PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Interrupted Time Series Analysis of the Impact of Generic Market Entry of Antineoplastic Products in China
AUTHORS	Guan, Xiaodong; Tian, Ye; Ross-Degnan, Dennis; Man, Chunxia; Shi, Luwen

VERSION 1 – REVIEW

REVIEWER	Dr Rose Cairns The University of Sydney and The Children's Hospital at Westmead, Australia
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	Thank you for inviting me to review this manuscript. This is an interrupted time series analysis of antineoplastic products following generic entry in China. The paper reports a positive effect of generic entry on medicine availability, accessibility and utilisation. Please find my detailed comments below. Methods: It would be good if the authors could comment on any data capture changes in CMEI over the study period (or if there are none, make that clear). Results: The ITS analysis of brand name drugs change is confusing. Page 10 Line 49 states "there was a significant increasing trend in the volume of brand-name Capecitabine, Decitabine and Imatinib" but the numbers written indicate a decreasing trend. The next sentence talks about the estimated decrease in the last month of the observation period. So is it an increase or decrease? Page 11 Line 8 - need to be clear which numbers belong to which drug. Page 11 Line 26 shouldn't this read "brand name imatinib" rather than "Imatinib"? It needs to be clear when the authors are referring to branded vs all products. Table 1: Is this the best way to display the data? I think the figure tells the story better, I wonder if Table 1 is necessary? Figures 1-2 - Legends need some work to be more explanatory and outline what is being shown in each panel. - Intervention time points need to be clearly labelled (currently the

	dashed lines have no explanation if viewing the figure in isolation) - The use of dashed lines to signify intervention time but also to show estimated trends is a bit confusing when printed in black and white. Supplementary Figure 1: I think the intervention time should be labelled on these figures too. Supplementary Table 1: Should define acronyms in footer Discussion: To aid readers who are not familiar with the Chinese health system, I think it would be useful to provide some context in the discussion. E.g. what is the role of drug committees in Chinese hospitals? Could this have influenced utilisation trends in certain hospitals? How are is healthcare paid for - government, private health insurance and individuals? Could government or private health subsidy have influenced results? I also recommend some expansion on hospital procurement practices (Pages 12-13) for those not familiar with the Chinese system. Can you confirm weather the 15% mark up rule is still in place (I read some reports it had been banned). Can you speculate on why capecitabine uptake of generic differs from the other two drugs studied? The paper could do with some english editing, e.g. Page 5, lines 33-43, 2 sentences starting with "From the perspective of..." Specialist statistical review is also recommended. Minor points: - Double check reference Pg 6 Line 19 - states reference 26 but shouldn't it be reference 24 (Jiang et al as stated at beginning of sentence)? - Page 7 (methods) line 3: I think this should read "Supplementary Table 1" rather than "Table 1"? - Page 10 (results) line 10: should include units (CNY) in DDDc reporting

REVIEWER	Brian Godman Division of Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden and Strathclyde Institute of Pharmacy and Biomedicial Sciences, Strathclyde University, Glasgow, UK
REVIEW RETURNED	23-Mar-2018

GENERAL COMMENTS	A) General I enjoyed reading the paper with a number of good points applicable to other situations in other countries. The methodology was sound as well – enhancing the robustness of the good conclusions. B) Specific I have though a number of suggestions to make that could potentially add to the paper and its impact. These include: a) Page 2 – Abstract. Lines 6 – 12. High prices of medicines typically

