Author’s response to reviews

Title: Antimicrobial policies in animals and human health

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Author’s response to reviews:

Reviewer reports:

Reviewer #1: This invited commentary provides a condensed overview of the past and present of antimicrobial use in livestock, highlighting the threats for public health caused - or supposedly so - by some unadapted, yet generalized practices in veterinary medicine.

The comment ends up with (technical) recommendations for the rational use of antimicrobials in animals.

GENERAL COMMENT

The topic is interesting as it aims at informing a public health audience with useful and often unknown / misunderstood historical information related to antimicrobial use in livestock and as such, deserves publication in the chosen journal.

A small point of discrepancy / discussion lies with the comment's title. Whereas the title points to (current or future) antimicrobial POLICIES in animals required to preserve human health, the MS mostly develops - in a great way and judicious style - the past and present livestock treatment practices having led to alarming levels of antimicrobial resistance (sometimes predictable, sometimes unexpected). The title may hence be reformulated to better reflect the MS content.

R: the title was changed accordingly:

Antimicrobial policies in animals and human health

Finally, the author may have considered aligning his ideas along the latest global initiatives aimed at fighting the raise in antimicrobial resistance into account, such as the "European One Health Action Plan" and its handling by the EU agencies in charge.

In this plan, EU is presented as a best practice region constantly revisiting its policies based on accurate research and monitoring data, promoting its successful experience globally. Since it is
noteworthy that the same care is not devoted by all countries in the World to control AMR emergence and spread, statements should be added in the MS - where appropriate - to stress out the need for a global joint action.

R: The author agrees that a global action plan is required. Despite attempts since 1969 (The Swann report), many good attempts have been made; but countries like Australia have been shown to more adequately respond to the crisis of Antimicrobial resistance. The author therefore cannot support the idea that the EU is the best practice region, which is exemplified in the MS (eg the ranking, so-called ban on AMGP).

P6 Epilogue. I personally don't think that mobile "spectrometric labs" is the best answer to improve diagnostics. Classical diagnostic labs are able to deliver very useful results in an affordable delay provided they are adequately solicited by the veterinarians (which supposes either the agreement of the farmer community and/or the launching of constraining policies), provide good quality samples, make the right links with the clinical presentation, take the farm disease history into account ... in an effort to correctly identify the pathogens and orient the antibiotic therapy in a rational way.

R: The author has considerable experience in the clinical laboratory and personally believes that one of the main reasons why bacterial diagnostics are not fully appreciated by clinicians is the traditional culture methodology with moderate sensitivity/specificity. Therefore this commentary aims to –gently- stimulates more rapid and accurate methodologies, such as spectrometrics.

P2 L34 intense instead of much ?
R: changed

P2 L50 the term "clonal complex" (CC398) may be more appropriate than "sequence type"
R: changes have been made accordingly throughout the paragraph

P2 L54 ... these organisms ....
R: changed
P2 L56 ... resistant to (instead of for, throughout entire MS)
R: changed

P3 L8 ..worldwide proportionally decrease .... sentence unclear, please rephrase
R: sentence has been rephrased

P3 L12 other BACTERIAL agents ....
R: changed

P3 L13 A verb is missing in the last part of this sentence
R: sentence rephrased

P3 L20 clostridial? Clostridium spp. ?
R: clostridial - changed

P3 L26 ... the ban of AMGPs (?)
R: changed

P3 L47 horizontally transferable elements (see also P4 L27)
R: changed

P3 L49&50 structurally
R: changed

P3 L52 Evidence has demonstrated ... please rephrase
R: changed

P3 L57 ... Under the assumption that
R: changed

P3 L58 ... let alone "any use" : rephrase ?
R: changed

P4 L4 ... next in line to have received
R: changed

P4 L21 Colistin currentky still is : please rephrase
R: rephrased

P4 L59 largely resemble
R: changed

P5 L19 concentration dose : rephrase ?
R : rephrased

P5 L40 registered antimicrobial (?)
R: changed

P5 L43 please explain what HGT stands for (Horizontal gene transfer, I suppose)
R: accordingly changed
Reviewer #2: First of all: I am not a veterinarian and the issues discussed in the paper are outside my field of expertise.

