Author's response to reviews

Title: Cholera risk factors, Papua New Guinea, 2010

Authors:

Alexander Rosewell (arosewell@yahoo.com)
Benita Addy (nurse_director@datec.net.pg)
Lucas Komnapi (nurse_director@datec.net.pg)
Frida Makanda (nurse_director@datec.net.pg)
Berry Ropa (berry_ropa@health.gov.pg)
Enoch Posanai (enoch_posanai@health.gov.pg)
Samir Dutta (samir_dutta@hotmail.com)
Glen Mola (glenmola@dg.com.pg)
WY Nicola Man (n.man@unsw.edu.au)
Anthony Zwi (a.zwi@unsw.edu.au)
C Raina MacIntyre (r.macintyre@unsw.edu.au)

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Author's response to reviews: see over
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Re: MS: 1071143279649139

Dear Dr Marshall

Thank you for providing our team with the thoughtful feedback provided by the two reviewers of our original research (MS: 1071143279649139). We would also like to thank the reviewers for sharing their expertise and insights in reviewing our original research – their suggestions are much appreciated.

We wish to request your further consideration of our revised manuscript and our responses that we anticipate should address the queries raised by the reviewers.

Please let me know should you wish for further information.

Yours sincerely

Alexander Rosewell

Prof Qadri

Point 1 – POC test

Thank you for your suggestion to provide more information regarding the evaluated rapid diagnostic test. We have conducted further literature searches for data on the rapid diagnostic test produced by SD bioline that was used in our field evaluation (One step *V. cholerae* O1/O139 Antigen Test), however no previous evaluations have been conducted. It appears that our field evaluation is the first on the performance of this test.

It was noted that the sensitivity and specificity were low and therefore cannot be used in an evaluation such as this one. We have performed our statistical analyses using established methods [1] and according to best practice have provided the estimates of sensitivity and specificity, as well as the 95% confidence intervals for these estimates [2]. We have reported these data as recommended when reporting on rapid diagnostic test evaluations [2]. In this sense, we feel readers have been provided with sufficient information to enable interpretation of the findings (estimate and confidence intervals). Prof Qadri highlights that our interpretation is appropriate and has been made in light of the wide confidence intervals that correspond directly to the number of participants in the study.

Most literature to date on cholera rapid tests comes from evaluations that have been conducted in sites with a good research infrastructure and extensive training for participants [3, 4]. Such findings cannot necessarily be extrapolated to the field, where these tools may be used globally by health care workers in similar contexts to the clinician researcher in our study. This is akin to the difference between measuring vaccine efficacy and vaccine effectiveness in real field settings. In this regard, we feel it is essential for the public health community to be aware of the issues associated with rapid diagnostic
tests in real field settings as they are made aware of vaccine effectiveness in addition and vaccine efficacy.

Point 2 – Town water

Please excuse the lack of clarity - town water has been modified to: “piped water distribution system”.

Point 3 – Testing controls

Thank you - we have updated the limitations section of our original research to address this issue, which we consider to be minor for the following reasons. We conducted our study using a similar methodology to the several cholera case control studies recently published in Emerging Infectious Diseases and other journals, where stool culture was not performed on controls [5–11]. While the suggested approach would minimise misclassification bias (but not eliminate), the measure of effect would only have been reduced, meaning any significant risk factors identified in our study (of which there were several) were indeed risk factors and should be reported and interpreted as such. In essence, this investigation was an outbreak investigation, where samples are generally not collected from controls.

Point 4 – Other aetiologies

Thank you for the suggestions to update the limitations section - we have updated the limitations section to address this issue. We conducted our study using a similar methodology to the several cholera case control studies recently published in the Emerging Infectious Diseases and other journals, where stool culture was not performed for other diarrhoeal pathogens [5–11]. While the contribution of non-cholera pathogens to acute watery diarrhoea outbreaks is recognised, especially following flooding [12, 13], the vast majority of presentations of acute watery diarrhoea to cholera treatment centres during outbreaks will be due to cholera [14]. This was the first time cholera had been reported in Papua New Guinea, meaning the cholera outbreak transmission was occurring among a completely naive population and may have be more intense compared with other non-cholera pathogens. This is a different context to studies in Bangladesh where cholera is an endemic disease and resultant rates of immunity are higher. In addition, it is conceivable the high case fatality ratio (3.2%) points towards poor management or health access issues associated with cholera rather than other less pathogenic non-cholera agents.

