PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Substandard and counterfeit medicines: A systematic review of the literature
AUTHORS	Almuzaini, Tariq; Choonara, Imti; Sammons, Helen

VERSION 1 - REVIEW

REVIEWER	Stuart MacLeod Professor, Pediatrics, University of British Columbia, Canada Senior Clinician Scientist, Child & Family Research Institute, Vancouver, BC Special Advisor, Office of Legislative and Regulatory Modernization, Health Canada, Ottawa ON I have no competing interests.
REVIEW RETURNED	15-Apr-2013

THE STUDY	Study addresses a very important question relevant to therapeutics, particularly in LMICs. The evaluation form provided is not entirely appropriate to a manuscript of this type, a systematic review of the literature. Because of the nature of the question asked, the authors are forced to rely on a literature base of limited quality with almost all relevant studies conducted in LMICs. The main outcome measure is not entirely clear because the authors have chosen to combine reports re counterfeit and substandard medicines in a single review. This is understandable because most published literature refers to substandard rather than counterfeit medicines, although counterfeit products are the major concern. The abstract/summary/key messages/limitations are reasonably complete but the message about limitations related to sampling methods is not clear from the abstract. The abstract is quite repetitive in describing the absence of data from upper middle income and high income countries. This is repeated three times in the abstract although this observation is of limited interest compared to the description of the situation in LMICs. In the results section of the abstract, the opening statement is not a sentence. Statistical methods are not described because they are generally not appropriate to a study of this kind. The standard of English is acceptable but the manuscript requires careful review for grammar. In some places the manuscript is confusing because the authors have referred to prevalence without specifying “prevalence of substandard or counterfeit medicines”.

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	While the references are up to date, they are sometimes described in cursory fashion and should be checked carefully. This is particularly true of the frequent references to WHO reports (eg, references 22, 23, 26). Many of the references have not been accessed for one or two years. There are no supplemental documents.
RESULTS & CONCLUSIONS	The results from the systematic literature review are relatively clear but the presentation is somewhat circumlocutory and the volume of text could probably be reduced by at least 30% to improve the manuscript's impact. The information is described in the text then presented in greater detail in a series of 9 tables. The main message of the manuscript will be clearer if some of these tables are omitted or their results presented only in the text. Perhaps the authors could select key emssages to be conveyed in the table.
REPORTING & ETHICS	A study of this kind does not require ethical review and consequently no issues are identified.
GENERAL COMMENTS	Supplementary comments: • Abstract - strengths & limitations: The intent of the second bullet comment is unclear and it should be reworded. • Introduction, line 4: "Even low priced medicines simply taken to relieve pain are vulnerable to counterfeiting." The meaning of this sentence is unclear and it should be rewritten. • page 4, lines 19-20: The statement of objective is "to explore and summarize the magnitude and extent of the problem of counterfeit and substandard medicines". The combination of these two concerns will create some confusion for readers. It is clear that substandard production of medicines is much more common in the reports cited than is actual counterfeiting. The complete absence of active medication obviously has greater clinical implications. • page 6, statistical analysis: "The median prevalence of these drugs was analyzed for each income level group." In this and several other places, prevalence is used with a clear implication that it is the prevalence of substandard and counterfeit medicines that is being described, but this needs to be explicit. • The discussion of the limitation encountered in drawing conclusions concerning counterfeiting is inadequate. Perhaps this specific limitation could be more fully described by the authors. • The discussion of pediatric formulations is based on two studies reporting on syrup/suspension formulations of antimalarials. This is an important area of concern in LMICs but the information found by the authors is inadequate to support inclusion in this paper or in the fuller discussion presented on page 9. • The statement at the end of the discussion (page 10) that "there are a number of national and international initiatives taking place led by WHO and it member states working group" is very weak.

