Dear editor,

Please find enclosed our revised manuscript. We thank the four reviewers for their comments. We have revised the manuscript accordingly and provide specific answers below.

22-Nov-2016

Dear Dr. Vong

# BMJ.2016.035878 entitled "Antibiotic Resistance Threat in South-East Asia Region: Risk Assessment"

Thank you for sending us your article, which we read with interest. Unfortunately we do not consider it suitable for publication in its present form. However if you are able to amend it in the light of our and/or reviewers' comments, we would be happy to consider it again. While we recognise that the topic is important, the style and format need work to be suited for The BMJ. We would like you to make this more transparent and readable for a non-expert reader, but we'll decide once we see the revision about whether this works for The BMJ or would be better in BMJ Global Health.

Please note that resubmitting your manuscript does not guarantee eventual acceptance, and that your resubmission may be sent again for review.

The reviewers' comments are at the end of this letter. The editors' comments are set out below:

1. The paper is quite a technical read at present. The introduction is very broad and may be focused on why they propose the model described in this paper. Need to make it more accessible for general readers.

   Response: we have made substantial changes in several part of the paper to address the editors’ comments

2. Table 1 on risk assessment is most useful, but it is not quite clear how you classify risks as negligible, high, low, moderate etc. How do they use the context and risk factors (exposure, pathogens) in the model?

   Response: we have changed the methods section to address the reviewer’s comment. We hope it is clearer.

   We restricted the analysis to some priority pathogens that we identified through the Hazard assessment (1st part of the risk assessment). The exposure assessment was then used to build a risk pathway that describes all the steps involved in spread of antibiotic resistance from animal and
environment reservoirs to humans (exposure routes in the scope of the priority pathogens identified above).

3. Is the model proposed to be applied by countries? Or does it help make a blanket statement for various risks? Has such a model been developed before? What is the background for it?

Response: Our main attempt was to build a model to bring together the main biological drivers of antibiotic resistance and to estimate their relative risks in the light of SEAR context, with the hypothesis that this context was highly increasing those risks.

As such, this model helps to assess the overall risk of spread in the SEA region, while describing the various reservoirs and risk pathways. We thus considered it as a blanket statement including the various risks at stake on antibiotic resistance spread, even if we are aware of the variability of context-related factors between SEAR countries. We plan to develop further this model to use it at country level, yet we may be limited by the paucity and unavailability of information on contextual factors at country level. In this first step of development of the model, we focused on regional level as we could collect a larger range of data on the regional context.

4. We would like you to make the paper more readable, engaging, and clearer about weaknesses/assumptions.

Response: A new paragraph on limitations was included in the discussion section.

5. You may more clearly make the case for model-based risk assessment, for example by expanding on the problem (paucity of data and weakness of surveillance systems) and by explaining why and how risk assessment could be an answer. i.e. explain what is the problem and how will this address it.

Response: We clarified the research question or risk question based on your comments. When considering the question of risk of antibiotic resistance spread in SEAR, we are limited by knowledge gaps on some biologic drivers of antibiotic resistance and on the regional situation regarding drivers of antibiotic resistance (e.g. quality of infrastructures, level of healthcare infection prevention and control, level of quality and implementation of antibiotic stewardship, social behaviors). Moreover, antibiotic resistance spread in a complex system with inter-related connections. It is thus impossible to quantify the risk triggered by each driver. In such data-scarce environments, qualitative risk assessment is often the only tool for estimating the level of risk of some public health events.

6. You may put some of the methodology in a box? We could keep the bits that give useful background (e.g. first paragraph) but where they are just describing what was done you may put in a box.

Response: We thank you for this useful suggestion. We defined risk assessment and its components and risk pathway in box 1.

7. For each of the three elements of overall risk assessment, please explain in more basic terms what each one means.
Response: This is now detailed in the box 1.

8. Avoid too many abbreviations and technical jargon. Spelling them out may make this more readable.

Response: We agree with the editor. We limited our use of abbreviations and only kept ARB, ARG, SEAR and WHO.

9. We need you to be clear about the evidence and reason underpinning both their methods and their overall risk characterization

Response: we made changes in the methodology section and discussion to address this comment.

