Author’s response to reviews

Title: Fluoroquinolone consumption and Escherichia coli resistance in Japan: An ecological study

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Point-by-point responses: Fluoroquinolone consumption and Escherichia coli resistance in Japan: An ecological study (PUBH-D-18-03077)

[Response to Reviewer 1]
Professor Željko VOJVODIĆ, M D (Reviewer 1): Major objections. Any analysis between antibiotic consumption and resistance without inclusion of disease prevalence (in this case urinary tract infections, and possibly respiratory infections) does not provide a meaningful interpretation. ….The main confounders should actually be data on prevalence of urinary tract infections and (perhaps to a lesser extent) respiratory infections. The authors should include this important factor in the analysis (if available) or at least emphasize it adequately in the Limitations.

We thank the reviewer for this comment. The present study was an ecological study that examined the possible association between fluoroquinolone use and the resistant E. coli, and we were not able to contrast our finding across space to UTI or respiratory infections. As these diseases are not notifiable diseases, we do not have an access to the dataset across geographic space. We emphasized the importance of associated disease burden including UTI in Discussion (P10L228-P11L232).

Other remarks. Page 5 lines 85-87. “For fluoroquinolone consumption, we used pharmaceutical sales data from wholesalers, representing the total amount of drug sold [22] by prefecture in 2015-2016, which has been publicly shared by the AMR Clinical Reference Centre, the National
Centre for Global Health and Medicine.” What are the proportions of outpatient and inpatient sales?

We agree with the reviewer that the fraction of oral administration among the total would be key for future consideration of antimicrobial stewardship. Although we don’t know if the administration took place in inpatient or outpatient settings, we added a note to Results stating that 98.6% and 98.5% were administered orally (P7L145-146).

Methods. Among „the number of physicians per 100 000 individuals” the authors did not specify the number of hospital and primary care physicians separately. If that was not possible, the authors should address that in the Limitations.

We had an access to the total count (i.e. 101,884 physicians at clinics out of the total of 296,845 physicians), but not by prefecture. We clarified this number and added the limitation to Discussion (P11L254-P12L258).

The authors should clearly separate outpatient and inpatient pharmaceutical sales, as well as proportions of outpatient and inpatient microbiological samples in the Methods. If that was not possible, they should elaborate that in the Limitations.

We thank the reviewer for this comment, and agree that the distinction between inpatient and outpatient would be critical to consider antimicrobial stewardship. This point was discussed in P12L258-262.

Page 5 lines 80-85. The information was retrieved from the clinical laboratory section of the Japan Nosocomial Infections Surveillance (JANIS) system [21] that encompasses the microbiological testing results of all registered medical facilities. What proportion of sample came from outpatient and what from inpatient setting?

We clarified in P5L96-97 that the microbiological samples were all obtained inpatient setting.
Page 11 lines 222-225 The sentences are unclear: Second, the JANIS data that we mined were not accompanied by information on the type of clinical specimen or sensitivity to other antimicrobial agents. More detailed insights into levofloxacin resistance by clinical and biological classifications could be gained by incorporating this information into the analysis.

We apologize for the confusion. The corresponding sentence was rewritten accordingly (P11L249-251).

[Response to Reviewer 2]

Professor Håkon Kaspersen (Reviewer 2): Major corrections. The manuscript lacks a description of what the purpose of the study was. It is stated that it is potentially the first study to assess the correlation between fluoroquinolone consumption and levofloxacin resistance - but why was it desirable to identify this potential correlation?

We thank the reviewer for this comment, because the previous draft indeed lacked a clear statement of purpose. We rewrote the corresponding part in P4L71-72, and also emphasized that our study could act as an important basis to restrict the use of levofloxacin as a countermeasure (P4L74-76).

The sample sizes are not given anywhere in the manuscript – downstream statistics therefore have no contextual meaning. Additionally, samples per prefecture would be advisable to add, as the authors compare the values for each prefecture. A table with sample size information would be practical.