The topic of the paper is certainly very important: antimicrobial resistance is a major concern for public health in human medicine and there is a lot of anxiety about the possibility of transfer of resistance from animal pathogens to human pathogens.

The content of the paper gives an interesting overview of mechanisms that enhance the risk of emergence of resistance in veterinary medicine and possible actions to avoid this, and ends with important recommendations.

- Livestock associated MRSA: is the point of this paragraph that decrease use of AMGP leads to increase of MRSA? This paragraph needs some restructuring to clarify what the author exactly wants to say.

R: this hypothesis is indeed offered, and the paragraph restructured to increase the clarity.

- Darwinian selection: I have read this paragraph several times, but again: what does the author exactly want to say - decrease of AMGP leads to increase of Clostridia infections and thus to increase of use of antibiotic to treat these infections? And this will be a temporarily phenomenon? I am not sure, so some restructuring of the text and clarification are necessary.

R: the title and paragraph have been modified and edited to improve structure of the MS.
The other paragraphs are more clear - although again they could use some restructuring to make the message more clear.

In summary, I like the content of the paper, but I think the text needs some editing to make it more palatable for non-veterinary and non-bacteriological readers.

p 4  HGT?
R: added: horizontal gene transfer

p 4  frequency of 10^-9?
R: modified : 1x10^-9

Reviewer #3: General comments:

This paper is written by a well-known expert in the field of antimicrobial resistance and it is indeed very well understandable that he was invited to write this commentary.

The topic of this paper could be viewed as controversial. To be complete, this paper should include the other missing parts of the multidrug resistant bacteria emergences. Indeed, after the reading of this paper, the reader could understand that veterinary practices are the main cause of the appearance of resistant bacteria, which might not be true. Of course, it's not because of the author who was forced to summarize some points of this very large topic, due to the limited allowed space. I believe that the narrow spectrum depicted by the title could lead to a misunderstanding. With other words, I think that this paper is too short to really explain the topic delineated by the title. Moreover, I think that this paper could also contain the different positive measures taken by the veterinarian to fight the antimicrobial resistance worldwide. Another aspect should be also the economical aspect (for the farmers) which should be discussed if some of the recommendations cited here should be adopted.

R: modifications have been made throughout the Manuscript. E.g. the title has been changed to limit the misunderstanding that veterinary consumption is the main driver for problems in human medicine. The economical aspects already have been included in the chapter ‘in feed, in water, in milk’. A final sentence has been added to demonstrate the paper mainly dealt with animal husbandry but hotspots for antimicrobial consumption in human medicine should also be included in the risk management.
The author should be careful to give proves of his assertions by quoting scientific references and, when this is lacking, clearly explain the associated uncertainty. In particular, the causal relationship between veterinary medical practices and human diseases caused by resistant bacteria does not seem to be truly demonstrated in the article.

R: partially agreed. The story of tetracyclines is a clear example with appropriate references that fully demonstrate this evidence of transfer, while simultaneously demonstrating that the problems in human medicine related to MRSA are decreasing. This puts the issue also into perspective.

Of course, this does not prevent to adopt a "prudent" attitude and recommend good practices aiming to reduce the appearance of these resistances in domestic animals; however, these recommendations need to be supported by evidence of efficacy in reducing resistance in animals.

Agreed: sentence has been added.

Specific comments:

Page 3 (Background)

Lines 34-37: Even if, of course, the ban of AMGP is a good thing, this sentence should be completed by a clear statement about the absence of demonstrated causal relationship between AMGP use and rise of antimicrobial resistance.