10. Please also explain how accurate and generalisable the model is.

Response: we clarify in the discussion section accordingly.
Concerning accuracy of the model, the knowledge gaps and uncertainties on several drivers and contextual factors lead to adopt a qualitative approach to estimate the risk. Yet we believe that, as a qualitative risk assessment, our estimations are accurate. Concerning generalizability, we aimed at developing a general model describing the biological drivers (first level) operating on the emergence and selection of antibiotic resistance and then identify the impact on contextual factors on the latters. The model could therefore be applied to a specific country, to analyze the impact of contextual factors on the risk of spread of antibiotic resistance, given the information is available.

Please don't hesitate to contact me if you wish to discuss this further. We would like you to revise and resubmit before December 10th, 2016 so the paper may be processed as part of the WHO collection in a timely fashion.

When submitting your revised manuscript please provide a point by point response to our comments and those of any reviewers.

Once you have revised your manuscript, go to https://mc.manuscriptcentral.com/bmj and login to your Author Center. Click on "Manuscripts with Decisions," and then click on "Create a Resubmission" located next to the manuscript number. Then, follow the steps for resubmitting your manuscript.

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IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

I hope you will find the comments useful.

Yours sincerely

Anita Jain
Clinical Editor The BMJ
ajain@bmj.com

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Reviewer(s)' Comments to Author:

Reviewer: 1

Recommendation:

Comments:
The authors have done an excellent job in developing a qualitative risk assessment framework for assessing and analysing the threat of bacterial AMR in South-east Asia. The information on the various inputs their model requires is very sparse (to say the least) in most countries in the region, and this One Health approach allows the evidence gaps to be clearly formulated.

The weaker (though more interesting to read) part of the manuscript is their attempt to assign risks to each of the drivers identified in their framework. As evidence on the impact of the various drivers is mainly absent or of poor quality, the assignment of risks is necessarily largely subjective. They do
though attempt to identify the level of uncertainty in their assessments and the gaps in evidence that need filling. However this doesn't always gel well - for example for 'Contact with ARB contaminated environment' the risk is assessed as negligible, though at the same time a high degree of uncertainty is identified in the parameters necessary to assess this. I would have thought the precautionary principle would dictate assignment of a slight higher initial risk (maybe low), as little effort can be expected to be put into researching the parameters in the pathway if the risk has already been assigned as negligible. On a tangential note Orientia tsutsugamushi, transmitted to humans through mite bites in rural areas and manifesting as scrub typhus, has been reported as being doxycycline resistant in Northern Thailand. To what extent is this an example of AMR selected for by antibiotics from agriculture contaminating the environment? We don’t know, but it is a reasonable and important question to ask.

Response: we agree with the reviewer’s suggestion on precautionary principle and have made the changes accordingly in the methodology paragraph and in Table 1 / Figure 3. We also acknowledge that we restricted our assessment to a very limited set of pathogens, and that our risk estimates for each pathway don’t reflect risk estimates that would be obtained for other pathogens: we added this limitation in the discussion.

Other comments:

1. Impact of particular AMR organisms or ARGs on human (and animal) health burden, for example expressed as AMR-attributable morbidity and mortality, do not appear to be in the framework either as inputs or outputs. If positive impact on health is the aim of tackling AMR, I would have thought that the relative importance of the threats and the risks of various drivers should be assessed in this context.

Response: In the present paper, we focused on a set of priority antibiotic resistant bacteria on the basis of their public health impact, including high attributable mortality but also high potential for spread and the possibility for emergence in several reservoirs. We thus considered ESBL- and carbapenemase-producing Enterobacteriaceae, and MRSA as most concerning in part because they are associated with infections resulting in high mortality rates.

2. Hazard assessment: priority pathogens. The authors go through the WHO list of important global pathogens that have been identified as displaying worryingly high levels of AMR globally. I would suggest that the framework should allow for other pathogens with high regional AMR-attributable impact, and identify research/surveillance gaps in this area. For example, a recently published study I was involved with (which the authors would not have seen before submission) found that in Thailand a high proportion of the AMR-attributable mortality in hospitals is caused by Acinetobacter infections (Lim et al. Elife. 2016 Sep 6;5. pii: e18082).

Response: This is indeed one of our limitations: the model was design based on a set of priority pathogens and is not applicable as such to other pathogens.