REVIEWER	Roggo, Yves F. Hoffmann-La Roche Ltd
REVIEW RETURNED	24-Apr-2013

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THE STUDY	I am not sur that the authors are using an adequate selection of the studies. I believe that there is a bias in the methodology. 15 papers have been selected out of 2363 only. - A large impact is give to the who publications (4 papers /15). - 2 papers from one journal (trop Med Int Healt)
RESULTS & CONCLUSIONS	No clear conclusion in this paper Large description of the methodology but only few conclusions

REVIEWER	Tim K. Mackey, MAS, PhD(c) Clinical Instructor (Health Services) UC San Diego, School of Medicine Senior Research Associate Institute of Health Law Studies
REVIEW RETURNED	10-May-2013

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript that attempts to conduct a systematic review of counterfeit/falsified/substandard medicine prevalence studies to establish some indication of the extent of this global health problem. Specific comments ========== 1. Abstract: I would rephrase the objective here. Clearly, there is no way to establish the extent of the global counterfeit problem simply by reviewing the current literature available as this literature may only represent one component of counterfeit (for a lack of a better term) medicines reporting. Indeed, the sample from the literature is not even representative of the problem and the complex issues regarding adequate surveillance and reporting make this objective basically impossible to achieve currently. Please rephrase appropriately to note these limitations. The conclusion statement should also be rewritten to acknowledge these limitations. This is only a subset of medicines that have been reviewed, so it should be acknowledged that based on the systematic review conducted, there appears to be a high-prevalence of counterfeit medicines for certain therapeutic classes in countries where studies were conducted. Something along those lines. I know this is mentioned in your strengths and limitations, but also needs to be reflected in these statements. 2. Introduction: First paragraph really needs to flush out the issue better. There is a huge diversity of counterfeited medicines and any medicine that is counterfeit has the potential to harm patients, regardless if it is a life-saving drug, lifestyle drug, etc. Any of these drugs has the potential for substandard or toxic contents. Also, counterfeit medicines such as the Avastin case in the USA have been detected, so this is not just an LMIC/LIC problem, though prevalence is arguably higher in these settings. The following citation may help though there are others available as well: Tim Mackey & Bryan A. Liang, The Global Counterfeit Drug Trade: Patient Safety and Public Health Risks, 100(11) JOURNAL OF PHARMACEUTICAL SCIENCE 4751-79 (2011) Instead of fake packaging I would say a product that is misleading about its origin or authenticity. Also, authors really need to talk about the controversy surrounding definitions now, and how different agencies/International organizations use different terms. At the least,

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	authors should mention WHO use of SSFFC term as an example. WHO estimates as published by IMPACT are really just a guess, authors should mention other sources of reporting as well (e.g. Pharmaceutical Security Institute) and the limitations of these data as well just to give readers some context (does not need a lot of detail). This data also shows up in the recent Institute of Medicine report (available: http://www.iom.edu/Reports/2013/Countering-the-Problem-of-Falsified-and-Substandard-Drugs.aspx) that really needs to be cited in this piece. 2. Methods: Authors should have also included the term "spurious" in their search or at least comment on whether there are any results in this search term. Also, authors need to explain why they used specific therapeutic classes (antimicrobials/antimalarials) in their search terms. I know this due to the high number of studies conducted for these drugs, but a justification is needed in the methodology. Also, did authors include articles that were in foreign languages (if any) or just English? 3. Data Collection process and data items: Does "stated issues" include the category of claimed incident (e.g. substandard drugs, fake packaging, no API, etc?), it appears that way in Table 6, but authors should list out these subcategories and what they are defined as. Also, I'm not clear on what authors mean by not attempting to compare a suspect sample of packaging. Do they mean the drug sample or just the package sample. Unclear on what is meant here. Would it not be simpler to stratify studies by how they were "confirmed" to be counterfeit? (i.e. lab tests, packaging fake, etc.) Box 1 change "was" to "were". 4. Results: Given that 10 of the 15 studies that meet the inclusion criteria were for antimicrobial drugs, we really are talking about a study that examines this subset of therapeutic class as there is not enough power in the sample to make any inferences regarding overall counterfeiting of drugs. I think this has to be made clear in the results section and that the findings should be limited to this subset of drugs. 5. Study Methodology: Would very much like to know what methods were used for drug analysis and in partnership with what organizations. This is critically important to assessing the validity and types of tests conducted. This should be listed out. I also am not clear about the statement that some studies were not originally designed to detect counterfeit medicines, I thought only studies examining counterfeit medicines were being assessed. Please clarify. I'm guessing that many of the study sponsors identified were in collaboration with several organizations, could you please elaborate if this was the case? 6. Study Location and prevalence…: Authors need to acknowledge that the reason for the geographic distribution here is due to the medicines that were examined, e.g. antimicrobial agents. This heavily influences where the studies are being conducted given regional prevalence of these diseases. 7. Prevalence according to where medicines are purchased…: I think this is a very interesting and substantial finding. Would like to have this paragraph more flushed out if additional information is available. 8. DISCUSSION: Most importantly, authors need to limit their conclusions in the discussion to the results of the review. Though this is addressed in the limitations section, it needs to be incorporated into the discussion of the paper upfront as findings from this review are significantly limited. Firstly, counterfeit drugs are a huge global problem, but the review conducted only looks at a small subsample of studies for an even smaller range of therapeutic

