Author's response to reviews

Title: Do patients with recurrent reported episodes of campylobacteriosis differ from those with a single disease event?

Authors:

Julie Arsenault (julie.arsenault@umontreal.ca)
André Ravel (andre.Ravel@phac-aspc.gc.ca)
Pascal Michel (pascal.michel@phac-aspc.gc.ca)
Olaf Berke (oberke@uoguelph.ca)
Pierre Gosselin (pierre.gosselin@inpq.qc.ca)

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Author's response to reviews: see over
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The Editorial Office
BMC Public Health

Dear Editor,

Please find enclosed our revised manuscript entitled “Do patients with recurrent episodes of campylobacteriosis differ from those with a single disease event?” All comments from the reviewers were addressed as described below. We would like to thank the reviewers for their constructive comments.

Best regards,

Julie Arsenault
Faculty of Veterinary Medicine
University of Montréal
3200 rue Sicotte
Saint-Hyacinthe, Québec
J2S 7C6
Canada
Julie.arsenault@umontreal.ca
+1 450-773-8521 ext.86040
Reviewer: Edith Gabriel

A. Major compulsory revisions

“Logistic regression analysis is not correct and does not answer “Do patients with recurrent episodes differ from those with a single episode?”

To answer this question, the authors should consider a multivariate logistic regression model in which the outcome would be the report of a previous episode of campylobacteriosis (yes/no) and the explanatory variables would be age, gender, urbanicity and their interaction (if any). Univariate analysis can be used both to analyse the link and the interaction between each characteristic of patient and recurrence of campylobacteriosis and as guidelines to select variables which can be included in the multivariate model. However, final variables, i.e. variables included in the multivariate model, are often chosen via backwards elimination.

An alternative model could be considered by using polytomous logistic regression analysis in which the outcome takes r>2 categories. For example with r=3, we can have ‘1’ for patients with one reported episode, ‘2’ for patients with two reported episodes and ‘3’ for patients with three reported episodes. Explanatory variables are similar to those in the previous model.”

The use of a multivariate logistic regression or a multivariate polytomous logistic regression analysis as proposed by the reviewer would have only been possible if we had limited the dataset to reported cases. In this option, this would have led to a dataset of 28 905 reported cases having had one or more campylobacteriosis episode, and the outcome of the statistical model could have been the report of more than one episode (yes/no). In fact, this is what we first did. However, after much consideration, we realized that this approach led to a significant drawback since it only allows the identification of risk factors that are present for all episodes, but not for those that are specific to recurrent cases. By using our approach, we can test the interaction between a “recurrent episode” variable and each risk factor (i.e. age, gender, urbanicity). In this context, a significant interaction means that the risk factor has an additional effect on the risk of campylobacteriosis for people having had a previous episode. In this study, the multivariate approach was not possible because we did not collect direct information from non-cases, and therefore we do not have the joint distribution of explanatory variables (age, gender, urbanicity) for the general population.

B. Minor essential revisions

1. “Table 2 must be set before Table 1 since it is listed first.”

The order of the table was changed as requested.
2. “Figures 1 and 2 reversed.”

The figures 1 and 2 were put in correct order.

Reviewer: Jennifer Weisent

A. Major compulsory revisions

1. “Discussion (Paragraph 1) The recurrence data captures what looks to be excess risk. However, previous studies estimate an overall risk of approximately 1%. Could the recurrence risk be merely an indication of more complete reporting after an initial exposure, as opposed to a true increase in the population risk?”

   Very good point. A sentence was added in the discussion at the end of paragraph 6 (discussion), on top of page 14. We also found a reference specific to Canada.

2. “Discussion (Paragraph 2) The statement that “The only documented evidence of acquired immunity…is with people professionally exposed…” is not entirely true. Miller et al. suggest that exposure over time leads to increased immunity (in the nation of Scotland).”

   Thank you for noticing. A sentence was added at the end of this paragraph (paragraph 2, discussion, pages 11-12), referring to this paper.

3. “Discussion (Paragraph 2) The statement that “…data did not show evidence of…species-specific immunity, since people with recurrent episodes were as likely to have been infected twice by the same Campylobacter species” is an overstatement. There is a significant body of molecular evidence to show that within-species genomic differences and subtypes suggest antigenic variability. Furthermore, the bacteria has a highly plastic genome, making ‘species-specific immunity’ very difficult to pin down without subtyping performed. Along these lines, the partial immunity demonstrated in children from underdeveloped nations is hypothesized to be due, not only to higher levels of exposure and contamination, but to simultaneous exposure to a multitude of Campylobacter strains.”

