Author’s response to reviews

Title: Systemic Fluoroquinolone Prescriptions for Hospitalized Children in Belgium, results of a multicenter retrospective drug utilization study.

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Author’s response to reviews:

Dear editor,

We thank you and the reviewers for the valuable comments and for this opportunity to revise our manuscript. In the forthcoming section we respond point by point to the comments. We uploaded the revised version of our manuscript (with track changes) separately.

Editor comments

1. Please name the specific ethics committee that approved the study in the ‘Ethics and consent to participate’ section

The name of the ethics committees (‘Commissie Medische Ethiek’ at UZ Brussel and ‘Commissie voor Medische Ethiek’ at Ghent University Hospital) were added to the ‘Ethics and Consent to participate’ section (lines 486-488).

2. Please include the following subsection in your declarations section: ‘Consent to publish-not applicable’

We added this section to our revised manuscript (lines 500-501).

Reviewer 1
1. It would have been interesting to have given data on whether the children were dosed based on actual body weight or ideal body weight, obesity is an increasing problem. This is important in the context of ‘underdosing.’

Children were dosed on their total body weight during the study period, as specific dosing recommendations of FQ for overweight and obese children were unavailable. We clarified this in line 150. There is an ongoing debate on the optimal body size metric for dosing FQ in overweight and obese children. We discuss this in more detail in lines 392-407. Furthermore, we added information on BMI, and the percentage of overweight and obese participants, to table 2 (line 637). Underdosing is similar between overweight/obese and normal weight participants (17.9% vs. 17.4%, p=0.956), which we added to lines 227-228.

2. Were there any local antibiotic prescribing guidelines (paediatric) that informed the prescribers? E.g. in the UK we have the Paediatric British Formulary, in addition to hospital paediatric guidelines.

There were no hospital or national guidelines available on FQ dosing during the study period. When prescribing FQ, physicians could have used different sources; such as labeling guidelines or the Dutch Paediatric Formulary. We clarified this in lines 151-153, and we elaborate on this in lines 355-357.

3. Surely use in these cases is justified.

We agree that there are limited antimicrobial options for treating Mycoplasma pneumoniae meningoencephalitis. We discussed this further in lines 265-273.

4. Lack of AMS teams does not justify dosing errors, there must be checks and balances in place from a patient safety and governance perspective for all medication being administered, antibiotics should not be an exception.

We do not want to justify dosing errors by the absence routine checks of all antimicrobial prescriptions by antimicrobial stewardship (AMS) programs, but this could be a (partial) explanation for the dosing errors in the study population. We tried to clarify this in lines 415-424.

5. How did you define ‘under-dosing’? Adequate dosing is debatable in children and different references will give varying data on this. Often based on anecdotal use and not RCTs.

We agree that adequate dosing is both debatable and challenging in children. Furthermore, there is no universal definition of underdosing. Different studies show that drug elimination in children is probably faster when compared with adults, we elaborate further on this in lines 384-391.
Therefore, we defined underdosing as a dose per kilogram of less than 95% of the minimum recommended dose per kilogram, while not exceeding the advised maximum dose. We added this criterion to our methods section (lines 178-80).

6. If FQs were not to be used what would be the alternative antibiotics for these indications? What is the evidence for using these other antibiotics?

We outlined alternative antibiotics and their evidence for the indications outlined in the discussion section (CNS infection lines 260-272, prophylaxis of febrile neutropenia lines 280-294, pneumonia lines 319-321, and skin- and soft tissue infections lines 333-338). Yet, local antimicrobial resistance patterns should be used when considering an appropriate antibiotic in other settings.

7. Should the authors have some recommendations?

Besides our recommendations on AMS programs, which we will discuss in more detail when responding to the next question, we recommend further pharmacokinetic studies on FQ in children. As both FQ prescriptions and resistance rates are rising, more knowledge on developmental pharmacokinetics in children would be desirable. This will result in individualized dosing recommendations that adjust for both patient and disease characteristics. We outline this in lines 309-312, 342-344, and 447-448.

8. Do you think an AMS team would make a difference? They would not have access to any more evidence than the practicing doctors. What would be the added value of the AMS team and what should they aim to do?

We believe that pediatric AMS programs will improve antibiotic therapies in hospitalized children. Such a multidisciplinary team (usually are at least a pediatric infectious diseases specialist, microbiologist, and pharmacologist involved) is essential in feedback, either prospectively or retrospectively, on antimicrobial treatments to prescribers. In our study population, an AMS program could have critically reviewed indications for FQ treatment, reduced IV courses, and optimized prescribed doses. In the recent study of Kreitmeyer et al, prescribed doses were significantly improved after implementation of an AMS program (reference 39). We discuss this in further detail in lines 414-424 and 445-446.

Reviewer 2

1. It would be interesting to provide data about comparative resistance to FQ and other antibiotics which should be used instead, like macrolides.
To the best of our knowledge, FQ resistance has not been reported worldwide for Mycoplasma pneumonia, while resistance to macrolides and tetracyclines is growing. We outline this in lines 269-272.

2. It would be interesting to put in discussion possible alternative groups of antibiotics which should be used instead FQ in most frequent infections for which FQ were prescribed.

This is basically the same question as the 6th question of the first reviewer. Therefore, we refer to our response to question 6 of reviewer 1.

Other comments

1. We reduced the number of affiliations of all authors.

2. We added a new key word.

We hope that these responses fulfill the reviewers’ comments. Please do not hesitate to contact me if anything would remain unclear.

We look forward to hearing from you.

Kind regards,

On behalf of all co-authors,

Kevin Meesters MD MPH