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	classes in select regions. Hence, the results cannot be generalizable to the global counterfeit drug trade and the results really point to the lack of available data on the topic and the need for better surveillance and research. Last sentence of pg.11 second paragraph that starts on line 26 needs citation ("governments can play an important role...) There are a number of international and national initiatives working on this, but they are not simply led by the WHO new member state mechanism. In fact, UNODC is becoming actively engaged, and Interpol has been involved for quite some time. WCO is also an active player now. The statement that all this is led by WHO and the MSM demonstrates that authors do not know what the current governance discussions are regarding addressing SSFFC. Additionally, I think a supplement of studies that were excluded from analysis (29) and their criteria score would be very helpful. For example, a study recently published in BMJ Open that was in the review period seems to meet a number of the criteria required for inclusion (see: http://bmjopen.bmj.com/content/2/3/e000854.full) I would like to know why some of these studies were excluded based on their criteria scores. Overall, this is an extremely important topic and a systematic review of prevalence in the literature is sorely needed. That said, the authors need to improve the manuscript based on the comments presented and really narrow the discussion and conclusions to the limitations of the review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Stuart MacLeod
Professor, Pediatrics, University of British Columbia, Canada Senior Clinician Scientist, Child & Family Research Institute, Vancouver, BC Special Advisor, Office of Legislative and Regulatory Modernization, Health Canada, Ottawa ON
I have no competing interests.

Reviewer's comment #1: Study addresses a very important question relevant to therapeutics, particularly in LMICs. The evaluation form provided is not entirely appropriate to a manuscript of this type, a systematic review of the literature. Because of the nature of the question asked, the authors are forced to rely on a literature base of limited quality with almost all relevant studies conducted in LMICs.
The main outcome measure is not entirely clear because the authors have chosen to combine reports re counterfeit and substandard medicines in a single review. This is understandable because most published literature refers to substandard rather than counterfeit medicines, although counterfeit products are the major concern.

Authors' response: Thank you very much for your valuable comments .The main outcome is to report the prevalence of counterfeit and substandard medicines reported by these studies. The majority of these studies were conducted to evaluate the quality of medicines. Only two studies took the analysis further to investigate the authenticity of these drugs and worked out the prevalence of counterfeit drugs. Therefore, it was difficult to work out the prevalence for each problem. Thus, we decided to combine the two terms as both are medicines with poor quality and can be harmful to patients.

Reviewer's comment #2: The abstract/summary/key messages/limitations are reasonably complete but the message about limitations related to sampling methods is not clear from the abstract.

Authors' response: Limitations of the review are now added into the abstract (please see abstract

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page no. 2)

Reviewer's comment #3: The abstract is quite repetitive in describing the absence of data from upper middle income and high income countries. This is repeated three times in the abstract although this observation is of limited interest compared to the description of the situation in LMICs.

Authors' response: We deleted the repetition from the abstract. (Please see abstract page no. 2)

Reviewer's comment #4: In the results section of the abstract, the opening statement is not a sentence.

Authors' response: The opening statement of the result is rewritten. (Please see abstract page no. 2)

Reviewer's comment #5: The standard of English is acceptable but the manuscript requires careful review for grammar.

Authors' response: We have reviewed the paper and corrected the grammar where appropriate.

Reviewer's comment #6: In some places the manuscript is confusing because the authors have referred to prevalence without specifying "prevalence of substandard or counterfeit medicines".

Authors' response: We have clarified this in the method section (page no. 6). We have also added another heading to the result section to discuss the prevalence of counterfeit medicines that has been worked out by studies that conducted packaging analysis (page no. 8)

Reviewer's comment #7: While the references are up to date, they are sometimes described in cursory fashion and should be checked carefully. This is particularly true of the frequent references to WHO reports (eg, references 22, 23, 26). Many of the references have not been accessed for one or two years.

Authors' response: We have updated the references.

