**Reviewer's report**

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

**Version:** 0  **Date:** 29 Oct 2018

**Reviewer:** Håkon Kaspersen

**Reviewer's report:**

The authors have studied the correlation between fluoroquinolone consumption and levofloxacin resistant E. coli in Japan, by looking at samples taken from 2015 and 2016 from all prefectures. The findings suggest that there is indeed a correlation between consumption and occurrence of levofloxacin resistant E. coli when accounting for potential confounding factors, and that there is a higher consumption and occurrence in western prefectures. The authors conclude that there is a nationwide association between consumption and occurrence, but that further studies are needed to further describe their relationship. The authors produced a well written manuscript with interesting findings. However, a few aspects of the manuscript need to be addressed.

**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?

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.

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?

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.

Minor corrections

- Line 126: Median consumption of fluoroquinolones (plural)
- 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?
- Line 132: Similar to above - how much is a "low" fluoroquinolone consumption defined as?
- Line 155: The α was set at 0.05, there is therefore no such thing as "marginally significant".
- Line 167: What defines a high and low value?
- Line 188: fluoroquinolones (plural)
- Line 189: Possibly change to "was removed" instead of "was not left"
- Line 198: fluoroquinolones (plural)
- Line 210: Are no exceptions
- Line 243: Escherichia coli is misspelled.

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 ColourBrewer for advice on map colouring if needed.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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