Author's response to reviews

Title: Antimicrobial susceptibilities of Proteus mirabilis: a longitudinal nationwide study from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) Program

Authors:

Jann-Tay Wang (14bcr@yahoo.com.tw)
Pei-Chen Chen (pagechen@nhri.org.tw)
Shan-Chwen Chang (changsc@ntu.edu.tw)
Yih-Ru Shiau (yihru@nhri.org.tw)
Hui-Ying Wang (iris@nhri.org.tw)
Jui-Fen Lai (juifen@nhri.org.tw)
I-Wen Huang (yvone@nhri.org.tw)
Mei-Chen Tan (maggietan@nhri.org.tw)
Tsai-Ling Lauderdale (lauderdale@nhri.org.tw)

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Author's response to reviews: see over
Philippa Harris, PhD  
Executive Editor  
BMC-series Journals  
BioMed Central  

Dear Dr. Harris:  

We thank the editor and reviewers for the careful review and all the constructive suggestions to improve our manuscript entitled “Antimicrobial susceptibilities of *Proteus mirabilis*: a longitudinal nationwide study from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) Program” (MS: 2042964301268313). We have revised our manuscript accordingly. Our point-by-point response to the editor and reviewer comments is below.  

Thank you again for the positive feedback and helpful comments. We look forward to hearing your decision on our revised manuscript.  

Sincerely,  

Tsai-Ling Lauderdale for all authors  
National Institute of Infectious Diseases and Vaccinology  
National Health Research Institutes  
35 Keyan Road, Zhunan Town, Miaoli County, Taiwan 350  
Phone: 886-37246166; Fax: 886-37586457  
E-mail: lauderdale@nhri.org.tw
Response to Editor and Reviewer Comments

Dear Editor and reviewers: Thank you for all the constructive comments and suggestions. Please note that due to revision, the page and line numbers have changed.

Editorial Comment:
The manuscript has been reviewed by two experts in the field, and is in need of some revisions. In addition, I have reviewed the manuscript, and the following issue needs to be addressed in more details. The authors tested imipenem in their AST panels. It is well known that P. mirabilis can present with higher MIC values against imipenem, compared to the other carbapenems (see line 129 in the manuscript). The authors should comment on this issue in more detail, and perhaps include data regarding the actual MIC values for imipenem compared to meropenem and/or ertapenem. The discussion should be amended accordingly as well.

Reply: We have added a couple sentences in Introduction (L98-L100) and more comments on this issue in Discussion (L283-L296).

Reviewer 1:
Overall impression
The manuscript is original in content and adds to the scientific knowledge about susceptibility of P. mirabilis in one geographical area. The manuscript is very well-written. The questions posed by the authors are well defined and the manuscript is well-structured. The methods are largely well-described and ethical approval for the study has been given. I have five points to make, with other minor suggestions for improvement.

Specific Comments
Point 1. The authors use the terms resistance and susceptibility inter-changeably, which is confusing for the reader. For example, in the summary (paragraph 1) mentions resistance in P. mirabilis, whereas paragraph 2 describes the results in terms of susceptibility. Another example occurs in the background section, paragraph 3. In the results section entitled ‘Susceptibilities of isolates carrying ESBL and AmpC β-lactamase genes’ the text is presented in terms of resistance, whereas in the Tables isolates are described as % susceptible.

Reply: We have revised the manuscript to describe our results in terms of susceptibility as much as possible, and changed %R to %S where appropriate.
A. In paragraph 1 of Abstract, “Longitudinal nationwide data on resistance in *Proteus mirabilis* from different sources are rare” has been changed to “Longitudinal nationwide data on antimicrobial susceptibility in *Proteus mirabilis* from different sources are rare”.

B. In the Background section, paragraph 3, L84-L89. We have revised this paragraph and added a couple recent references on rates of susceptibility to this. The initial % applied to resistance, not susceptibility. We are very sorry for the mistake and have corrected these also.

C. In the Results section (L224-L249) entitled ‘Susceptibilities of isolates carrying ESBL and AmpC β-lactamase genes’, we have revised the data to reflect susceptibility throughout this paragraph.

D. In Discussion, we changed resistance or resistant at several places. For example, at L249-L253. We changed the paragraph to say “In addition, compared to recent reports from the United States, Canada, and United Kingdom, our results showed that *P. mirabilis* in Taiwan have lower rates of susceptibility to cefotaxime (85.7% vs. > 97% in US, Canada, and UK) and gentamicin (57.7 % vs. > 90%) [12, 15-17]. Susceptibility to ciprofloxacin was also much lower than rates found in the United States and Canada (68.7% vs. > 80%). At L254, the sentence was changed to start with “The lower rate of cefotaxime-susceptibility…”

**Point 2.** I would like to see the threat of carbapenemases in *P. mirabilis* mentioned in the background section (Background, paragraph 2).

**Reply:** We have added a few sentences to the end of paragraph 2 in Background (L78-L83) and references have been revised accordingly.

**Point 3.** In the Data Analysis section of the methods there is no mention of the data that will be analysed; however, in the results section ‘Factors associated with ESBL and AmpC carriage’, age and patient location are mentioned with no definitions of the age groups (i.e. what constitutes paediatric, adult and elderly, ICU, non-ICU and outpatients?).

**Reply:** We have added information on these issues in the Data Analysis section of the Methods (L166-L174). The age group definition has also been added to the footnote of Table 4.

**Point 4.** I would like to see a clearer statement in the results/discussion that there was only n=1 isolate with non-susceptibility to ertapenem and that carbapenemases do not currently appear prevalent in *P. mirabilis* in this location.

