Author's response to reviews

Title: High Carriage Rate of High-Level Penicillin-Resistant Streptococcus pneumoniae in a Taiwan Kindergarten Associated with a Case of Pneumococcal Meningitis

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Author's response to reviews: see over
Dear Editors of the BMC Infectious Diseases:

We wish to thank the reviewers for their expert comments and suggestions on our manuscript entitled "High Carriage Rate of Penicillin-Resistant Streptococcus pneumoniae in a Taiwan Kindergarten Associated with a Case of Pneumococcal Meningitis" (MS: 1473614662762383). We have revised our manuscript according to the points raised by the reviewers where possible. Our reply to each of the specific points raised by each reviewer is listed below.

■ Reply to Comments by Reviewer #1 (Dr. John S. Bradley):
  1. The index case and his classmates did not receive conjugate pneumococcal vaccine. This statement has been added to the revised manuscript in the first paragraph of Results section on page 6.
  2. The method used for obtaining the nasopharyngeal samples in the present study is the same method used in our previous study (Chiou et al, JCM 1998). The same method was used for consistency in order to compare with results from our previous work.
  3. We did pick multiple S. pneumoniae – like colonies from the primary culture plate of each study subject for subsequent workup. The colony morphology of S. pneumoniae isolates from each study subject appeared the same and we only found one serotype from each child. Dr. Bradley’s comment is well taken and we will look more carefully for different S. pneumoniae colonies for possible multiple serotypes from the same subject in future studies.
  4. Dr. Bradley suggested that the case description of the index case be shortened. However, Dr. de Andrade (reviewer #2) suggested that additional clinical data be added. Thus we decided to keep the case description pretty much the same way since the information may be of interest to some readers. We added the statement that no otitis media or sinusitis was noted upon patient’s admission on page 3 in the first paragraph of Case report.
  5. We are sorry that we failed to find a published reference from Medline on meningococcus being the most common bacterial pathogen causing meningitis in countries with universal conjugate pneumococcal vaccination, so we did not make this statement. We did state in Conclusion on page 9 that S. pneumoniae and N. meningitidis became the leading causes of meningitis after the introduction of Hib vaccine. We then discussed the effects of 7-valent conjugate pneumococcal vaccination on reducing pneumococcal infections.

■ Reply to Comments by Reviewer #2 (Dr. Ana Lucia de Andrade):
  Because Dr. Bradley suggested that the case description of the index case be shortened and Dr. de Andrade (reviewer #2) suggested that additional clinical data be added. We decided to keep the case description pretty much the same way and chose to answer some of the questions raised by Dr. de Andrade here.

Case Report.
  1. We did culture both of the parents and the younger sibling of the index case for S. pneumoniae colonization and found them to be non-carriers. This information has
been added to the manuscript in Methods and Results sections on pages 4 and 6, respectively.

2. No otitis media or sinusitis was noted upon patient’s admission. This statement has been added in the first paragraph of Case report on page 3.

3. Although the patient had high blood pressure at the time of hospital admission, he did not proceed to septic shock. We agree with Dr. de Andrade’s observation that the high blood pressure of the patient at the time of admission was due to the intracranial hypertension. That was our judgment also. This reply is not added to the manuscript.

**Discussion.**

4. We have incorporated in Discussion and Conclusion the points raised by Dr. de Andrade from some of the references she kindly provided. This included nasopharyngeal carriage of daycare center attendees with high-level penicillin and multi-drug resistant *S. pneumoniae* (page 7 first paragraph of Discussion), increased diseases and carriage rates with prior use of antibiotics (end of page 9 in Conclusion) and the genetic linkage between the strains causing meningitis and those carried in the patients nasopharynx (page 8, second paragraph of Discussion).

5. Although we did not find *S. pneumoniae* carriage in the parents and the young sibling of the index case, spread of *S. pneumoniae* and antibiotic-resistant serotypes from day-care center attendees to their siblings has been reported. This statement had been added to the Discussion with the references added (page 9 in Conclusion).

6. Genetic transformation of the 19F serotype isolates at the time of invasion may have occurred but we did not include this statement because we felt that we had no evidence to support this hypothesis at this time. Because the patient’s isolates from nasopharynx, blood, and CSF were identical by PFGE, we felt that most likely the patient was colonized by the same strain, which subsequently caused the invasive infection.

7. Although we had stated in our manuscript that “it is well recognized that nasopharyngeal colonization precedes pneumococcal infection”, we have added a sentence to stress the genetic link between nasopharyngeal and CSF strains in Discussion (page 8, second paragraph).

8. Regarding prophylaxis for the children in the kindergarten, because none of the other children in the kindergarten were ill, antibiotic prophylaxis was not given to the other children. Conjugate pneumococcal vaccine was not available at the time of the study in Taiwan.

9. We agree with Dr. de Andrade’s comment that vaccination of kindergarten attendees with the 7-valent conjugate vaccine would prevent the further spread of multidrug resistant *S. pneumoniae* in Taiwan. We have ended our conclusion with “It is hoped that a combination of restraint in antibiotic use and implementation of childhood immunization with conjugate pneumococcal vaccine can reduce the burden of pneumococcal illness and multidrug resistant strains in Taiwan and other countries”. The Conclusion of the Abstract has also been revised to reflect this.

10. The two typing mistakes have been corrected. Thank you.
We thank the reviewers for their insightful and helpful comments and look forward to hearing your decision on our revised manuscript.

Sincerely,

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