We thank the reviewer for noting this point. Indeed, the underlying sample size was missed as the description. In this revision, we have clearly stated in Methods as to how many medical facilities are registered across Japan to JANIS surveillance system (P5L90-97), and also that how many isolates of E. coli were tested for their sensitivity to fluoroquinolones in Results (P7L140-142).
In the study design, it is not stated which criteria is used for categorizing the E. coli as resistant or non-resistant. Is the EUCAST cut-off values for clinical resistance used, or epidemiological cut-off values? What methods were used for assessing these values, and if various methods were used, what was done to group the E. coli into resistant/non-resistant groups?

We have clarified that the resistance was microbiologically judged adhering to CLSI 2012 (M100-S22) in P4L85-87.

In the results section, it is unclear what the authors mean with "rate of resistance" and "proportion of resistance". Is the rate of resistance the occurrence of levofloxacin resistant E. coli, by percentage? It would be easier for the reader if only one description was used, with an explanation. Otherwise, occurrence of levofloxacin resistant E. coli may be a better alternative. It is unclear whether the percentages in the results section is based on the total amount of levofloxacin resistant E. coli from the 2015 and 2016 annual JANIS report, or a selection, since no description of amount of samples were given in the manuscript.

We have eliminated all “rate” statement to avoid any confusion, and consistently used “proportion” (P4L67, P7L140,150, P10L219). Moreover, we have defined that the proportions given in Results section are calculated among the total isolates of E. coli (P7L143).

Minor corrections: - Line 126: Median consumption of fluoroquinolones (plural)

Corrected accordingly (P7L144).

- Line 129: "The proportion of levofloxacin resistance in E. coli was low" - compared to what? What is the cut-off for specifying a "low" level?

Corrected accordingly (P7L149).

- Line 132: Similar to above - how much is a "low" fluoroquinolone consumption defined as?

Corrected accordingly (P7L153-154)
- Line 155: The α was set at 0.05, there is therefore no such thing as "marginally significant".

Corrected accordingly (P8L175-176)

- Line 167: What defines a high and low value?

We have clearly noted that we did relative comparison (P8L187-18).

- Line 188: fluoroquinolones (plural)

Corrected accordingly (P10L209).

- Line 189: Possibly change to "was removed" instead of "was not left"

Corrected accordingly (P10L210).

- Line 198: fluoroquinolones (plural)

Corrected accordingly (P10L219).

- Line 210: Are no exceptions

Corrected accordingly (P10L235).

- Line 243: Escherichia coli is misspelled.

Corrected accordingly (P13L281).

Figures- Figure 1: The resolution of the figure is of inadequate quality to be able to differentiate between the various prefectures. Please adjust the resolution accordingly for clearer boundaries. Additionally, a colour-scale for the different percentages is recommended for better interpretation due to the amount of prefectures. Please see Colour Brewer for advice on map colouring if needed.
We apologize for the low resolution to clearly identify geographic distributions in the earlier draft. In this revision, we used color scale, and moreover, ensured that the resolution is high enough to distinguish high density areas from others.

[Response to Reviewer 3]

Professor Shazia Jamshed (Reviewer 3): It is a well planned and well executed study done with a limited time frame of 2015 and 2016. The main concerns and justifications are required: 1) Why spatial dataset from 2015 and 2016 were only analyzed?

Antimicrobial consumption data were available only in these two years and thus, we specifically analyzed 2015 and 2016. This point was clarified in Methods (P4L82-83).

2) Generalization of your data is questionable even in the national context. If you consider this study to provide background data for national antimicrobial management policies to reduce antimicrobial resistance then why not an ecological study spanning a decade be considered?

As responded in the earlier comment 1, antimicrobial consumption data were available only in 2015 and 2016. However, in the future, longer time series data could potentially be accessed and strengthen the causal link. This point was mentioned in Discussion (P12L262-266).

3) Do you consider a digital map for the geocoding of your cases?

Following the comment from the reviewer 2, we have prepared a color-scale figure in this round, and moreover, ensured that the resolution is high enough to distinguish high density areas from others. At the moment, we do not have geocoding of administrative level (by prefecture), and we would like to publicly share mesh statistics once it becomes available.