Additional Questions:
Reviewer: 2

Recommendation:

Comments:
Thank you for the opportunity to review your manuscript titled “Antibiotic Resistance Treat in South-East Asia Regions: Risk Assessment”. The article present the proposed qualitative risk assessment to characterise the risk for antibiotic resistance with the focus on the World Health Organization’s South-East Asia region.

Overall the authors have presented the importance of focusing on this important topic. From the write-up, I presumed that this article is part of a special issue focusing on antibiotics. However, it was unclear at how the author derived the model in Fig 2 and 3, based on Fig 1 from Table 1. Usually when developing such a complex model some explanation of the statistical methods used to derived the models need to be included.
Response: We hereby present a general functional model illustrated in Fig 2 (now Fig 3) based on scientific literature and experts opinions, with no statistical method or implementation. The model only uses a combination matrix that we now present in new Fig 1. Former Fig 3 was an illustration of a possible development of such model. But as it did not bring more information for the present article and would require more explanation, we decided to remove it from the revised version.

Some parts of the write-up are difficult to understand. The extensive use of non-standard abbreviation make reading the article frustrating, as we need to constantly refer to the original words.

Response: we agree with this remark and made limited our use of abbreviations accordingly.

Specific consideration:

Title:
1. The title needs to be revised, as the use of South-East Asia region in general means the area covering the countries in the South-East Asia and not the WHO SEAR. WHO SEAR covers both counties in the South-East Asia and South Asia regions.

Response: we did not change the title but listed the member states of SEAR in the introduction, to address the reviewer’s comment.

Introduction:
2. Similar concern as highlighted in (1), the use of South-East Asia region needs to be specific to WHO SEAR.

Response: as above.

Model-based risk assessment methodology
3. I feel that ‘Risk assessment’ in general should be considered a ‘methods’, and only different risk assessment methods should be considered a tool. There are many different risk assessment tools that are used to assess different risks.

Response: We agree and changed the terminology. We also detailed in a box the method we used for this risk assessment, which is WHO’s methodology.

4. The risk assessment methods although have been well described in text, is difficult to follow, as it consists of many different levels with different criteria for each. I suggest to summarise the information in a flow diagram.

Response: We thank you for this suggestion. We summarized the risk assessment method in a box format and detailed the process of risk characterization in a new Figure 1.

Hazard assessment: priority pathogens
5. The paragraph described the pathogens of high priority as identified by WHO, however, there was no reference to the relevance with the current report.
Response: we provided a reference to the WHO Global report on surveillance of antimicrobial resistance.

Exposure assessment: One-Health approach to contain antibiotic resistance dissemination in humans
6. There should be a sentence or two explaining the One-Health approach as this is a new concept and some readers may not understand the meaning

Response: We defined One health approach in a exposure assessment subtitle and we provided a reference.

Context assessment: the concerning levels of antibiotics resistance drivers in SEAR
7. South Korea (page 4, line 36/37) is not part of the SEAR WHO, is should be Democratic People’s Republic of Korea, which is North Korea.

Response: We deeply apology for this typo error and corrected it. Thank you.

8. The sentence “ARB transmission in the community is increased by low access to sanitation and promiscuity” (page 5, lines 13-15) need to be qualified, I am not sure how these two activities are related, and the individual relationship to ARB.

Response: We agree that this was unclear and clarified the sentence by replacing “ARB transmission” by “bacterial transmission” which is more accurate. Promiscuity was not the correct word and was replaced by high density population

9. The information in this sentence is also not clear; “As a consequence, infection and colonisation rates by ESBL-producing Enterobacteriaecae and MRSA are among the highest worldwide (86% MRSA in Sri Lanka, 70% ESBL-producing Enterobacteriaecae colonization in Thailand)” (Page 5, lines 18-22).

Response: we agree about the lack of clarity. The sentence is now: “In SEAR, high proportion of healthy carriage or infections by ESBL and MRSA are observed \(^{3,13-17}\) (86% of nosocomial S. aureus isolates in Sri Lanka in 2006 were MRSA, 70% of sampled population in Thailand in 2010 was colonized by ESBL-producing Enterobacteriaecae).”

