Reviewer’s report

Title: Pharmacodynamic evaluation of commonly prescribed oral antibiotics against respiratory bacterial pathogens

Version: 2 Date: 25 May 2011

Reviewer: Michael B Kays

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Major Compulsory Revisions

1. The PK/PD terminology used by the authors is not correct. Probability of target attainment (PTA) is used when evaluating pharmacodynamics at a specific MIC value. Cumulative fraction of response (CFR) is the correct term when evaluating a population of microorganisms. Since the authors are evaluating the PD of the oral agents against a population of microorganisms, they should use CFR, not PTA. See J Antimicrob Chemother 2005;55:601-607.

2. Since the authors are adamant at evaluating only antimicrobial regimens from the 2006 survey in Sao Paulo, the objectives should be changed to include Sao Paulo.

3. Abstract, Results - PD data are only reported for S. pneumoniae, but the other organisms are equally important considering the empiric nature of antibiotic use for these infections. Suggest to report results for all 3 pathogens and not just one.

4. Are we to assume TID is the same as q8h and BID is the same as q12h? At my institution, TID is 9 am, 1 pm, and 5 pm. Clarification is needed on how simulations were performed for TID and BID regimens.

5. The microorganisms in this study were obtained from multiple sites, including throat and nasopharyngeal swabs. The authors should report how many strains came from each of the anatomical sites. Should throat and nasopharyngeal swabs even be included since these do not likely represent infection?

6. Methods, Pharmacokinetics - In line 4, the authors state that studies had to use a 1- or 2-compartment model to fit the data. However, reference #18 used a non-compartmental model. This must be corrected. What is the rationale for normalizing clearance and volume to body weight for the beta-lactams only? Why not the other drugs? What body weight was then used to simulate the PK profiles for the beta-lactams? Those data are required for the reader to correctly interpret the data.

7. Methods, Pharmacodynamics - To simulate oral beta-lactam regimens, was bioavailability or absorption rate included in the model? If not, how was the absorption phase modeled? For fluoroquinolones and azithromycin, how exactly
were the Monte Carlo simulations performed? From reading the paper, I am assuming that AUC was estimated as dose/clearance but I am not certain. If this is so, why would PK studies have to use a 1- or 2-compartment model to fit PK data? For FQs and azithromycin, is it even correct to say a non-compartment model was used if clearance was the only PK value incorporated into the simulations?

8. Page 7, Discussion - Reference 26 should be removed since it was done in kids and is not relevant to this paper in adults. In paragraph 3, line 6, the authors state that the Rx and microbiologic data were both from 2004-2005. This contradicts the statement in the first paragraph that the micro data are from an earlier time period (2003-2004). Please correct and clarify.

9. Page 8, Discussion - At the end on paragraph 1, the authors comment on how poorly azithromycin performed against H. influenzae "in this scenario" which follows a sentence referring to scenario 2. However, the numbers quoted by the authors are from the first scenario. Please correct.

10. The references should be corrected. Reference #1 needs a web address so the reader can find the information. The journal name for reference #3 should be corrected. Some references list issue numbers, others do not. Some article titles capitalize the first letter of every word, others do not. Please correct to the Instructions for Authors for this journal.

11. Table 3 - The data reported for amoxicillin and co-amoxclav are identical and do not need to be repeated since only the amoxicillin component was simulated and not the clavulanic acid. Under antibiotic, suggest to list amoxicillin +/- clavulanate. Are the data for protein binding of amoxicillin and cefaclor correct? These look like free fractions to me since amoxicillin is only 20% protein bound. Are the CL and Vc values for cefaclor correct when normalized for body weight? Vc is really 29+ L/kg? I highly doubt it.

12. I continue to suggest re-arrangement of drug list in tables 4 and 5 to put like drugs together. It makes it easier for the reader to compare the different dosing regimens for the same drug.

Minor Essential Revisions

1. Results, paragraph 1, regimens - The last sentence should be included in the Methods, not Results.

2. Results, paragraph 2, Microbiology - The second sentence should be deleted as it has already been stated in the Methods.

3. Results, paragraph 3, PK parameters - This should be moved to the Methods since use of log gaussian distributions is a Method, not a Result.

Discretionary Revisions

1. Conclusion - The authors state that cefaclor and low dose levofloxacin should be avoided. What other regimens should be avoided due to poor
pharmacodynamics? Levofloxacin 500 mg since it is poor against S. pneumoniae? Azithromycin 500 mg since it is poor for H. influenzae? Additional regimens can be added.

**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 statistician.

**Declaration of competing interests:**

I declare that I have competing interests.