	in a number of countries refer to new biological medicines especially for cancer and orphan diseases with generics in some European markets as low as 2 – 4% of originator prices pre patent loss – so may be better to say 'high prices of new medicines'. I would also add in health authorities alongside consumers since in a number of countries medicines are provided at either no cost or low cost as part of universal access, e.g. Western Europe. I would also add in that looking at anti-neoplastics as these are high costs for new medicines causing concern b) Page 5 • Line 6 – Not sure ref 1 here is the right reference – not sure these needs a reference • Lines 7 – 12. Concerns though recently with the level of profitability of some new medicines challenging this statement, e.g. new Hep C medicines were priced with a gross profitability of over 99.9% in Europe and USA (Phelan M, Cook C. A treatment revolution for those who can afford it? Hepatitis C treatment: new medications, profits and patients. BMC Infect Dis. 2014;14 Suppl 6:S5), the cost of goods of new cancer medicines have recently been estimated at only approx. 1% of the selling price in some countries (Hill A et al. Estimated generic prices of cancer medicines deemed cost-ineffective in England: a cost estimation analysis. BMJ open. 2017;7(1):e011965; Hill A et al. Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. BMJ open. 2016;6(1):e009586) and good quality generics can be priced as low as 2% of originator pre-patent loss prices (Woerkom M et al. Ongoing measures to enhance the efficiency of prescribing of proton pump inhibitors and statins in The Netherlands: influence and future implications. Journal of comparative effectiveness research. 2012;1:527-38). There are also concerns with the oftern quoted fifure of US! – 2bn for developing a new medicine (The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts. Blood. 2013;121(22):4439-42) • Lines 13 – 15 – Generics also have societal benefits – I would move ref 23 to here • Lines 19 – 21 – The quality statement needs references as there still is scepticism about the quality of generics across countries with some countries having low use – so would include a number of publications of Kesselheim and others here as references to support this statement • Lines 28 – 30 – It is difficult for oiginators to increase their prices in Europe – any price rise has to be accepted by the national reimbursement committees. We are though seeing prices of generics rise especially low volume ones and where manufacturers change – e.g. for some generic cancer medicines (Hawkes N. Drug company Aspen faces probe over hiking generic prices. BMJ. 2017;357:j2417.). • Lines 33 – 38 – This sentence does not make sense as acurrently written • Line 40 – This depends on the European market and the ongoing reforms to increase the prescribing of generics and whether internal reference pricing such as Croatia. Greece still limited acceptance/ prescribing of generics (Labiris G et al. Greek Physicians' Perceptions on Generic Drugs in the Era of Austerity. Scientifica. 2015;2015:251792). c) Page 6 • Line 12 – Not sure Ref 24 is right here – should this be ref 26?

	Similarly line 19 – should this be ref 24 rather than 26? • Line 21 – before going into the Objective it would be good to give some input regarding China as perverse in terms of limited salaries to healthcare professionals and limited national funding of hospitals have encouraged hospitals (where most prescribing takes place) to use the procurement process to make up this shortfall as well as encourage the over use of IV medicines – as a result tendency to prescribe/ dispense originators vs generics. Possible refs include among others (i) Mao W, Tang S, Chen W. Does perverse economic incentive lead to the irrational uses of medicines? Expert Rev. Pharmacoecon. Outcomes Res. 2013; 13, 693–696; (ii) Reynolds L, McKee M. Serve the people or close the sale? Profit-driven overuse of injections and infusions in China's market-based healthcare system. Int J Health Plann Mgmt 2011; 26: 449–470; (iii) Chen Y, Schweitzer SO: Issues in drug pricing, reimbursement, and access in China with references to other Asia-Pacific region. Value Health 2008;11:124–29 (iv) Wagstaff A, Lindelow M. Can insurance increase financial risk? The curious case of health insurance in China. J Health Econ. 2008 Jul;27:990-1005; (v) Jingang A. Which future for doctors in China? The Lancet 2013; 382: 936-7; (vi) Zeng W. A price and use comparison of generic versus originator cardiovascular medicines: a hospital study in Chongqing, China. BMC Health Services Research 2013 13:390; (vii) Zeng W et al. Analysis of the influence of recent reforms in China: cardiovascular and cerebrovascular medicines as a case history to provide future direction. Journal of comparative effectiveness research. 2014;3:371-86; (viii) Zeng W et al. Prescribing efficiency of proton pump inhibitors in China: influence and future directions. BMC health services research. 2015;15:11. This is in additon to ref 36 which can be moved earlier. It would be good to include a comment about high co-pays in China (e.g. Barber S et al. The reform of the essential medicines system in China: a comprehensive approach to universal coverage. J Glob Health. 2013 June; 3: 010303 and others) as the use of lower priced generics should help here. d) Page 7 o Line 19 – 26. The WHO Norway Centre does not give DDDs for these 3 cancer medicines in view of different indications, etc. Consequently – the authors need to state this as well as how they arrived at the DDDs used. o It would be good also to convert CYN prices to US$ for key statements to help the readers with the interpretation of this paper – if inserted then the reference for any conversion rate e) Page 10 – line 42 – may be better to say 'Before generic entry, the volume of …' f) Page 11 • Line 50 – Not sure ref 30 is correct here as this refers to drug concentrations with ibuprofen • Line 50 – 55. Reduced co-pay should enhance access particularly where this has been high as seen in China with a number of authors showing that co-pays do impact on adherence, etc. (Shrank et al and e.g. Simoens S, Sinnaeve PR. Patient co-payment and adherence to statins: a review and case studies. Cardiovascular drugs and therapy. 2014;28:99-109. We have also seen in some countries that restrictions for prescribing have been eased following generic availability to increase use, e.g. Lithuania contained in Garuoliene K et al. Differences in utilization rates between commercial and administrative databases: implications for future

