Reviewer's report

Title: Unexpected Increase in Fluoroquinolone Resistance after Introduction of Moxifloxacin: An Observational Study

Version: 1 Date: 15 November 2007

Reviewer: Joseph M Blondeau

Reviewer's report:

General
This is a well written, well presented manuscript describing an interesting observation with moxifloxacin use and increasing resistance of gram negative bacilli to fluoroquinolones

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Three items of concern to me that I believe require further discussion are as follows:

1) First, the authors refer to moxifloxacin as a 4th generation fluoroquinolone. While this designation is used in the ophthalmic literature, it is not widely used in the systemic infectious diseases literature.

2) The authors also state that moxifloxacin is not excreted in the urine at therapeutic doses, however, it is my recollection that approximately 33% of the dose is excreted renally - can the authors confirm this or refute and reference. With many coliforms, MIC's are low to moxifloxacin (<0.125ug/ml) and as such, should a third of the dose be renally excreted, there is likely to be urine drug concentrations in excess of these values. Could the authors be asked to deal with this specific issue as part of their arguments - ideally presenting and referencing specific data i.e. pharmacology data and MIC data in text.

3) The third point deals with the specific limitations identified by the authors. The authors state "a causal link between moxifloxacin usage and increasing fluoroquinolone resistance cannot be established" and this relates to the retrospective nature of the study. This one statement is, in my opinion, contradictory to the title which specifies the "unexpected increase in fluoroquinolone resistance after introduction of moxifloxacin" - this title implies moxifloxacin is responsible for the increased resistance. I think more discussion with this point is warranted.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
1) under background, the authors indicate moxifloxacin is indicated for community acquired pneumonia. In fact, it is also indicated for therapy for acute bacterial exacerbations of chronic bronchitis, acute maxillary sinusitis, skin and soft tissue infections and now intrabdominal infections in some countries.

2) in the sentence "Gatifloxacin was removed from use..., there is a mistake with the sentence structure

3) in the sentence "However, it is also excreted at sub-therapeutic doses in the urinary system" I think here specific data needs to be provided along with coliform MIC data.

4) The authors need to be more speculative as to why this observation is seen with moxifloxacin and not ciprofloxacin - is it simply due to urine drug concentrations and if so, how does this fit with the potential for resistance when quinolones are used to treat infections outside the urinary tract and where achievable and sustainable drug concentrations are lower and variable with the various different quinolones used.

5) table 1 and table 2, the organism names should be italicized

6) in figure 1, the graph appears to show a downward trend in quinolone usage over the study period. Moxifloxacin usage also declined from 2003 to 2004 and through 2005. Also, ciprofloxacin use also seems to have declined (with fluctuations) over the study period. How as such observations impacted on the data if at all.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

In the past 5 years, I have received research grants and/or served on advisors boards or on speakers lists for the companies associated with all of the fluoroquinolone compounds reported in this manuscript.
I do not have any other financial interests as specified above.