Reviewer's comment #8: The results from the systematic literature review are relatively clear but the presentation is somewhat circumlocutory and the volume of text could probably be reduced by at least 30% to improve the manuscript's impact.

Authors' response: We have tried to summarise the results and decrease the volume of text.

Reviewer's comment #9: The information is described in the text then presented in greater detail in a series of 9 tables. The main message of the manuscript will be clearer if some of these tables are omitted or their results presented only in the text. Perhaps the authors could select key messages to be conveyed in the table.

Authors' response: The article now contains 3 tables with more details in the text. Extra data is available as supplementary online data.

Supplementary comments:
Reviewer's comment #10: Abstract - strengths & limitations: The intent of the second bullet comment is unclear and it should be reworded.

Authors' response: The second point of the strength and limitations is reworded. Please see page no. 3

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Reviewer's comment #11: Introduction, line 4: "Even low priced medicines simply taken to relieve pain are vulnerable to counterfeiting." The meaning of this sentence is unclear and it should be rewritten.

Authors' response: We have deleted the sentence and we have rewritten the first paragraph in the introduction. Please see page no.4

Reviewer's comment #12: Page 4, lines 19-20: The statement of objective is "to explore and summarize the magnitude and extent of the problem of counterfeit and substandard medicines". The combination of these two concerns will create some confusion for readers. It is clear that substandard production of medicines is much more common in the reports cited than is actual counterfeiting. The complete absence of active medication obviously has greater clinical implications.

Authors' response: Please look at our response to the point no. 1and 6

Reviewer's comment #13: Page 6, statistical analysis: "The median prevalence of these drugs was analyzed for each income level group." In this and several other places, prevalence is used with a clear implication that it is the prevalence of substandard and counterfeit medicines that is being described, but this needs to be explicit.

Authors' response: Please see explanation given above on clarification of the terms used.

Reviewer's comment #14: The discussion of the limitation encountered in drawing conclusions concerning counterfeiting is inadequate. Perhaps this specific limitation could be more fully described by the authors.

Authors' response: These limitations are now discussed in the first paragraph of the discussion (page 9) and in the limitation section (page 11).

Reviewer's comment #15: The discussion of pediatric formulations is based on two studies reporting on syrup/suspension formulations of antimalarials. This is an important area of concern in LMICs but the information found by the authors is inadequate to support inclusion in this paper or in the fuller discussion presented on page 9.

Authors' response: As you have suggested, we have deleted table 4 and result section on paediatric formulations. We have also deleted the discussion on this area.

Reviewer's comment #16: The statement at the end of the discussion (page 10) that "there are a number of national and international initiatives taking place led by WHO and it member states working group" is very weak.

Authors' response: We have strengthened this statement by adding other recent relevant initiatives going on to combat the problem. Please see the last paragraph of the discussion on page no. 10-11.

Reviewer: Yves Roggo
F. Hoffmann-La Roche Ltd

Reviewer's comment #1: I am not sur that the authors are using an adequate selection of the studies. I believe that there is a bias in the methodology. 15 papers have been selected out of 2363 only.
- A large impact is give to the who publications (4 papers /15).

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- 2 papers from one journal (trop Med Int Healt).
No clear conclusion in this paper.
Large description of the methodology but only few conclusions

Authors' response: Thanks for your comments. It is usual to have a large number of papers at the beginning of a systematic review and therefore the numbers to be significantly reduced once the inclusion/exclusion criteria and quality assessment takes place. WHO publications make up a large number of papers as they have strong methodology, and are active in the regions studied. The journals were not preselected and all searched.
We have now strengthened the conclusions in the paper.

Reviewer: Tim K. Mackey, MAS, PhD(c)
Clinical Instructor (Health Services)
UC San Diego, School of Medicine
Senior Research Associate
Institute of Health Law Studies

Reviewer's comment #1: Abstract: I would rephrase the objective here. Clearly, there is no way to establish the extent of the global counterfeit problem simply by reviewing the current literature available as this literature may only represent one component of counterfeit (for a lack of a better term) medicines reporting. Indeed, the sample from the literature is not even representative of the problem and the complex issues regarding adequate surveillance and reporting make this objective basically impossible to achieve currently. Please rephrase appropriately to note these limitations.