	health-economic and cross-national studies. Expert review of pharmacoeconomics & outcomes research. 2016;16:149-52 g) Page 12 • Lines 13 – 17 – Not sure ref 33 is correct here as this ref has to do more with the fact that these measures did not realise the price reductions for generics as anticipated – so good to re-look at this. Encouraging countries to increase the prescribing of generics vs. originators as well as generics vs. patented products in a class can lead to considerable savings and/ or appreciably increased use at similar costs vs. those countries with limited reforms as seen for the PPIs and statins in e.g. Germany, Sweden and UK vs. Ireland in ref 29 (correct place). More recently in Scotland - Bennie M et al. Multiple initiatives continue to enhance the prescribing efficiency for the proton pump inhibitors and statins in Scotland. Expert review of pharmacoeconomics & outcomes research. 2012;12:125-30 • Line 31 – Ref 29 – not the correct place for this reference when discussing segmentation of the market • Lines 44 – 49 – Accept this in some countries, e.g. Nigeria – Fadare JO et al. The prescribing of generic medicines in Nigeria: knowledge, perceptions and attitudes of physicians. Expert review of pharmacoeconomics & outcomes research. 2016;16:639-50 - not sure should be the case in China with increasing scrutiny over the quality of medicines made available. Good to comment on this.

VERSION 1 – AUTHOR RESPONSE

Response to editor's Comments	
We appreciate your attention. The two reviewers are familiar with China's health care system and their comments are positive and helpful. We have made extensive modifications to the manuscript according to the comments.	
Along with your revised manuscript, please include a copy of the CHEERS checklist indicating the page/line numbers of your manuscript where the relevant information can be found.	Thank you for your suggestion. Since our research was related to the health policy, some content in our research may not well match this CHEERS checklist. We have filled the checklist as we can and uploaded it with the revised manuscript.
BMJ Open now require authors of all submissions to the journal to include a Patient and Public Involvement statement.	Since no direct contact with human subjects was conducted in the study, ethical approval was not required according to the relevant requirements for conducting this type of survey in China. We now state this in the Ethical Statement section.
Please revise the 'Strengths and limitations' section of your manuscript (after the abstract). This section should relate specifically to the methods of the study.	Thank you for your suggestions. We have rewritten the strengths and limitations section at the end of the Discussion, highlighting the specific strengths and weaknesses of our study data and methods.
Response to reviewers' Comments	

