Reviewer's report

Title: Epidemiology of serotype 19A isolates from invasive pneumococcal disease in German children

Version: 2 Date: 11 December 2012

Reviewer: Walter Demczuk

Reviewer's report:

Major Compulsory Revisions:
1) The claim that increased use of cephalosporin is driving the increase of serotype 19A is tenuous at best. The data presented in this manuscript does not support this. On page 12, line 15 the author states “This shows the main burden of serotype 19A is caused by the expansion of existing clones.” This statement seems to contradict the claim of selective pressures of antibiotic use are responsible. Figure 2 describes the percentage of 19A has dramatically increased during 2006/2007, however there is no indication of similarly dramatic increased antibiotic usage at this time, and very little change in DDDs of penicillin and macrolides. 19A levels seem to increase concurrently with antibiotic use and no causal relationship can be established.

Minor Essential Revisions:
2) Page 2, line 4: Indicate which pneumococcal vaccine was recommended, I assume it was PCV7.
3) Page 2, lines 5-11: This section discussing the distribution of clonal complexes is very confusing. I suggest re-wording to create a more concise and summarized account of when the groups of CC’s appeared.
4) Page 2, line 13: This seems to indicate that the increasing use of cephalosporins is the direct cause of the increase in antimicrobial resistance. I do not think this has been positively established yet. Suggest using “has coincided with.”
5) Page 3, line 4: Start sentence with words “Ninety three”, not a number. Perhaps combine this sentence with the previous one?
6) Page 5, lines 1-5: The authors describe an active surveillance study in the first sentence, then refer to it as a passive system in the second sentence. Is the second sentence referring to the laboratory-based surveillance? Please clarify this section.
7) Page 5, line 6: This is the first time “ESPED” is introduced, should indicate what the acronym indicates.
8) Page 6, line 1: Define what the authors consider “multi-drug resistant,” for example “resistant to two or more classes of antimicrobials.”
9) Page 6, lines 16-23: Define PCV13, GKV, WIdO, ATC/WHO.
10) Page 6, line 22: “..European Surveillance of Antibiotic Consumption project (ESAC)..”

11) Page 8, lines 15-16: Awkward wording of “..resistant plus intermediate isolates..” in this sentence can be changed to include the penicillin non-susceptible terminology. On line 16 “NS” is not yet defined.

12) Page 10, line 7: Remove orphaned right parenthesis.

13) Page 11, line 7: Indicate what the units for “average 6.4 isolates” are. Is it per year?

14) Page 11, lines 20-22: This is a very tenuous claim, since the data presented does not clearly support this. According to figure 2, although a slight increase in cephalosporin use occurs concurrently with the increase of 19A, the use of penicillin and macrolides has remained constant over time.

15) Page 12, line 1: It is not clear what this sentence is related to. In begins “Second, when..” but there was on “Firstly..” previous to this sentence.

16) Page 13, line 16: It is not clear if the increase stated is in overall IPD incidence, or MDR 19A only?

17) Page 19, table 3: Title on lower part of table should read “Post-vaccination?”

18) Page 21, Figure 2: It is not clear what the authors are attempting to represent in this figure. Although the percentage of 19A has dramatically increased during 2009/2010, there is no indication of increased antibiotic usage at this time, and very little change in DDDs. It refutes/disproves the suggestion that increased usage of antibiotics is in some way linked to increased 19A, since 19A levels increased first (or concurrently), then a slight increase in antibiotic use followed. The figure can be simplified by removing the PCV doses line that is redundant since the text describes PCV introduction in 2006.

Discretionary Revisions:

19) Page 3, line 1: This is an awkward sentence. Perhaps “Streptococcus pneumoniae is a major cause of infectious disease globally, especially in children.”

20) Page 5, line 8: Is there any geographical bias? For example, a higher rate of sampling in certain regions?

21) Page 9, line 15: Suggest “The increased proportion of MDR isolates were mainly associated with increased proportions of CC230.”

22) Page 12, lines 2-5: Discuss what is the significance/interpretation of these differences in CCs before and after the PCV?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a