Authors' response: Thank you so much for reviewing of our manuscript and your valuable comments. The objective of the review is rephrased according to the above suggestion. Please see page no. 2

Reviewer's comment #2: The conclusion statement should also be rewritten to acknowledge these limitations. This is only a subset of medicines that have been reviewed, so it should be acknowledged that based on the systematic review conducted, there appears to be a high-prevalence of counterfeit medicines for certain therapeutic classes in countries where studies were conducted. Something along those lines. I know this is mentioned in your strengths and limitations, but also needs to be reflected in these statements.

Authors' response: The conclusion is rewritten to highlight that the evidence is only for antimicrobial medicines as follows "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"

Reviewer's comment #3: Introduction: First paragraph really needs to flush out the issue better. There is a huge diversity of counterfeited medicines and any medicine that is counterfeit has the potential to harm patients, regardless if it is a life-saving drug, lifestyle drug, etc. Any of these drugs has the potential for substandard or toxic contents. Also, counterfeit medicines such as the Avastin case in the USA have been detected, so this is not just an LMIC/LIC problem, though prevalence is arguably higher in these settings. The following citation may help though there are others available as well: Tim Mackey & Bryan A. Liang, The Global Counterfeit Drug Trade: Patient Safety and Public Health Risks, 100(11) JOURNAL OF PHARMACEUTICAL SCIENCE 4751-79 (2011).

Authors' response: The first paragraph is reworded now to reflect your suggestion, please see page no. 4. The reference above is also added, reference no 3.

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Reviewer's comment #4: Instead of fake packaging I would say a product that is misleading about its origin or authenticity.

Authors' response: The term fake packaging is a part of the definition that is given by the WHO. We have clarified this in the paper by using your suggested terms as well. Please see the second paragraph of the introduction page no. 4

Reviewer's comment #5: Also, authors really need to talk about the controversy surrounding definitions now, and how different agencies/International organizations use different terms. At the least, authors should mention WHO use of SSFFC term as an example.

Authors' response: As you suggested we have added the new term "SSFFC" medicine used by the WHO and issues surrounding using it. Please see the second paragraph of the introduction, page no 4.

Reviewer's comment #6: WHO estimates as published by IMPACT are really just a guess, authors should mention other sources of reporting as well (e.g. Pharmaceutical Security Institute) and the limitations of these data as well just to give readers some context (does not need a lot of detail). This data also shows up in the recent Institute of Medicine report (available: http://www.iom.edu/Reports/2013/Countering-the-Problem-of-Falsified-and-Substandard-Drugs.aspx) that really needs to be cited in this piece.

Authors' response: As you suggested the IMPACT estimate is removed and replaced by Pharmaceutical Security Institute data with its limitations. We also added all the references that you mentioned above. Please see last paragraph of the introduction on page No. 4 and reference no. 10.

Reviewer's comment #7: Methods: Authors should have also included the term "spurious" in their search or at least comment on whether there are any results in this search term. Also, authors need to explain why they used specific therapeutic classes (antimicrobials/antimalarials) in their search terms. I know this due to the high number of studies conducted for these drugs, but a justification is needed in the methodology. Also, did authors include articles that were in foreign languages (if any) or just English?

Authors' response: When limiting the search to 'drugs', 'medicines', and 'pharmaceuticals' this resulted in important studies on antimicrobials being missed. The term spurious drug is mentioned in the India's Drug And Cosmetics Act 1940 and recently included in the new WHO "SSFFC". It has been rarely used in the literature with only three editorials and one review available, all from India. As you suggested a justification for the use of the term antimicrobials is added now in the methods section, first paragraph page no. 5.
The search was not limited to English language. Foreign language abstracts were electronically translated and assessed for inclusion. Full papers were translated when relevant. We have added a statement at the end of the methods section, second paragraph on page no. 5. We found one paper in French which was assessed but didn't meet the methodological quality for inclusion.

Reviewer's comment #8: Data Collection process and data items: Does "stated issues" include the category of claimed incident (e.g. substandard drugs, fake packaging, no API, etc?), it appears that way in Table 6, but authors should list out these subcategories and what they are defined as.

Authors' response: we have now added table to define these subcategories. Please see page no. 5 (at line 49-50) and supplementary table 2.

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Reviewer's comment #9: (i) Also, I'm not clear on what authors mean by not attempting to compare a suspect sample of packaging. Do they mean the drug sample or just the package sample. Unclear on what is meant here. (ii) Would it not be simpler to stratify studies by how they were "confirmed" to be counterfeit? (i.e. lab tests, packaging fake, etc.) (iii) Box 1 change "was" to "were".

