Author's response to reviews

Title: The Second Study of Infectious Intestinal Disease (IID2): Increased rates of recurrent diarrhoea in individuals aged 65 years and above

Authors:

Clarence C Tam (clarence.tam@lshtm.ac.uk)
Laura Viviani (laura.viviani@unimi.it)
Laura C Rodrigues (laura.rodrigues@lshtm.ac.uk)
Sarah J O'Brien (s.j.obrien@liverpool.ac.uk)

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Author's response to reviews: see over
15 May 2013

Dear Editor,

Re: MS 7141468109267314 - The Second Study of Infectious Intestinal Disease (IID2): Increased rates of recurrent diarrhoea in individuals aged 65 years and above

Thank you for the opportunity to re-submit the above manuscript and address the reviewers’ comments. Please find enclosed a detailed response to each of the reviewers’ comments, together with a revised version of the manuscript.

We hope that you will find this new version suitable for publication in BMC Public Health.

Yours sincerely,

Dr Clarence Tam
Corresponding author
Response to reviewers’ comments

Reviewer 1:

Introduction: Please provide supporting literature that the IID in older population is a problem elsewhere too. The literature quoted is from developing countries and for children. Since the focus of the paper is elderly population. Please support with literature for the same population. If there is no literature please justify the absence.

We have added some additional information and references on the burden of IID among the elderly, although we stress that we are not aware of previous studies that have looked specifically at recurrent disease in this age group.

- Please describe if the analysis was designed at the time of study planning. It looks like a secondary data analysis to me. There is nothing wrong with such analysis, but it should be clearly mentioned in the study design section.

This was a secondary analysis of data from a cohort study originally designed to measure the frequency of IID in the UK. We have clarified in that this was a secondary analysis (Introduction, last sentence).

- Please clearly mention the primary exposure of the study and the design. In case the study is cohort design (which it is), please clearly mention what exposure variable was considered. The first para of the analysis section in methods does not correspond to a cohort design. This is also evident from the tables, as the groups are not based on the exposure but on outcome.

We have made it clearer in the methods and results the cohort design and the primary exposure of interest. We believe the confusion arises from the fact that we first compare the characteristics of individuals with no IID, a single episode and multiple episodes, and then go on to analyze the data longitudinally, taking follow-up time into account using Cox regression methods. We have now split the methods and results into sub-sections with sub-headings to clarify these two different analyses.

- Please describe censoring clearly and how person time contribution was calculated.

We believe this is clearly explained in the last two paragraphs on page 5. We have, however, amended the text and explicitly used the term ‘censored’ where relevant, to clarify what we mean.

- It will be helpful to have the total number of individuals followed up that provided the person time (not necessary but since this article will be read by people in different regions with a variety of educational background, therefore will help them understand the paper more).

The number of individuals followed up, and their total contribution to follow-up time is given at the beginning of the results section. We have moved this to the first sentence to make it clear.
It is also unclear that if each episode was considered independent, then why would the authors think that the previous episode will have an effect on the incidence of the next episode. If that is the case then, the data need to be analysis as correlated and the hierarchical nature adjusted.

In our final model, and the results in Table 3, we allow for the dependence of episodes within individuals by using robust standard errors, which relax the assumption of independence and generally give wider 95% CIs. This is a standard method for dealing with clustering. A second issue is whether there is conditional dependence of episodes within individuals, that is, whether experiencing one IID episode is associated with a greater risk of experiencing a subsequent episode. This is dealt with in our analysis by including a time-dependent variable denoting the number of previous episodes an individual has experienced. These two issues are thus adequately addressed in our analysis. We stress that the point being made in the last paragraph of the Analysis section is not related to the adequacy of our regression modelling framework, but to the limitations of the likelihood ratio test for model selection when data are not independent. For this reason, we use both the likelihood ratio test in a modelling strategy that assumes independence (which is more familiar to general readers) and Akaike’s information criterion in equivalent models that use robust standard errors. Both approaches yield the same final model.

Reviewer 2:

MINOR COMPULSORY REVISIONS:

1. It is only a minor point, but I would imagine that the authors did not use Stata version 12.0 to conduct the analyses, but more like version 12.1.

We thank the reviewer for pointing out this error, which has now been corrected.

2. I am sure the case definition of gastroenteritis in the study has been validated, but it is a little vague in terms of symptoms of diarrhoea and vomiting. I would be keen to see what happens to the predictors of recurrent episodes if a stricter case definition was used. I presume that this is possible given the extensive nature of the study.

We thank the reviewer for this suggestion, although we do not agree that this is very pertinent to the paper, nor do we feel that it is clearly justified. Our case definition is perhaps less strict than those used in other studies (for example, those that define an episode of diarrhoea as 3+ loose stools in a 24 hour period). However, we see no evidence in our data that a stricter definition of diarrhoea is beneficial. For instance, in the IID2 Study there was no difference in pathogen identification between cases with <3 and 3+ loose stools. Secondly, while using a different case definition could result in different estimates of IID rates, it is unlikely to impact estimates of the effect of recurrent episodes, unless the frequency of symptoms is markedly different between individuals who have one and more than one episode. Again, we see no evidence in our data that this is the case. For example, there is no evidence that the distribution of cases with <3 loose stools is different between those with one or more than one episode of IID (p=0.3).

DISCRETIONARY REVISIONS:
1. It seems like the reasons for the higher rate of recurrent episodes in older people is just a list of possibilities. Did the IID2 study collect data on antibiotic usage, chronic disease, etc. that could inform this finding?

_Unfortunately, we have no data on antibiotic usage or comorbidities that could inform this finding. The IID2 Study was designed specifically to estimate disease burden, but not to identify risk factors for IID._

2. I would like to see some public health interpretation of the findings of this study. What do these results mean for infectious intestinal disease prevention?

_We have added a comment on the study’s implications in the last paragraph of the discussion._

Reviewer 3:

Minor Essential Revisions

Are the 17 million cases of IID annually attributable to the 12 most common IID pathogens (as indicated in the abstract) or all causes of IID (as suggested in the introduction).

_We thank the reviewer for pointing out this error. The 17 million cases refer to all causes of IID. We have corrected the abstract accordingly._

Discretionary Revisions

Where are data collected on comorbidities or immunocompromising conditions?

_Unfortunately, we have no data on antibiotic usage or comorbidities that could inform this finding. The IID2 Study was designed specifically to estimate disease burden, but not to identify risk factors for IID._