Thanks for your careful reading and valuable suggestions to us. After having carefully considered the comments, we have revised the manuscript accordingly. We hope that it will be more smooth and rigorous. If there is anything we still need to improve, please let us know.	
Reviewer 1' Comments	**Authors' reply**
Methods	
It would be good if the authors could comment on any data capture changes in CMEI over the study period (or if there are none, make that clear).	Thanks for your suggestion. We improved the description of data in the paper to clarify this point, CMEI is a large database covering procurement information of 1117 hospitals in 2016. We conducted a search of 115 antineoplastic agents (all antineoplastic agents in the database) from January 2011 to June 2016, and only found 3 drugs that experienced first entry of a generic substitute in the study period. A total of 699 tertiary hospitals had complete procurement records in this period and these are included in our study. (First paragraph in the Methods section)
Results	
The ITS analysis of brand name drugs change is confusing. Page 10 Line 49 states "there was a significant increasing trend in the volume of brand-name Capecitabine, Decitabine and Imatinib" but the numbers written indicate a decreasing trend. The next sentence talks about the estimated decrease in the last month of the observation period. So is it an increase or decrease?	We are truly sorry for this careless mistake. We have rechecked the results and corrected them in the paper. (The expression "*there was a significant increasing trend in the volume of brand-name Capecitabine, Decitabine and Imatinib*" has been revised with the sentence "t*here was a significant decreasing trend in the volume of brand-name capecitabine, decitabine and imatinib*")
Page 11 Line 8 need to be clear which numbers belong to which drug.	We have clarified this in the manuscript.
Page 11 Line 26 shouldn't this read "brand name imatinib" rather than "Imatinib"? It needs to be clear when the authors are referring to branded vs all products.	Thank you for your comment. We meant to use 'imatinib' to refer the brand-name, and 'imatinib' for generic, but we now realize that this needs to be clearer. We now use lower case throughout to refer to the three medications and added "brand-name" whenever we referred specifically to the brand product.
Table 1: Is this the best way to display the data? I think the figure tells the story better, I wonder if Table 1 is necessary?	Thank you for your comment. We agreed that the figure could tell the story better, but it could not present the statistical findings. We therefore included both in the article.
Figures 1-2 - Legends need some work to be more explanatory and outline what is being shown	Sorry for this error. We have made the appropriate changes as suggested.

in each panel. - Intervention time points need to be clearly labelled (currently the dashed lines have no explanation if viewing the figure in isolation)	
Supplementary figure1 -I think the intervention time should be labelled on these figures too. -Supplementary Table 1: Should define acronyms in footer	We have made the appropriate changes as suggested.
Discussion	
To aid readers who are not familiar with the Chinese health system, I think it would be useful to provide some context in the discussion. E.g. what is the role of drug committees in Chinese hospitals? Could this have influenced utilisation trends in certain hospitals? How are is healthcare paid for - government, private health insurance and individuals? Could government or private health subsidy have influenced results?	Thank you very much for your suggestions. We also wondered whether to make the article more concise, or to give more background about China's healthcare system. We have now added a paragraph in the Introduction (paragraph 4) to give more information about the factors might be related to prescribing behavior of physicians, and a paragraph in the Discussion (paragraph 3) to talk about health insurance in China. We hope that this will help readers to understand our context better. Paragraph 4 in Introduction section: *China still faces challenges in transformation from a profit-oriented public hospital-centered system to an integrated primary care-based delivery system. Health care facilities customarily obtain medicines from eligible suppliers through province wide centralized bidding and supply chain system at agreed prices negotiated by government and suppliers. Zero markup policy was introduced to remove perverse economic incentives for over prescription. Nonetheless physicians are still driven by themselves to make a profit from medicines.* (Paragraph 3 in Discussion section: *Current studies have demonstrated that insurance coverage enhanced medicine adherence and access. Although China has reached to near-universal coverage after health reform since 2009, only twenty targeted antineoplastic agents were approved by CFDA before 2017 and none of them was listed in the National Reimbursement Drug List. Thus how to reduce co-payment for these high-cost medicines in China is urgently needed.*