10. The information in this sentence is also not clear; “Given our regional context, the spread of such pathogens is likely to be worse in the region although its extent is unknown” (Page 5, lines 27-30). What is the ‘regional context’ that will make the problem worse? How can you justify your assertion if there are no available information?

Response: we made changes to address the reviewer’s comment. The sentence is now “Given the regional context described above and in Table 1, the spread of such antibiotic resistant pathogens is likely to be worse in the region compared to other regions.”

11. The sentence “To our knowledge ...” (Page 5, lines 33/34) and the following sentence, need to be reviewed, since the authors of this manuscript originate from WHO SEARO, it would be better to provide statistics from SEARO regarding the laboratory diagnostic capacity in the region.
Response: we made changes as follows: “Our recent situation analysis of national AMR prevention and containment program in most WHO SEAR countries (ref: Kakkar et al in same issue), showed limited microbiology and antibiotic susceptibility testing capacity in most public hospitals in the region (WHO SEAR unpublished data)”. But no statistics or publications can be provided.

Risk characterization: Level of risk in SEAR, a model-based case study
12. The information about how the models was developed from the information in Table 1 are not clearly described.

Response: We used the estimations of likelihood of occurrence of key-steps from Table 1 in the figure and the risk pathways detailed from Figure 2 (former Fig 1) to build a model including relative risk estimates for all pathways.

13. The content and concept of model in Figure 2 and 3 need further explanation.

Response: Former Figure 3 was deleted as it was not informative and would have needed more explanations. The process used to build the model in new figure 3 (former figure 2) is now detailed in a new figure 1.

Figure 1
14. A simple to understand representation of the transmission of ARB.
Figures 2 and 3
15. Need further explanation in the text regarding these figures, as the concept is not clear.

Response: see above.

Additional Questions:
Please enter your name: Victor Hoe

Job Title: Associate Professor

Institution: University of Malaya

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No
Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

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Reviewer: 3

Recommendation:

Comments:
This topic area discussed in this paper has long been overdue and thus provides important and relevant insights for consideration by a range of key stakeholders including health (human and animal), social and environmental care professionals, those in the farming and food industry, and policy makers in the South-East Asia region, possibly also to other lower- and middle-income countries. This paper provides key contributions to an area where such information is dearth.

Overall, the authors provided a balanced and comprehensive account of the issues surrounding the threat of antibiotic resistance using a holistic and systems approach. The assessment of issues using a whole systems approach/One Health Approach is wholly appropriate and very much needed when risk assessing the complicated problem of antibiotic resistance.

However, there was no mention of any theory that underpins the risk assessment model/framework that the authors had developed. There are many existing risk assessment methods/frameworks that have been used in other non-health industries and increasingly, more of these have adapted or designed for use in healthcare contexts, underpinned by theory. As the paper anchors on the risk assessment, it would be crucial to make clear the framework’s theoretical underpinning and justify why the approach taken was appropriate.

Response: We detailed in a box the method we used for this risk assessment, which is WHO’s methodology. We were also clearer in the introduction to justify to use of qualitative risk assessment.

To help readers contextualise the study, more information about which countries constitutes “South-East Asia region of the World Health Organisation” is needed as the manuscript mentions some countries in South-East Asia and not others. For example, Singapore and Malaysia are in South-East Asia but they are not part of the WHO South East Asia Region. It thus follow that the discussion could be made much clearer and more balanced in terms of where the threat is greatest within South-East Asia and why this might be the case.

Response: We listed the countries belonging to WHO’ SEA region which are thus considered in this assessment.
Figure 1 is not specific to South-East Asia region (looking at the references used) and the readers might be led to think so considering the topic of this manuscript. The authors should make this clear and explicit. That aside, Figure 1 provides a good visual summary of the various sources of potential exposure to antibiotic resistance.

Response: As mentioned by the reviewer, this figure illustrates the general reservoirs and exposure routes in antibiotic resistance emergence and circulation: It is not specific to SEAR. We attempt to make it clearer in the figure legend and in the method section.

Table 1, pg 11 row 1 second last column says “Most farms are smallholders ......high promiscuity with animals” – is this true or is this a typographical/grammatical error?

Response: this was corrected for high contact rates (promiscuity was not the correct term).

