encompassed the development of regulations, training of drug inspectors in good manufacturing and pharmacy practice, and implementation of legal actions.

- ➔ **Multi-faceted interventions may be effective in decreasing the prevalence of counterfeit and substandard drugs. The certainty of this evidence is low.**
- ➔ **The Promoting Quality of Medicine (PQM) programme may lead to a decrease in the prevalence of counterfeit drugs or in the failure rates of drugs undergoing quality testing. The certainty of this evidence is low.**
- ➔ **Implementing the Quality Assurance System (QAS) probably leads to a reduction in the proportion of drugs that are substandard (from 46% to 22%) and to the proportion of (probably counterfeit) samples with no active ingredients (from 3.3% to 1%). There is probably little or no difference between the 'active intervention' pharmacies, which involved two extra inspections, and the 'regular intervention' pharmacies in improving the quality of medicine. The certainty of this evidence is moderate.**
- ➔ **No studies were found on the impact of multi-faceted interventions on the prices of drugs or access to medication, particularly among marginalized groups.**

4) Other interventions

The authors identified single studies for each of the following interventions: the deployment of handheld spectrometry technologies at inspection points; an international cross-disciplinary model of collaboration; and a public awareness campaign on the danger of counterfeit medicines from illicit drug outlets.

- ➔ **It is uncertain whether deploying spectrometry technology for product authentication at point of sale, or applying an international cross-disciplinary model of collaboration, reduces the prevalence of counterfeit drugs as the certainty of this evidence is very low.**
- ➔ **It is uncertain whether a public awareness campaign on the danger of counterfeit medicines changes purchasing behaviours as the certainty of this evidence is very low.**

Relevance of the review for low-income countries

➔ Findings	▷ Interpretation*
APPLICABILITY	
➔ The studies were all undertaken in low- and middle-income countries. **➔ The results suggest that drug registration, WHO prequalification of drugs, and multi-faceted interventions may be effective in reducing the prevalence of counterfeit drugs.**	*▷ The findings are applicable to low- and middle- income settings. However, a country's existing pharmaceutical supply chain and infrastructure, the availability of routine data on drug quality, the availability of qualified and skilled personnel, and financial resources may affect the transferability of the findings.* *▷ While registration may be effective, it should probably encompass both domestic manufacturers and importers, and be complemented by routine post-marketing surveillance to maintain the quality of drugs circulating in the market.* *▷ Countries that rely heavily on imported drugs may consider opting for drugs that are WHO prequalified. However, even among WHO prequalified products, the quality may vary depending on the country of export.* *▷ Implementing multifaceted interventions requires collaboration with drug regulatory bodies, skilled human resources and technical capacity for routine drug inspections.*
EQUITY	
➔ The included studies did not provide data regarding the differential effects of the interventions on underprivileged populations.	*▷ It is important to consider whether there might be differential effects of interventions according to the individual's socioeconomic status and the baseline conditions in disadvantaged settings.* *▷ It is important to consider if the establishment of WHO prequalification programmes will lead to an increase in the prices of drugs sold to consumers as this can increase inequity, especially in settings where out-of-pocket payments for medicines are necessary.* *▷ Regulatory measures that influence access to generic drugs may have a negative impact on equity if they decrease the availability and increase the cost of medicines.* *▷ Research is needed to evaluate the potential impact of the different anti-counterfeit strategies on equity.*
ECONOMIC CONSIDERATIONS	
➔ The systematic review does not sufficiently address economic consideration.	*▷ The three-level testing approach in the Promoting the Quality of Medicine (PQM) programme (a multi-faceted intervention) may be explored by regulators in settings with limited resources as a potentially cost-effective method for monitoring drugs.* *▷ Further research is needed to evaluate the costs and cost-effectiveness of the included interventions.*
MONITORING & EVALUATION	
➔ The review highlights a need for methodologically rigorous studies to address the limitations of the available evidence and allow robust conclusions to be drawn about the effectiveness of interventions to combat or prevent drug counterfeiting.	*▷ Anti-counterfeit interventions should be pilot-tested with close monitoring before implementation on a large scale.* *▷ The impacts of anti-counterfeit interventions on the quality of medicines and equity should be rigorously evaluated, ideally using randomised designs. The costs and cost-effectiveness of interventions should also be examined.*

*Judgements made by the authors of this summary, not necessarily those of the review authors, based on the findings of the review and consultation with researchers and policymakers in low-income countries. For additional details about how these judgements were made see: www.supportsummaries.org/methods

Additional information

Related literature

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This summary was prepared by

Racha Fadlallah, Fadi El-Jardali, and Elie Akl. American University of Beirut. Lebanon.

Conflict of interest

Racha Fadlallah, Fadi El-Jardali, and Elie Akl are authors of the systematic review on which this summary is based. For details, see: www.supportsummaries.org/coi

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About certainty of the evidence (GRADE)

The "certainty of the evidence" is an assessment of how good an indication the research provides of the likely effect; i.e. the likelihood that the effect will be substantially different from what the research found. By "substantially different" we mean a large enough difference that it might affect a decision. These judgements are made using the GRADE system, and are provided for each outcome. The judgements are based on the study design (randomised trials versus observational studies), factors that reduce the certainty (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and factors that increase the certainty (a large effect, a dose response relationship, and plausible confounding). For each outcome, the certainty of the evidence is rated as high, moderate, low or very low using the definitions on page 3.

For more information about GRADE:
www.supportsummaries.org/grade

SUPPORT collaborators:

The Cochrane Effective Practice and Organisation of Care Group (EPOC) is part of the Cochrane Collaboration. The Norwegian EPOC satellite supports the production of Cochrane reviews relevant to health systems in low- and middle-income countries .
www.epocoslo.cochrane.org

The Evidence-Informed Policy Network (EVIPNet) is an initiative to promote the use of health research in policymaking in low- and middle-income countries. www.evipnet.org

The Alliance for Health Policy and Systems Research (HPSR) is an international collaboration that promotes the generation and use of health policy and systems research in low- and middle-income countries.
www.who.int/alliance-hpsr

Norad, the Norwegian Agency for Development Cooperation, supports the Norwegian EPOC satellite and the production of SUPPORT Summaries.
www.norad.no

The Effective Health Care Research Consortium is an international partnership that prepares Cochrane reviews relevant to low-income countries. www.evidence4health.org

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