I also recommend some expansion on hospital procurement practices (Pages 12-13) for those not familiar with the Chinese system. Can you confirm weather the 15% mark up rule is still in place (I read some reports it had been banned).	Thank you for your advice. As mentioned above, we added some background information about the factors influencing physicians' prescribing behavior in the Introduction. Actually, we believe that hospitals encouraged doctors to prescribe more medicines because of the 15% mark-up rule, not the centralized procurement practice, so we deleted this sentence in the paper and made some amendments to the last sentence. Indeed, the 15% mark-up policy has now been banned in most hospitals in China as you mentioned, but it was abolished gradually in different levels of hospitals: primary healthcare institutes (2009-2011, national essential medicine policy); county hospitals (2012-2015, implementation date varied in different counties); and finally in tertiary hospitals (in Beijing, for example, the policy began to be implemented on Apr. 8, 2017). Therefore, during our study period (2011-2016), we believe that the 15% mark-up was still an important issue.
Can you speculate on why capecitabine uptake of generic differs from the other two drugs studied?	Thank you for your question. We thought that might be because capecitabine was the only drug of the three listed in the National Reimbursement Drug List since 2009. Under the pressure of increasing deficits in China's medical insurance system, physicians are forced to prescribe generic drugs. This might explain why uptake of generic capecitabine differs from the other two drugs studied. We have added this description in the paper. (Paragraph 3 in Discussion)
The paper could do with some english editing, e.g. Page 5, lines 33-43, 2 sentences starting with "From the perspective of..."	Truly sorry for the mistake. We have corrected this section and edited the English in the entire paper.
Specialist statistical review is also recommended.	Thank you for your suggestions. To ensure our methodology was correct, we have re-checked our results. Prof. Ross-Degnan has published several papers using ITS models and is a respectable scholar in this field.
Minor points	
Double check reference Pg 6 Line 19 - states reference 26 but shouldn't it be reference 24 (Jiang et al as stated at beginning of sentence)?	We are very sorry for these mistakes. We have carefully revised them in the corresponding parts.
Page 7 (methods) line 3: I think this should read "Supplementary Table 1" rather than "Table 1"?	

Page 10 (results) line 10: should include units (CNY) in DDDc reporting	
Reviewer 2' Comments	**Authors' reply**
Abstract	
Lines 6 – 12 High prices of medicines typically in a number of countries refer to new biological medicines especially for cancer and orphan diseases with generics in some European markets as low as 2 – 4% of originator prices pre patent loss – so may be better to say 'high prices of new medicines'. I would also add in health authorities alongside consumers since in a number of countries medicines are provided at either no cost or low cost as part of universal access, e.g. Western Europe. I would also add in that looking at antineoplastics as these are high costs for new medicines causing concern.	Thank you very much for your every suggestion. We made the revisions according to your comments. Paragraph 1 in Abstract section: *The high prices of new drugs especially for cancer are also a concern for stakeholders. Generic drugs are a major price-reducing opportunity and provide more societal value.*
Introduction	
Page 5 Line 6 Not sure ref 1 here is the right reference – not sure these needs a reference.	Thank you for your suggestion. We have re-checked the citation and removed this reference as you suggested.
Page 5 Line 7-12 Concerns though recently with the level of profitability of some new medicines challenging this statement, e.g. new Hep C medicines were priced with a gross profitability of over 99.9% in Europe and USA, the cost of goods of new cancer medicines have recently been estimated at only approx. 1% of the selling price in some countries and good quality generics can be priced as low as 2% of originator pre-patent loss prices	Thank you for the important comments. It is more appropriate to say that brand-name manufacturers maintain high prices to maximize profit. We have made appropriate revisions in the abstract and text.
Page 5 Lines 13 – 15 Generics also have societal benefits – I would move ref 23 to here	We appreciate the positive comment and move ref 23 here to show the societal benefit of generics.
Page 5 Lines 19 – 21 The quality statement needs references as there still is scepticism about the quality of	Thank you for your suggestion. Here we added some references to support our statements as recommended.