Additional Questions:
Please enter your name: Dr Rosemary Lim

Job Title: Lecturer in Pharmacy Practice

Institution: University of Reading

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Recommendation:
We would like to thank you for your deep reading and your useful comments, which helped us to strongly improve the clarity of the article, particularly the discussion.

This is a hugely ambitious paper and the authors are to be commended for taking on the Herculean challenge of marshalling such a large body of evidence into a risk assessment and addressing such an important topic. I learnt quite a lot by reading the tables (particularly about AMR in water sources) and found many of the conclusions reached to be intuitively plausible.

While I am not familiar with acceptable methodology for qualitative risk assessment (almost all of my work is quantitative), I do have some concerns about methodological aspects of the work (which may well extend to the whole genre). It seems that for key questions, rather than systematically search the literature and making systematic attempts to assess the strength of the evidence accounting for internal and external validity, there is a more improvised approach at collating and assessing the evidence. Perhaps this approach is standard practice for this type of study (and perhaps it is understandable given the huge subject area that this paper aims to cover), but it is not what I am used to from systematic reviews, and my concern would be that it leaves the research vulnerable to potential distortion e.g. conscious or unconscious cherry-picking of findings that support one particular point of view. I've no evidence this has happened here, but this is one of the problems systematic reviews were designed to address. In this respect the work should probably be considered to provide a similar level of evidence to a traditional narrative review, with subjective assessments on the strength and relevance of the findings. At the very least I think these limitations need to be acknowledged.

Response.

A recent article by Thanner et al (Antimicrobial Resistance in Agriculture, mBio, 2016) detailed the knowledge gaps related to AMR in plant and animal agriculture and the role of these reservoirs in spread of AMR in humans. Here is one of the points in the discussion: “With the gaps in our data and use of non-comparable methodologies, at this time it is almost impossible to develop a risk analysis based on the actual situation”.

A similar conclusion is reached by Ashbolt et al (Human Health Risk Assessment (HHRA) for environmental development and transfer of antibiotic resistance, Environmental health perspectives, 2013): “In general terms, an MRA [microbial risk assessment] appears suitable to address environmental human health risks posed by the environmental release of antibiotics, ARB, and ARG; however, at present, there are still too many data gaps to realize that goal.”

While we agree on the challenges posed by knowledge gaps and absence of quantitative assessments of most biological drivers on the emergence and spread of AMR, we must not wait for all these issues to be resolved before proposing tools to identify, prioritize and in the end try to minimize the risk of AMR spread.

We did not conduct a systematic literature review as it was not the scope of this study. Our goal here was to propose a tool that would allow to take into account the impact of contextual factors in the estimation of risks. These contextual factors are the drivers that can be mitigated by policies/guidelines/programmes, they are the focal point for interventions. But we agree that
systematic reviews are deeply needed in that vast subject. Systematic reviews carried out on specific subsystems will allow in the future to refine the risk estimates, and may be to allow to shift our model to a semi-quantitative risk assessment instead of a qualitative one. We now discuss these limitations in a paragraph in the Discussion section, and insisted on the numerous knowledge gaps and uncertainties.

My second concern, is that in a number of places statements are made which do not seem to be supported by any cited research. I expand on this second point in some of the comments below.

Response: some contextual data come from unpublished reports from WHO. We also tried to stick to the limitation of references requested by BMJ and may have deleted some references in the first version submitted. Here, we included most of the references to support our statements.

Detailed comments

1. In several places the paper refers to “Context-driven factors “ playing an important role in the emergence and spread of resistance. This may just be me, but I don’t understand what is meant by this term (google has not helped). To put it another way, what factors would not be context driven? Can the authors list (perhaps in a table or box) those factors which are context driven and those which are not?

Response: We agree this is technical vocabulary that may be unknown by the BMJ readers. We now define contextual factors in Box 1 and in the text.