Authors' response: (i) We have clarified this point, please see page no. 6 last paragraph in Data collection process and data items. (ii) We mention this in supplementary table 4. We have also added another section in the result (Counterfeit medicines, page no. 8) to clarify which studies assessed the packaging and in turn determined the prevalence of counterfeit medicines in their samples. (iii) We have now changed it.

Reviewer's comment #10: Results: Given that 10 of the 15 studies that meet the inclusion criteria were for antimicrobial drugs, we really are talking about a study that examines this subset of therapeutic class as there is not enough power in the sample to make any inferences regarding overall counterfeiting of drugs. I think this has to be made clear in the results section and that the findings should be limited to this subset of drugs.

Authors' response: We have added this statement in page no. 8 (This prevalence is mainly representative of antimicrobial drugs, as these accounted for the bulk of the tested samples). We have also clarified this in the abstract, discussion and conclusion.

Reviewer's comment #11: Study Methodology: (i) Would very much like to know what methods were used for drug analysis and in partnership with what organizations. This is critically important to assessing the validity and types of tests conducted. This should be listed out. (ii) I also am not clear about the statement that some studies were not originally designed to detect counterfeit medicines, I thought only studies examining counterfeit medicines were being assessed. Please clarify. (iii) I'm guessing that many of the study sponsors identified were in collaboration with several organizations, could you please elaborate if this was the case?

Authors' response: (i) All methods of testing are now listed in online supplementary table 4. (ii) Regarding studies that assessed counterfeiting we clarified this point in page no. 6 last paragraph in Data collection process and data items. (iii) We added a column in table 4 (supplementary table) to detail the chemical analysis and in which places were carried out. We have also clarified this in the last paragraph of study methodology on page no. 7

Reviewer's comment #12: Study Location and prevalence...: Authors need to acknowledge that the reason for the geographic distribution here is due to the medicines that were examined, e.g. antimicrobial agents. This heavily influences where the studies are being conducted given regional prevalence of these diseases.

Authors' response: As suggested, we acknowledge that the limitation to antimicrobials is due in part to study locations and the high burden of disease in these areas. We added this to the second paragraph of the discussion, page no. 9.

Reviewer's comment #13: Prevalence according to where medicines are purchased...: I think this is a very interesting and substantial finding. Would like to have this paragraph more flushed out if additional information is available.

Authors' response: Unfortunately, there is no additional information can be added as we have found only five studies that compare the drug quality in licensed and unlicensed outlets.

Reviewer's comment #14: DISCUSSION: Most importantly, authors need to limit their conclusions in

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the discussion to the results of the review. Though this is addressed in the limitations section, it needs to be incorporated into the discussion of the paper upfront as findings from this review are significantly limited. Firstly, counterfeit drugs are a huge global problem, but the review conducted only looks at a small subsample of studies for an even smaller range of therapeutic classes in select regions. Hence, the results cannot be generalizable to the global counterfeit drug trade and the results really point to the lack of available data on the topic and the need for better surveillance and research.

Authors' response: We have shortened and focussed our discussion around our results and have highlighted that they point to a lack of good quality studies being available.

Reviewer's comment #15: Last sentence of pg.11 second paragraph that starts on line 26 needs citation ("governments can play an important role...)

Authors' response: As you suggested references are now added. Please see the second paragraph on page no. 10 (at line 22)

Reviewer's comment #16: There are a number of international and national initiatives working on this, but they are not simply led by the WHO new member state mechanism. In fact, UNODC is becoming actively engaged, and Interpol has been involved for quite some time. WCO is also an active player now. The statement that all this is led by WHO and the MSM demonstrates that authors do not know what the current governance discussions are regarding addressing SSFFC.

Authors' response: We reformed the statement as you suggested. Please see the last paragraph of the discussion, page no. 10-11

Reviewer's comment #17: Additionally, I think a supplement of studies that were excluded from analysis (29) and their criteria score would be very helpful. For example, a study recently published in BMJ Open that was in the review period seems to meet a number of the criteria required for inclusion (see: http://bmjopen.bmj.com/content/2/3/e000854.full) I would like to know why some of these studies were excluded based on their criteria scores.