R: not true: clear evidence can be found here:
landmark article doi: 10.1128/AAC.01411-06
landmark article doi: https://www.ncbi.nlm.nih.gov/pubmed/11408222

Page 4

Lines 6-7: It may be also better to repeat here the absence of demonstration of causal relationship.

Not true: see above

Line 11: this sentence is quite understandable. What is the link with the previous statements?
R: agreed: modifications have been made to explain the link and increase the clarity of the sentence.

Also the last part of this sentence (starting by "and therefor(e)..." should be clarified Line 30: the selection of animal breeds more.. is sustained.

R: agree: changed accordingly

Line 31: What were the breed selection efforts put in force in Sweden? It appears to be extremely difficult to select animal breeds on an infectious disease resistance trait.

R: Quote: a classification system for breeding farms and production farms.

“According to that system, a special bonus is given for good animal management and care, which improves the total level of quality of the production. The main reason was that the basic population density in chicken production is 20 kg per square meter. Producers who satisfy specified requirements according to the classification system were permitted a higher limit—up to 36 kg per square meter. In that way, the best growers can be rewarded by being allowed higher populations without risking that this will be done at the expense of animal welfare. The system with differentiated population densities makes it possible for poultry growers to make investments to reach the top classification for population density. If they provide good livestock care, they can reach a production level that is economically competitive, while still retaining the best animal welfare. Growers with low standards are, on the other hand, forced out of business”


Line 37: a. What does mean: "a similar accommodation to the new environment"? Are there the bacteria or the animals that accommodate to the new environment? This needs also to be quoted by relevant references.

R: sentence has been modified and two references have here been added.

b. With what kind of effects? Total removal and replacements were carried out to eliminate the infectious agent and not animals that could be eventually more susceptible to these agents.

R: agreed; paragraph has been rewritten taken this remark into account
Line 54: I do not understand the relationship between the first part of the sentence and the second part, about "reserve drug" even when reading the following sentence. This sentence should be rephrased.
R: agreed: sentence has been rephrased

Page 5:
Line 18: Is this really true? It seems to be a very fast judgment of the behaviour of veterinarians. Evidence for that?
R: colistin was also, in the experience of undersigned, deemed to be unresponsive to antimicrobial resistance mechanisms. Gram-negative coliforms were always classified susceptible because of this dogma, combined with the false impression given by the traditional disk diffusion techniques to determine colistin susceptibility. I strongly belief veterinarians were aware of the problem but colistin was looked upon as a solution more than a contributing factor.

Line 36-42: This statement presupposes the fact that antimicrobial therapy in animals has an effect in the rise on resistant bacteria in humans. I did not see any supportive evidence of that in this article. Please comment.
R: clear evidence can be found here:
landmark article doi: 10.1128/AAC.01411-06
landmark article doi: https://www.ncbi.nlm.nih.gov/pubmed/11408222

Page 6:
Line 43: Meaning of HGT?
R: explained now in the text: horizontal gene transfer

Line 53: Please go to the consequences.
Page 7:
Line 15: could you precise the difference between cleaning and cleansing in term of biosecurity?
R: cleaning is removing dirt and blemishes from the surfaces of the stable. Cleansing refers to chemical or thermal cleaning.

Line 27: this is very sensitive. Do you have evidence for that? It needs to be carefully supported by a reference...
R: reference that reviews recent evidence is included (RONAFA)

Line 30: I do not understand
R: sentence was rephrased

Line 35: these are guidelines although evidences of efficacy for all these items cannot be provided. Which are the following items best supported by scientific evidences?
R: given that it is a commentary, a sentence referring to the upcoming evidence has been added. The level of evidence of these recommendations is currently under investigation.

Line 42: the term biosecurity has not been used before.
R: term changed into ‘infection control measures’

Line 48: the term "as always" is maybe too strong for this statement?
R: Would agree for a regular scientific article, but not for a commentary

Line 54: it will help to lower … and the efficacy of the process should be established
R: changed accordingly.