2. A key message is that “isolated interventions in given sectors are likely to have limited impact on reducing overall risk, pointing at the necessary One-health approach for antibiotic resistance containment”. This sounds like a reasonable thing to say, but I struggled to locate the findings that supported this conclusion (and, to be fair, I struggle conceptually with how such a qualitative risk assessment could reach such conclusions about the likely magnitude of impact of interventions). An alternative point of view (which to my knowledge would not be contradicted by any strong evidence) is that antibiotic use in humans is the primary driver of resistance in humans and effective interventions to reduce the huge overuse of antibiotics in SEAR (for example, banning over the counter and unauthorised sales) could have an enormous impact in reducing overall prevalence. Currently, I don’t believe there is sufficient evidence presented here (or available anywhere) to clearly distinguish between these competing hypotheses (A - one health approach essential ; B - restricting human use to appropriate levels would suffice). I would need to be convinced that a purely qualitative approach can answer this question. Essentially this comes down to what is the reproductive number of different resistance genes and what factors influence these - but clearly, a single intervention that could reduce the reproduction number below one (the tipping point) would lead to very large declines in resistance (provided importation rates [e.g from other countries] were sufficiently low]). Incidentally the Netherlands provides anecdotal support of hypothesis B. The Netherlands has the lowest human per capita antibiotic consumption in Europe but at the same time very high levels of use in animal husbandry (Vandenbroucke-Gauls 2014 PMCID: PMC3900872). Rates of resistance in humans remain very low. Moreover, while being a pig-farmer in the Netherlands is a major risk factor for MRSA carriage on hospital admission, it has been shown that the pig-MRSA strains spread very inefficiently between humans and do not pose a major risk to other patients (Hetem et al, EID 2013
Our model must be applied to a specific region and even better, if possible, to a specific country. Many factors can explain why antibiotic resistance remained so low in humans in the Netherland: IPC in hospitals, surveillance during farm-to-fork processing, diagnostic tools. In this situation, as stated by Vandenbroucke-Grauls, “low antibiotic use in a population can help to resist the introduction and spread of resistant strains in that population, even when the pressure for introduction is high”. Our model applied to The Netherlands may lead to the same conclusion. But as Vandenbroucke-Grauls indicates in the end of her article: the resistance rates have been increasing in human population the last years in the Netherlands (this trend must be confirmed), which suggests that other drivers are at stack allowing now the spillover from animal husbandry to human. Moreover, the situations between a country where resistance rates in the population is low, as The Netherlands, and a country where resistance rates in the population is high, as Thailand, are very different: preventing the introduction of resistance does not require the same interventions as lowering already very high resistance rates (it is now strongly suggested that reversibility of resistance in bacteria is low even when antibiotic pressure is removed).

We agree that very little is known on the potential for spread or for HGT rates of bacterial strains from animal origin in humans. Following your suggestion, we insisted on that point in the limitation paragraph.

We also agree that a purely qualitative approach can not answer such a complex question. Further refinement of the present model, could allow in the future to shift to semi-quantitative risk assessments and to give better answer to this question.

3. p2 l17-18: “isolated interventions may have little impact and co-ordinated actions are required to contain ABR emergence and spread”. It is certainly true that some isolated interventions may have little impact (some may have none and some may have negative impact), but it is a very strong statement to say that in all cases co-ordinated actions are required to contain ABR emergence and spread. For some resistance problems single interventions (such as not using a given antibiotic) may be all that is required. Of course, co-ordinated actions sound like a good idea and I don’t want to argue against these, but I do think more care is needed when making strong statements about necessity for a problem with so many large knowledge gaps.

Response: Isolated interventions may have a satisfying impact on reducing resistance in 1 pathogen; Pneumococcal resistance rates decreased after introduction of vaccination or after reduction of antibiotic consumption in countries were these measures were introduced. However, this decrease was not observed for all pathogens; selective pressure exerted by antibiotics may not always be reversible as reversibility strongly relies on the fitness cost associated with resistance genes. Consequently, it is unlikely that isolated interventions will have a satisfying impact on the overall antibiotic resistance. We believe that, when considering antibiotic resistance as a whole, including different mechanisms of emergence and selection and different modes of transmission, there is a need for more global actions (IPC for example, which is not specific of a resistant pathogen) and broader scope (One Health).

4. p2 l20-21: “but is thought to be large” A reference would help here.
Response: Sentence was rephrased.

5. p3 l27-28 “ABR emergence and persistence in human and livestock is driven by selective pressure exerted by antibiotic overuse and misuse in human”. Is it not driven by total use, including appropriate use?
Response: Following your suggestion, we modified to wide use as a generic driver of emergence and indicated that misuse/overuse is common in regional context.