Authors' response: This is a very important study that you have highlighted. It was excluded from our review as samples were ordered on the internet. Websites offer counterfeit drugs often conceal their physical address and therefore are not representative of a geographical area. As you suggested, table of excluded studies with their criteria scores are now added as a supplementary data (supplementary table 3).

Reviewer's comment #18: Overall, this is an extremely important topic and a systematic review of prevalence in the literature is sorely needed. That said, the authors need to improve the manuscript based on the comments presented and really narrow the discussion and conclusions to the limitations of the review.

Authors' response: We have tried to achieve this with our amended manuscript. Thank you for your comments to help us do this.

VERSION 2 – REVIEW

REVIEWER	Tim K. Mackey, MAS, PhD Clinical Instructor (Health Services) UC San Diego School of Medicine Tim K. Mackey (TKM) is the 2011-2013 Carl L. Alsberg MD Fellow of the Partnership for Safe Medicines (PSM), a non profit organization focused on combating counterfeit medicines which supports his

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	general research activities. TKM receives travel expenses once per year to attend the PSM annual meeting. TKM report no other relationships or activities that could appear to have influenced the submitted work.
REVIEW RETURNED	03-Jul-2013

RESULTS & CONCLUSIONS	Shouldn't page 8 line 34 be titled something else. This section looks at results from studies that analyzed the packaging correct? I'm not sure this qualifies under the definition of counterfeit unless you want to make that distinction. Though also looks like some of these studies did assess API? Perhaps rename this section or combine it with the prior. You could also differentiate by mentioning that these are studies from S.E. Asia. I also didn't see discussion to my original comment below. Please explain why it is excluded from discussion or address: Authors need to acknowledge that the reason for the geographic distribution here is due to the medicines that were examined, e.g. antimicrobial agents. This heavily influences where the studies are being conducted given regional prevalence of these diseases. p.10, lines 19-22: I would say this might work, but the national government has to implement a robust regulatory regime and also ensure that domestically produced medicines are actually utilized for the domestic market not the export market. p.10 line 56: IMPACT is pretty much dead and no longer viable after WHO withdrew support, so I wouldn't mention them as they are not active. Other than the minor revisions above, authors have done a good job focusing the manuscript to the main results of their study.
GENERAL COMMENTS	If authors address my minor comments, no further review is needed from me.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Tim K. Mackey, MAS, PhD
Clinical Instructor (Health Services)
UC San Diego School of Medicine

Reviewer comment #1: Shouldn't page 8 line 34 be titled something else. This section looks at results from studies that analyzed the packaging correct? I'm not sure this qualifies under the definition of counterfeit unless you want to make that distinction. Though also looks like some of these studies did assess API? Perhaps rename this section or combine it with the prior. You could also differentiate by mentioning that these are studies from S.E. Asia.

Authors' response: Thanks for the comments. These studies assessed the packaging by comparing the suspected samples packaging authenticity with the original samples packaging from relevant manufacturers. Mislabelled and misleading information were identified as to the origin of these samples. We have now combined this section with the section before it, to reflect your suggestion. Please see page 8.

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Reviewer comment #2: I also didn't see discussion to my original comment below. Please explain why it is excluded from discussion or address: Authors need to acknowledge that the reason for the geographic distribution here is due to the medicines that were examined, e.g. antimicrobial agents. This heavily influences where the studies are being conducted given regional prevalence of these diseases.

Authors' response: We have addressed this point in the second paragraph of the discussion (page 9). We acknowledge that the high prevalence antimicrobial medicine is because there is a high demand for antimicrobials in the countries where the prevalence studies have been carried out, because of the considerable burden of infectious diseases in these countries.
Our search was comprehensive to all medicines, but there were only a few studies found that assessed the prevalence of other classes of medicines, in the literature. There may be some cases of counterfeit medicines of other therapeutic classes seized in high income countries but these were reported by enforcement agencies, not in the literature.

Reviewer comment #3: p.10, lines 19-22: I would say this might work, but the national government has to implement a robust regulatory regime and also ensure that domestically produced medicines are actually utilized for the domestic market not the export market.

Authors' response: we have edited this sentence according to your suggestion. It now reads as follows: "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".

Reviewer comment #4: p.10 line 56: IMPACT is pretty much dead and no longer viable after WHO withdrew support, so I wouldn't mention them as they are not active.

Authors' response: the sentence is rewritten without mentioning IMPACT. Please see the last sentence on page 10.

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