generics across countries with some countries having low use – so would include a number of publications of Kesselheim and others here as references to support this statement	
Page 5 Lines 28 – 30 It is difficult for originators to increase their prices in Europe – any price rise has to be accepted by the national reimbursement committees. We are though seeing prices of generics rise especially low volume ones and where manufacturers change – e.g. for some generic cancer medicines.	Thank you for your advice. We have rechecked it and removed some inappropriate citations (i.e., ref 9 & 10).
Page 5 Lines 33 – 38 This sentence does not make sense as acurrently written.	Truly sorry for the mistake. We have corrected it.
Page 5 Line 40 This depends on the European market and the ongoing reforms to increase the prescribing of generics and whether internal reference pricing such as Croatia. Greece still limited acceptance/ prescribing of generics	Thanks for the comments. We have replaced the reference as you recommended.
Page 6 Line 12 Not sure Ref 24 is right here – should this be ref 26? Similarly line 19 – should this be ref 24 rather than 26?	We are sorry for this mistake and we have corrected it.
Page 6 Line 21 before going into the Objective it would be good to give some input regarding China as perverse in terms of limited salaries to healthcare professionals and limited national funding of hospitals have encouraged hospitals (where most prescribing takes place) to use the procurement process to make up this shortfall as well as encourage the over use of IV medicines – as a result tendency to prescribe/ dispense originators vs generics.	We really appreciate this positive suggestion. We have added a paragraph in the Introduction (paragraph 4) to give more information about the factors might be related to prescribing behavior of physicians.
Methods	
Page 7 Line 19-26 The WHO Norway Centre does not give DDDs for these 3 cancer medicines in view of different indications, etc. Consequently – the authors need to state this as well as how they	Thank you for your suggestion. WHO did not provide the defined daily doses (DDD) for the three medicines used in the paper. We used the recommended daily amounts for each study medication based on the dosage regimen recommended in the manufacturer's instructions of

arrived at the DDDs used.	the three products as approved by China Food and Drug Administration (CFDA). We have made appropriate changes in the revised manuscript.
It would be good also to convert CYN prices to US$ for key statements to help the readers with the interpretation of this paper – if inserted then the reference for any conversion rate.	Thank you for your advice. All expense data in the key points are now reported both in Chinese Yuan and US Dollars (1 CNY = 0.155 USD based on the 2011 exchange rate).
Discussion	
Page 10 Line 42 May be better to say 'Before generic entry, the volume of …'	Thank you for your suggestion. We have corrected it.
Page 11 Line 50 Not sure ref 30 is correct here as this refers to drug concentrations with ibuprofen.	Truly sorry for the careless mistake. We have removed the citation.
Page 11 Line 50-55 Reduced co-pay should enhance access particularly where this has been high as seen in China with a number of authors showing that co-pays do impact on adherence, etc. We have also seen in some countries that restrictions for prescribing have been eased following generic availability to increase use	Thanks for your comments. As previous research has shown, reduced patient out-of-pocket payments should enhance access, particularly in China. We have added some discussion of the importance of insurance coverage. (Discussion section paragraph 3) *Current studies have demonstrated that insurance coverage enhanced medicine adherence and access. Although China has reached to near-universal coverage after health reform since 2009, only twenty targeted antineoplastic agents were approved by CFDA by 2017 and none of them was listed in the National Reimbursement Drug List. Thus how to reduce co-payment for these high-cost medicines in China is urgently needed.)*
Page 12 Line 13-17 Not sure ref 33 is correct here as this ref has to do more with the fact that these measures did not realise the price reductions for generics as anticipated – so good to re-look at this. Encouraging countries to increase the	We are so sorry for making this mistake. We have removed it after careful consideration.