6. p3 l35-36 “wastewater treatment plants (WWTP) and manure are now considered as a hotspot for antibiotic resistance emergence”
   “It's good that there are some references here so we have a good idea of who is doing the considering, but wouldn’t it also be helpful to have an critical assessment of the evidence in support for this viewpoint?
Response: we provided evidence by adding a reference (Rizzo et al, Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. Sci Total Environ 2013).

7. p3 l47-48. “In the community, poor hand hygiene and failures in sanitation play an important part in inter-human ARG/ARB transmission”. It sounds plausible, but is there published work that supports this assertion? If not, I think better to say that it is plausible (and there are good CRCTs of hand hygiene in the community that suggest reduced transmission of a number of pathogens).
Response: We agree that this was unclear and clarified the sentence by replacing “ARB transmission” by “bacterial transmission” which is more accurate. Promiscuity was not the correct word and was replaced by high density population.

8. p3 l49-40 “ARB are introduced into HCS by admitted patients but also alongside healthy carriers like healthcare workers and visitors [25]”
I am pretty sure that reference 25 does not support this assertion (it’s a modelling study and I am the first author). Again, it is likely to be true, but I am not aware of good evidence to suggest the visitors and HCWs are important sources of onward transmission to patients (and recent molecular data tends to suggest HCWs carriage plays a limited role for S. aureus at least (Price et al, LID 2016 PMID: 27863959)). I think it would be more useful to have a summary of the relevant literature + assessment of strengths, limitations, generalisability and what is and isn’t known (bearing in mind that there might be substantial geographic variation).
Response: We agree that no reference support the role of visitors in the introduction of ARB in hospitals. Yet, several articles tend to show that HCW can carry MRSA on their uniforms (Gaspar, JHI 2009) or be colonized (Dulon, BMC inf dis, 2014). A summary of the relevant literature as suggested here, even if most needed, would involve a systematic literature review, which is not the scope of this study. But we added a limitation paragraph to insist on the knowledge gaps and uncertainties.

9. p4 l4-5 “strains from hospital, ...or livestock associated strains often differ, suggesting the importance of HGT over clonal diffusion”
   Couldn’t this also suggest that in some cases livestock associated AMR may have little interaction
with AMR in humans? A nice example is from Stewardson et al, (ICHE 2014, PMID: 24602942 ) which found 92% of chicken samples from a hospital kitchen in Geneva were ESBL positive but the CTX-M genes in chickens and patients tended to be very different.

Response: This is again an interesting comment that emphasizes the knowledge gap related to cross-species transmission, as raised in the same paragraph. Although some resistance bacteria or genes may successfully cross the species barrier, other may not. We thank the reviewer for proposing this reference. The cited study was carried out in a hospital in Switzerland, where hygiene procedures may differ strongly from the community and even more from SEAR. On the other side, in a recent study from Japan, food handlers were shown to be frequently colonized with ESBL in the long term (Nakane 2016 Appl environ microbial PMID 26746714), providing opportunities for transmission among humans in the community.

10. p4 l9-10 “The potential contribution ....was estimated “ . Methodological details are needed here. What did the estimation procedures involve, how was the strength and generalisability of the evidence judged, how exactly were risk levels selected? Who did the estimating? More than one person? Was it independent? Was there good concordance between “estimates”? How were differences resolved? Did this estimation follow a specified protocol? etc

Response: We added one sentence in the methods section and in the discussion section to address the reviewer’s concern:

Methods section (“Model-based risk assessment”):
The likelihood of occurrence of each step arising from the main driver(s) was rated by the authors providing expert inputs and relying on the scientific review papers.

Discussion section:
Some knowledge gaps were major challenges which hampered our estimates of risk. To address these gaps we provided uncertainty levels for all steps to make the risk assessment more transparent and adopted a precautionary principle by considering higher level of risks when uncertainty is high. Such risk assessment model is intended to evolve and be improved in accuracy along with increasing scientific knowledge.

We did not further expand as we are limited the words count and the BMJ’s Analysis type paper. In addition this Analysis format has allowed us to argue and take stands with respect to knowledge gaps.

11. p4 l26 “These context-specific drivers are in alarming rates in SEAR countries “ Meaning?

Response: we rephrased the sentence

12. p4 l33-36. References needed. Is wastewater management capacity really no more than 60% in S Korea? And what does the 60% refer to? 60% of water or 60% of people with access? Or something else?