Point 5 – Vaccine

Thank you for the update on the cholera vaccine pre-qualification process, we have amended the text as requested and included literature about vaccine trials in Haiti as it relates to Papua New Guinea.

Point 6 – Discussion length

The discussion has been significantly shortened from 1352 words to 1034, as recommended.
Prof Sack

Point 1 – Cholera identification

The main concern was we have not correctly identified cases of cholera for the case control study.

Thank you for raising this important discussion point which we have reflected upon extensively. “Cholera” is the common nomenclature for case control studies conducted during cholera outbreaks where suspected cholera cases are recruited based on a clinical case definition, rather than microbiological confirmation [5–11, 15]. We conducted our study using a similar methodology to these 7 case-control studies titled as “cholera studies”. While the suggested approach to only include laboratory confirmed cholera cases is a scientifically sound way to minimise misclassification bias, by using a clinical case definition for inclusion (as used by most other cholera case control studies [5–11]), the measure of effect would only have been reduced, meaning any significant risk factors identified in our study (of which there were several) were indeed risk factors and should be reported and interpreted as such. In fact, studies have shown that isolation failure from suspected cholera stools by traditional culture methods during acute diarrhoea outbreaks may be explained by the inactivation of *V. cholerae* by in vivo vibriolytic action of the phage and/or nonculturability induced as a host response [16]. The cholera isolation rate was similar to published cholera outbreak reports (47%) in other settings [15]. There would also be misclassification bias, with cases who were not tested, but who had cholera, being misclassified. The positive predictive value of a consistent clinical presentation in the setting of an outbreak of diagnosed cholera cases is high, and so we believe clinical cases should be included for completeness of ascertainment. This is supported when looking at our data by confirmed case status only. While the contribution of non-cholera pathogens to acute watery diarrhoea outbreaks is recognised, especially following flooding [12, 13], the vast majority of presentations of acute watery diarrhoea to cholera treatment centres during outbreaks such as the outbreak in Papua New Guinea will be due to cholera [14]. This was the first time cholera had been reported in Papua New Guinea, meaning the cholera outbreak transmission was occurring among a completely naive population and may have been more intense compared with other non-cholera pathogens. This is a different context to studies in Bangladesh where cholera is an endemic disease and resultant rates of immunity are higher. In addition, it is conceivable the high case fatality ratio (3.2%) points towards poor management or health access issues associated with cholera rather than other less pathogenic non-cholera diarrhoeal diseases. The terms “suspected cholera”, “cholera” or “acute watery diarrhoea” are used interchangeably within the World Health Organization cholera guidelines due to the fact that during epidemics, they are mostly talking about one and the same thing, so we feel the choice of words are appropriate. Finally, diarrhoeal cases not meeting the strict clinical case definition for acute watery diarrhoea were not admitted to the cholera treatment centre and were managed in the observation area and did not participate in this study.

Point 2 - Matching

We consider the act of not matching in our study as one of the strengths of our study, especially in terms of power. Studies have shown that the same results are achieved in epidemiological case-control studies irrespective of matching or not matching [17]. Matching is done to reduce confounding. In most epidemiological studies the procedure of multivariate analysis is instead preferable to handle confounding situations in the analysis, as long as potential confounders are identified and added to the model. We intentionally did not match cases in our study to enable the evaluation of age as a risk factor.
for disease in our model. Any variable which is matched in a case-control study cannot be analysed as a predictor of the outcome of interest. If we had conducted direct age-matching, we would not have had this strength to our study. Frequency matching may have been a possibility; however we elected for the simplest approach for field staff.