**Reply:** A statement has been added to the Discussion section (L268-L270) to say “Of note, there was only one isolate with non-susceptibility to ertapenem (MIC = 1 mg/L). Therefore, carbapenemases do not currently appear to be prevalent in *P. mirabilis* in Taiwan.”
Point 5. Relating to Point 4, one limitation of the study for discussion is that the isolates were collected biennially during a three month period; therefore, the results presented here are a representation of the total number of \( P. \) mirabilis circulating in Taiwan.

Reply: At L314-L318 of Discussion, we added “One limitation of the present study is that isolates were collected biennially during a three months period. However, our isolates were from 28 hospitals located in all four regions of Taiwan, 25 of which participated in all 6 rounds of TSAR between 2002 and 2012. These 28 hospitals included 12 medical centers, 15 regional hospitals, and one local hospital. Therefore, the results presented here are a representation of the total number of \( P. \) mirabilis in Taiwan.”

Suggestions for improvement – Minor issues not for publication

Section Page Paragraph Suggestion

Abstract
2 37 Replace ‘largest impact’ with significant impact and add the p value.
Reply: ‘largest impact’ has been changed to “significant impact” in Abstract and Discussion, The \( P \) value has been added to Table 1 footnote d and in Discussion.
2 43 Add the \( P \) value to indicate significance for the values 0%-7%.
Reply: \( P \) value added
2 44 The word gene should be plural.
Reply: “gene was ------ type, respectively.” changed to ‘genes were ------ types, respectively”
3 46 The sentence should begin ‘A significant increase’.
Reply: “Significant decrease” changed to “A significant decrease”

Background
5 64 ‘P. mirabilis had alkaline pH urine. Would the present tense improve this sentence?
Reply: “had” changed to “have”
5 65 Spelling of magnesium.
Reply: Changed. Sorry for the oversight.
5 67 Use of the term ‘used to be’.
Reply: “used to be” changed to “was”

5 72,75,141,204,216,221 \( \beta \)-lactamases producing isolates, should read \( \beta \)-lactamase-producing isolates.
Reply: “\( \beta \)-lactamases producing isolates” changed to “\( \beta \)-lactamase-producing isolates” throughout the manuscript.
6 91 P. mirabilis remained. Would the present tense improve this sentence?
Reply: “remained” changed to “remains”

Methods
7 103, 104 Numerical values 1 and 4 should be written in full.
Reply: “1” and “4” changed to “one” and “four”
7 107 Specifying species. What is meant by this?
Reply: It means we did not ask to collect P. mirabilis specifically.
8 118 GN cards were used.
Reply: “GN card was used” changed to “GN cards were used”
9 128 Spacing ATCC 35218.
Reply: space added between
10 162 Add type after the word specimen.
Reply: “type” added after specimen.

Results
11 171 Change ‘these 1157 isolates’ to ‘the 1157 isolates’.
Reply: “these” changed to “the”
13 214 Change ‘while only 6.4%....did’ to ‘compared with 6.4% of the AmpC-positive isolates’.
Reply: “while only 6.4% of the AmpC-positive only isolated did” changed to “compared with 6.4% of the AmpC-positive only isolates”

Discussion
14 226 Tab beginning of paragraph.
Reply: fixed
14/16 229,231,233,262 Non-susceptibility.
Reply: “Nonsusceptibility” changed to “Non-susceptibility”, and “nonsusceptible” changed to “non-susceptible” throughout the manuscript.
15 245-248 Repetitive.
Reply: Sorry for this. The repetitive part has been deleted and the sentence now reads “Studies from Taiwan on other species of Enterobacteriaceae have found CTX-M-type ESBL and CMY-type and DHA-type AmpC β-lactamases to be prevalent, including Escherichia coli, Klebsiella pneumoniae, and Enterobacter spp.”.
15 251 Change ‘huge drop’ to ‘marked decrease’.
Reply: ‘huge drop’ changed to ‘marked decrease’

17 281 Punctuation missing at the end of the sentence
Reviewer 2.
The authors of this publication reported on the antimicrobial susceptibilities of *Proteus mirabilis* from data compiled from the Taiwan Surveillance of Antimicrobial Resistance (TSAR) program. Generally, many antibiotic resistances increased over the decade, with additional increases in ESBL genes throughout. Overall, this article is well-written and merits publication, with suggested minor revision.

Minor Comments
1) Methods
a. Isolate Collection - For those unfamiliar with the geography of Taiwan, a simple map highlighting the locations of the 26 participating hospitals would be appreciated. Furthermore: Were there any patterns associated regarding resistance/susceptibility based on geographic area?
Reply: We have added a map of Taiwan showing the proximate locations of the 28 participating hospitals (Figure 1). Consequently, the original figure 1 is now figure 2. Figure legends have been revised accordingly also. We did not find significant pattern associated with susceptibility based on geographic regions.

b. Antimicrobial susceptibility testing - adding a reference for the CLSI guidelines would be appreciated (line 123.) Additionally, the antibiotics listed should include their manufacturers. If acquired from different sources, include this information.
Reply: We have added s CLSI reference to this place (now Line 137). Thank you for the reminder. We purchased MIC panels prepared by Trek diagnostics and did not acquire any antibiotics from manufacturers.

This paper is simple in its premise and execution. The authors sufficiently demonstrated the changes in antibiotic susceptibility in Pm over time. While additional information would be appreciated, including thoughts for the reason of increased AmpC b-lactamase prevalence, the authors themselves acknowledge that it is outside the scope of this article. The comparison using the updated CLSI breakpoints was appropriate, and appreciated.
Reply: Thank you for the positive feedback.