Response: It was clarified in the text. 60% of the volume of wastewater is treated in wastewater treatment plants. The rest is not treated and rejected in the environment.
13. p4 l39 “The prevalence of ARB colonisation in livestock is among the highest in Asia “ I think the intended meaning here is that some of the highest prevalences are found in Asia. Can this really be explained by the absence of “low infection control practices in farms and the absence of antibiotic stewardship”? Are these the factors keeping ARB in livestock much lower in Africa?

Response: The sentence was rephrased. According to Van Boeckel, it is mostly associated with changes in agricultural model: in order to meet the increasing demand for protein intake from meat in some middle income countries, agricultural model is shifting or is expected to shift in coming years to more intensive livestock production system. This shift is expected by 2030 for South Africa but may come later in more low-income African countries.

14. p5 l4-6. “Consumers are also exposed to contaminated food in case of poor handling and cooking habits.” Is this meant to suggest that there is evidence of unusually poor handling and cooking habits in Thailand (in which case a reference would help), or is this just saying that if such habits were poor (which they might be) then consumers will be exposed? Again, significance of animal ESBL contamination for human health should not be taken for granted, as PMID: 24602942 indicates (see point 9 above).

Response: Row meat and lack of hygiene can lead to contamination and therefore increase the risk of bacterial acquisition in general. In Thailand in particular, but this might also be true in other SEARO countries, some of typical specialties include row meat. We can give the example (see reference Swetwiwathana A, MESC 2015) of Nham, “an indigenous fermented sausage of Thailand that has gained popularity and acceptance among Thais. Since Nham is made from raw meat and is usually consumed without cooking, risks due to undesirable microorganisms such as Salmonella spp., Staphylococcus aureus, and Listeria monocytogenes, are frequently observed.” In order to clarify, we modified the sentence as follows: “At the end of the food chain, consumers are more likely to be exposed to contaminated food in case of risky handling and cooking habits”

15. p5 l14-15 “ARB transmission in the community is increased by low access to sanitation and promiscuity.” It’s not entirely clear if the authors are using promiscuity in the usual English sense (“def. promiscuous : having or characterized by many transient sexual relationships”), though presumably this would be a risk factor for drug-resistance STIs. The discussion of promiscuity in the context of health care settings in the next sentence, however, suggests the meaning is just a high rate of contact with other people. If that’s the case I would suggest rewording.

Response: Absolutely, we thank you for raising this issue. We remove “promiscuity” and replaced it by “contact rates between people”.

16. p5 l32-33 “Data are lacking on early diagnosis and active surveillance, thus delaying the implementation of efficient and specific infection control measures “. The authors might also add that efficient and specific infection control measures are also lacking for Gram-negatives. I’m not aware of strong evidence for any infection control measures for resistant Gram-negatives and even the benefits of hand hygiene in this case are debatable.

Response: We agree with the reviewer but we believe that this discussion may be too technical for this analysis paper.

17. p6 “This confirms the absolute requirement of One-Health approach...” I don’t see that this
assertion holds: in what way does it confirm it? In what sense is it an absolute requirement? Why not just say that in light of the uncertainties a One-Health approach seems like a reasonable idea?

Response: We agree that this needs to be mitigated, so did we.

18. P12 Three references are given for transmission in the community: 85, 86, & 87. 85 and 86 refer only to S. aureus, while 87 considered ESBL-producing bacteria but only in the Netherlands. I would question the extent to which results from the Netherlands would generalise to settings in SEAR where levels of antibiotic usage in the community are orders of magnitude higher.

Response: We included more references on ESBL transmission in households. The last point, generalizing to SEAR settings, is precisely our aim in this study: assess the impact of SEAR context on the risk raised by generic drivers of antibiotic resistance spread. But we agree we did not discuss the impact of high antibiotic consumption on SEAR countries on the transmission of resistant strains at population level, which is an important driver as nicely presented by Lipsitch, & Samore (EID, 2002) but too complex for this analysis paper targeting an audience that is not specialized in antibiotic resistance.

Additional Questions:
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Reimbursement for attending a symposium?: No

A fee for speaking?: No
A fee for organising education?:

Funds for research?: No

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