prescribing of generics vs. originators as well as generics vs. patented products in a class can lead to considerable savings and/ or appreciably increased use at similar costs vs. those countries with limited reforms as seen for the PPIs and statins in e.g. Germany, Sweden and UK vs. Ireland in ref 29 (correct place). More recently in Scotland.	
Page 12 Line 31 Ref 29 not the correct place for this reference when discussing segmentation of the market	Sorry again for the mistake. We have revised it.
Page 12 Lines 44-49 Accept this in some countries, not sure should be the case in China with increasing scrutiny over the quality of medicines made available. Good to comment on this.	Thank you for your advice. Generic drugs in China are usually registered based on a single in vivo comparative bioavailability study for the demonstration of bioequivalence to the originator drug. Without demonstrating clinical interchangeability based on comparable clinical efficacy and safety, doctors doubt the efficacy and quality of generic drugs manufactured domestically. Therefore, the Chinese State Council released a policy in 2016 to ensure the interchangeability by re-evaluating the quality and efficacy of generic drugs to address the concern (B Huang et al. Make up a missed lesson -New policy to ensure the interchangeability of generic drugs in China). But this policy is still under reform.
Please include Figure legends at the end of your main manuscript.	We totally agree and have now included legends for the figure.
Other revisions	
1.We are truly sorry for the careless mistake in the abstract. We have rechecked the results and corrected them. 2.In order to make the content more concise, we made some amendments in the Introduction section. (second paragraph) 3. Professor Ross-Degnan has done a reasonably careful edit of the English throughout again.	

VERSION 2 – REVIEW

REVIEWER	Brian Godman Karolinska Institute, Stockholm, Sweden
REVIEW RETURNED	15-May-2018

GENERAL COMMENTS	Thank you - you have addressed my concerns.

REVIEWER	Dr Rose Cairns The Children's Hospital at Westmead, and The University of Sydney, Australia
REVIEW RETURNED	30-May-2018

GENERAL COMMENTS	Thank you for comprehensively addressing the issues brought up in the previous review. The paper is much clearer as a result and I think this paper will be an important addition to the literature. The following should only involve minor revisions for editor review only: 1. Page 4 Lines 22 and 27 - please revise the english here- I think there are some missing words. e.g. "One limitation of this study was that it was unable..." and "the second limitation was that although we..." 2. Regarding DDDs mentioned by the other reviewer: You might want to consider using a different term if these doses were not defined by the WHO. I understand that WHO does not give DDDs for these three medicines however calling them DDDs implies that these are measures defined by WHO. DDDs are meant as aggregate measures of drug exposure in a population and your estimates were based on manufacturer recommended dose so these are really two different concepts anyway.

VERSION 2 – AUTHOR RESPONSE

Response to reviewers' Comments	
Thanks for your careful reading and valuable suggestions to us. After having carefully considered the comments, we have revised the manuscript according to reviewer's suggestions. We hope that it will be more smooth and rigorous. If there is anything we still need to improve, please let us know.	
Reviewer 1' Comments	**Authors' reply**
Page 4 Lines 22 and 27 please revise the English here- I think there are some missing words. e.g. "One limitation of this study was that it was unable..." and "the second limitation was that although we..."	We are truly sorry for this careless mistake. We have rechecked the results and corrected the expression error in the paper.
Regarding DDDs mentioned by the other reviewer: You might want to consider using a different term if these doses were not defined by the WHO. I understand that WHO does not give DDDs for these three medicines however calling them DDDs implies that these are measures defined by WHO. DDDs are meant as aggregate measures of drug exposure in a population and your estimates were based on manufacturer recommended dose so these are really two different concepts anyway.	Thanks for your comment. After having carefully considered it, we have changed the expression of DDD into daily dose (DD) in this paper.
Other revisions	

In order to make the content more concise, we made some amendments in the paper.