**Point 3 - Control ratio**

We agree with the statement that three controls were not recruited for each of the cases. However, as discussed in the limitations section, this reduction in recruitment ratio did not impede the identification of statistically significant risk factors in the multivariate model, which was the objective of the study. The slightly reduced ratio resulted in an extremely minor reduction in the power of the study. For example, retrospective power calculations indicate that power for a bivariate analysis was only reduced from 91% to 89% for an alpha of 5%, exposure of 50% in cases (which approximates the proportion of cases having river as a drinking water source) and minimum odds ratio of 3 when recruitment ratio was reduced from 3 (the targeted ratio) to 2.25 (the current ratio).

**Point 4 – Field evaluation**

The lack of experience of the person with the cholera assay was cited as an issue.

We recognise the important comment made by Prof Sack regarding the field evaluation and agree that our setting was not that of a good research infrastructure where extensive training is conducted prior to usage of the test kit to be evaluated. We wish to share data from a field trial of this rapid diagnostic test (the first of this particular test) in a real life setting (where the researcher is not aware an evaluation will be conducted) to determine how effective it may be for health authorities globally in future outbreaks. This is actually a point of the conclusions of a previous paper on the same by WHO Geneva and MSF colleagues “It remains unknown how well the test performs directly in the hands of primary healthcare providers at a patient’s bedside. We expect the performance will be similar as our findings during the first month of our study. Further studies are indicated to evaluate this assay in crisis situations, but the logistics may make such an undertaking even more challenging.”

We consider this a selling point of our research, as the literature to date on cholera rapid tests comes from evaluations that have been conducted in sites with a good research infrastructure and extensive training for participants [3, 4]. Such findings cannot necessarily be extrapolated to the field, where these tools may be used globally by health care workers with little or no training in similar contexts to the clinician researcher in our study. This difference in field evaluations is akin to the difference between measuring *vaccine efficacy* in a controlled environment and *vaccine effectiveness* in real field settings. In this way, we feel it would be useful for the global public health community to be aware of the issues associated with rapid diagnostic tests in real field settings as they are made aware of vaccine effectiveness. To our knowledge, this is the first field evaluation report on this rapid diagnostic test – a test which will likely be used in future cholera outbreaks globally.

We have performed our statistical analyses using established methods [1] and according to best practice have provided the estimates of sensitivity and specificity, as well as the 95% confidence intervals for
these estimates [2]. We have reported these data as recommended when reporting on rapid diagnostic test evaluations [2]. In this sense, we feel readers have been provided with sufficient information to enable interpretation of the findings.

**Point 6– Limitations not fully described**

Thank you for raising the issue of incomplete limitations with the team - we have updated the limitations section to include some additional important points that Prof Sack and Prof Qadri have raised, these include the exclusion of non-cholera aetiologies and discussion around the field evaluation.

**Point 7 - Acceptance**

The paper was rejected as it provides no new information to our understanding of cholera transmission. We wish to request that you would reconsider the new information we are offering. We wish the paper be published for the following 4 reasons:

- Cholera risk factors have been never previously studied in this population (Urban Papua New Guinea).

- This the first report of a field evaluation of the SD Diagnostic cholera rapid diagnostic test. This test will be used by health care workers in similar settings in future outbreaks globally, so reporting on its evaluation is important.

- This is the first evaluation we are aware of that has not been conducted in a “controlled” research environment. This is the first report of the “effectiveness” of such tests in real field situations where the researcher was unaware an evaluation would be conducted, versus the “efficacy” in a research setting.

- Global attention and support from donor and technical agencies (CDC, PAHO/WHO etc.) has been thrust upon cholera in Haiti. Despite Papua New Guinea experiencing case fatality ratios in excess of those in Haiti in some jurisdictions, getting similar support for cholera in Papua New Guinea has been a major challenge [18]. Publishing studies from small countries with high mortality like Papua New Guinea is urgently required to garner global attention and support to address the issues.

**References**


