Author’s response to reviews

Title: Pandemics, public health emergencies and antimicrobial resistance - putting the threat in an epidemiologic and risk analysis context

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Author’s response to reviews:

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Dear Editorial Board Reviewers,

Thank you for the opportunity to revise our manuscript. We have provided a detailed response to reviewers below, and attach the revised manuscript.

Thank you again for your consideration of our revised manuscript for publication.

Please let us know if there are any further questions.

Yours sincerely,

Professor Raina MacIntyre

Reviewer #1

This well written commentary explores risk assessment background for a pandemic in which antimicrobial resistance is a key factor. Strong point is the approach to include AMR from both viral and bacterial origin in this context. A formula is provided but not applied with reference material.

Authors’ response:

We have added reference to the basic risk formula in the text. See page 6 paragraph 1: “This equation is adapted from the “risk triangle” concept [2] which is widely used in disaster
management, whereby ‘risk’ refers to potential lives lost and is proportionally dependent on three components: hazard, exposure and vulnerability.”


Introduction

(pages indicated refer to the pdf numbering)

p. 7 Remark- does a placebo effect when treating AMR infections might worsen the situation or decrease the number of casualties in case of antimicrobial resistance?

Authors’ response:

This is an interesting question. On the one hand, placebo treatments are likely to worsen a pandemic situation as those receiving a placebo treatment will be unable to have the best chance of surviving – there will also be ethical considerations for providing placebo treatments during a pandemic. We feel the use of placebo is beyond the scope of our short commentary.

p. 8 spell out Staphylococcus aureus in italic

Authors’ response:

We have corrected this error.

p. 12 : consider the incubation period as determining for an efficient pandemic.

Authors’ response:

We have added a statement regarding the incubation period as a determinant of an efficient pandemic affected by AMR. Page 9, first paragraph: “…These factors are influenced by inherent characteristics of the pathogens themselves in addition to external contextual factors. For example, the ability of the microbe to spread is determined by epidemiological parameters including R0, incubation period and transmission rates.”

p. 12 morbidity and mortality is only slightly touched in the descriptions of the AMR influenza cases, this might be considered.
Authors’ response:

We have added further details regarding morbidity and mortality of AMR influenza.

Page 10, first paragraph: “The largest documented community outbreak …Clinical outcomes for those in this cluster typically resulted in influenza-like-illnesses, but severe disease and fatalities were not reported [8].”

Page 11, second paragraph: “During the 2003-2004 influenza season in the US, there were 18 people reported to have severe secondary bacterial infections associated with MSRA. Of these 18 people, the median age was 21 years, five had an underlying illness, 81% required intensive care, 62% required positive pressure ventilation and 29% died [4, 12].”

p. 13: Streptococcus (2x) should be written with a capital (pneumonia not), and indeed italic.

Authors’ response:

We have corrected these errors.

It is mentioned that 25% of Streptococcus pneumonia are resistant for penicillin - please soften this percentage with more recent references, since it has been shown that the definition of resistance largely depends on the board of microbiologists involved and these criteria are highly variable. Een example of such publication is: Goossens et al. 2013 Antimicrobial resistance to benzylpenicillin in invasive pneumococcal disease in Belgium, 2003-2010: The effect of altering clinical breakpoints. (2013) Epidemiology and Infection, 141 (3), pp. 490-495.

Authors’ response:

We have revised this percentage with the reference you have provided, and we also provided a reference to a review of more recent surveys. Page 10, last paragraph: “The most common bacterial infection in a pandemic is Streptococcus pneumoniae – the percentage of these bacteria resistant to penicillin varies widely according to resistance definitions (from <1% to up to 9.4% in one study [9]) and region [10], and up to 25% in other studies [12].”


p. 13: Remind the secondary bacterial infections listed largely are involved in respiratory tract infections and sequelae (e.g., bloodstream infection) and are examples of acquired AMR, whereas this is not the case for *Clostridium difficile* (intestinal disorder caused largely by intrinsic AMR).

Authors’ response:

We have revised our statement to reflect the different groups of pathogens causing acquired and intrinsic AMR. Page 11, third paragraph: “Other multi-drug resistant bacteria with the potential to impact morbidity and mortality during an influenza pandemic especially in ventilated ICU patients include (i) those which cause acquired AMR such as vancomycin resistant Enterococcus (VRE), *C. difficile*, *Pseudomonas*, *Acinetobacter* and drug resistant pneumococci, and (ii) those which cause intrinsic AMR such as *Clostridium difficile*.”

p. 18: The added value of the formula provided, only in the section 'conclusions' is questionable. It might be considered to feed the formula with reference numbers or a simulation to make interpretation of this formula more intuitive. For this, a separate section prior to the conclusions might be added.

Authors’ response:

The application of the AMR formula requires a much larger body of work (e.g., involving extensive data collection and sensitivity testing) and is outside the scope of this more descriptive Commentary article, but is something we are presently working on in our research.

Reviewer #2

I have very much enjoyed reading this paper. It is clearly exposed and present a feasible and systematic approach regarding AMR in different scenarios.

The manuscript assume the fact that AMR is an endemic condition, which is true since it is a worldwide condition and acts as a risk factor in local and regional epidemics or pandemics when there are drugs to tackle them.

Feasibility of different scenarios described is clear and the formula provided can work worldwide. However Regions have different context in health care availability, access and quality. For that reason I suggest authors to include some comments especially regarding overall quality of care, since AMR impact also strongly depends on quality of health care provided. I would like to mention the context of TB (DOT context and other issues). Besides, there are other conditions also acting as risk factors and generating even more complicated epidemic scenarios,
one example is the legal framework to Access and obtain Antimicrobial drugs (free Access in pharmacies or other facilities). For all these reasons I would suggest authors to attribute a wide range of values for AMR depending on contexts, since there are different factor influencing from regional to local context.

Authors’ response:

We have added additional statements which highlight how contextual differences can influence the development and extent of an AMR pandemic: Page 9, first paragraph “…The burden of AMR during a pandemic will also vary for different regions – for example, low income regions will likely suffer a higher burden due to poorer health care standards in hospitals, greater crowding, limited access to laboratories, widespread purchasing of antimicrobials without prescription and poor regulatory frameworks for antibiotic use.”

Finally, I would recommend to go over references, since there is some ones partially included (Ex: Ref 3; Severe influenza and S. aureus pneumonia: for whom the bell tolls?, etc...)

Authors’ response:

We have updated all reference metadata in our reference management program.