Author's response to reviews

Title: Suboptimal clinical response to ciprofloxacin in patients with enteric fever due to Salmonella spp. with reduced fluoroquinolone susceptibility: a case series

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Dear Editors and Reviewers,

Thank you for the comments provided by the 2 reviewers regarding our paper MS: 1855201613555441, Suboptimal clinical response to ciprofloxacin in patients with enteric fever due to Salmonella spp. with reduced fluoroquinolone susceptibility: a case series.

Reviewer 2 recommended that the MS be accepted without revision. Reviewer 1 had a number of comments and suggestions, and we have attempted to answer all of these below to your satisfaction.

Background:
We have added more information regarding the ongoing debate as to whether MIC interpretive criteria for Salmonella when tested with fluoroquinolones should be changed, and have referenced the approach (ref 5) of Threlfall mentioned by the reviewer of reporting high level and low level resistance categories. We have also mentioned the NCCLS approach in the background section. The pros and cons of these different testing strategies are discussed in more detail in the discussion section. We hope these additions will make the current state of affairs regarding the issue of recognizing reduced fluoroquinolone susceptibility, and the reasons for our study, more clear to the reader.

Materials and Methods
We have provided the manufacturers' names for the antibiotics and media used, as requested. The inoculum size and preparation are those standardly used, as described in by the NCCLS and we have added additional references to these NCCLS methodologies. If the editorial staff feels more details these are essential, we can provide these in detail, but we feel readers can readily refer to the NCCLS documents if needed.

We have added to methods that we tested other antibiotics (ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol) by disk diffusion, as requested by the reviewer.

Results
We have referred to Table 1 as start of clinical results section.
We have provided details regarding antibiotic susceptibilities for ampicillin, trimethoprim-sulfamethoxazole and chloramphenicol for all isolates and given the specific results for these antibiotics against strains with reduced fluoroquinolone susceptibility.
We have added more information to discussion regarding clinical aspects of fluoroquinolone therapy (clinical failure rate, relapse rate, stool carriage rate, microbiological failure rate) in comparison to other agents, based on pooled analysis of reference 1.

Discussion:
We have changed term suboptimal clinical response: to delayed clinical response, and have explained pharmacodynamic terms used (MIC, peak to MIC ratio, AUC to MIC ratio) to make more clear for readers.

We have added more discussion regarding pros and cons of use of NA as a screening test, versus
obtaining MICS directly, including issues related to accuracy, cost and ease of use. We have indicated that
the NCCLS recommended nalidixic acid screening method is simple and inexpensive, but is not 100%
accurate. Directly obtaining MICs may be preferred by some laboratories. We felt we cannot be dogmatic
about which method is used, and that individual laboratories will need to decide which method best meets
their needs.
We have mentioned chloramphenicol as a possible treatment, as requested. However, given that 3 of 7
(43%) of our nalidixic acid resistant strains were also resistant to chloramphenicol, we do not feel we can
recommend this agent for empiric therapy.

Conclusion
We have stated that our key point is that laboratories must institute some method of screening for reduced
fluoroquinolone susceptibility in extra-intestinal Salmonella infections, since finding this will have an impact
on antibiotic treatment selection and clinical outcomes.

We hope these changes are satisfactory to you and the reviewers. Please let me know if further changes
are necessary and we will try to provide these as quickly as possible,
Sincerely,

Robert Slinger