   We agree. Two sentences were added in this paragraph to add more precision (paragraph 2, discussion, pages 11-12).

B. Minor essential revisions

1. “Because this study is making a direct statement about immunity, basic details
of Campylobacter immunity should be included in both the background and then related to the discussion/conclusion statement (such as):

Thank you for these suggestions and for pointing us good references, which helped us to improve the paper.

a) “Infection confers short term immunity of unknown duration by stimulating antibodies in approximately five to seven days of infection.”

   Added in 3rd paragraph of background, page 3.

b) “The antibody peak occurs within 2-4 weeks, declines over several months (detected in serum and mucosal secretions)”

   Added in 3rd paragraph of background, page 3.

c) “Example of other pertinent facts about immunity as they relate to your article: An immune host may render the bacteria nonpathogenic.”

   I do not understand how this sentence relates to the paper.

d) “Partial immunity is thought to be a primary reason why children in developing countries excrete the organism for shorter duration than those in developed countries, and is thought to explain why travelers are disproportionately at higher risk.”

   A sentence was added in 2nd paragraph of the discussion (page 11).

e) “Also, it is hypothesized that acquired immunity may result in declining rates in some regions.”

   A sentence was added in 2nd paragraph of the discussion (p.11-12).

2. “Background (Paragraph2). “One of the potential areas of exploring possible protective effect of immunity is through studying recurrence.” Please provide a sentence or two to clarify why.”

   A sentence was added for clarification (background, paragraph 4, page 3).

3.”Case Data/Population Data: Is urbanicity defined as a function of population density? Please include the Statistics Canada definition of these important characteristics.”
The definition used by Statistics Canada was added (Methods – Case data, page 4).

4. “Methods/Date of Onset. The proxy estimation technique should be discussed in terms of any potential bias. For example, could the high recurrence ‘spike’ between month 3 to 6 be due to chronic cases or be captured due to discrepancies in the estimated dates? The exact duration of shedding should be referenced as well, to help clarify why the first three months were excluded.”

A sentence was added in discussion, paragraph 8 (page 14).

5. “Results(Paragraph 3) Are the C.coli cases equally distributed across the three regions of interest? Specifically, it would be very interesting to note if C.coli cases were all found in rural regions.”

The frequency of C.coli isolation for recurrent episodes was not different according to region. A sentence was added in results, paragraph 3 (page 9).

6. “Discussion (Paragraph 4) This paragraph needs to be expanded. Any underlying disease (inclusive of hypogammaglobulinemia and corticosteroids use) which compromises the host immune system may render that individual more susceptible to campylobacteriosis and its potential recurrence. Specifically, include AIDS, chronic intestinal illnesses (IBS, IBS, celiac disease), rheumatism. Susceptible subgroups also include people who may have altered defense mechanisms, with subsequently increased disease acquisition, as a result of antibiotic and antacid use.”

We added two sentences and modified another one following your comment (discussion, paragraph 5, page 13).

7. “For example: A follow-up study on the recurrent cases might reveal the importance of these patient characteristics. Ie. What if the recurrent cases all have underlying conditions or use antibiotics and antacids? This idea might add insight to your final discussion or conclusion paragraph. Or it could be discussed that the lack of information on these characteristics is an important weakness of surveillance data.”

Very nice idea. We added a sentence in last paragraph of discussion (page 16) and another one in conclusion (page 16).

C. Discretionary revisions

1. “Background (Paragraph2). Please change wording ...their protective role is ‘misunderstood’. Consider ‘unclear’ or poorly understood.”
2. “Results (Paragraph 2): My manuscript copy mislabels Figures 1 and 2 in the text.”

Figure labels were changed.

3. “Discussion (Paragraph 6) “Likewise, the impossibility...of the risk of recurrent episodes through underestimating the number of cases of recurrent episodes.” This sentence is difficult to follow. Please rephrase if possible.”

The sentence was rephrased. We hope it is now easier to follow (discussion, paragraph 8, page 15).

4. “Discussion (Paragraph 9) Consider rephrasing “the impossibility of adjusting for”. Perhaps 'This is due to data limitations which render stratum-specific adjustments impossible, or 'inability to adjust for stratum-specific baseline results'. Or mention that population at risk data are unavailable.”

Done (discussion, paragraph 9, page 15)

D. Quality of written English

“Needs some language corrections before being published”

The quality of written English article has been reviewed by a professional (modifications are shown in track changes).