PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety of Azithromycin in paediatrics: a systematic review protocol
AUTHORS	xu, peipei; Zeng, Linan; Xiong, Tao; Choonara, Imti; Qazi, Shamim; zhang, lingli

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Kalle Hoppu Institution and Country: Finland Competing interests: None
REVIEW RETURNED	05-Mar-2019

GENERAL COMMENTS	Good basic work

REVIEWER	Reviewer name: Michael Rieder Institution and Country: University of Western Ontario. London, Ontario, Canada Competing interests: None
REVIEW RETURNED	11-Mar-2019

GENERAL COMMENTS	This is a protocol proposal to study the safety of azithromycin in children pursuant to the recent WHO call for mass distribution related to trachoma. The authors propose to consider this with a focus on events such as QT prolongation. This is a well written protocol and an interesting question. One issue that might be considered is that the QT risk with azithromycin - as with many QT prolonging drugs - is related to known risk factors which classically include age, renal or cardiac disease and - very germane in this case - age. There is a recent manuscript suggesting that age is a key risk factor, i.e. age older than 65 and thus in this population risk may be quite low (Biomed Res Int. 2018 Oct 14;2018:1574806). The authors might want to consider expanding on this point. As a minor point there needs to be a capital N in New Zealand in the appendices

REVIEWER	Reviewer name: E. Jacqz-Aigrain Institution and Country: Institution and Country, Hopital Robert Debré - APHP, Paris France Competing interests: No competing interest to declare
REVIEW RETURNED	13-Mar-2019

GENERAL COMMENTS	The authors aim to conduct a literature review on the potential adverse effects secondary to the use of azithromycin in children in different situations, including mass drug administration and therapeutic use, different age groups…

	The questions asked by the author are important and the design is developed with the contribution of by an expert namely Imti Choonara. Methodology is clearly descried and adapted to the aim of the review. General comments. Please add that initial judgments will be made independently first …and precise the competences of the reviewers: initially students or trained pediatricians or pharmacists … Are the authors thinking of discussing causality of the events (in particular when including case reports and small series of cases) ? Is an analysis of potential risk factors planned ? if yes, which variables will be collected for this : age, context of administration, associated treatment….that may be included and available in the reports ?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 - Kalle Hoppu

Good basic work (suggest to accept)

Reviewer 2 - Michael Rieder

1. One issue that might be considered is that the QT risk with azithromycin - as with many QT prolonging drugs - is related to known risk factors which classically include age, renal or cardiac disease and - very germane in this case - age. There is a recent manuscript suggesting that age is a key risk factor, i.e. age older than 65 and thus in this population risk may be quite low (Biomed Res Int. 2018 Oct 14;2018:1574806). The authors might want to consider expanding on this point.

Thanks for your suggestions. We have added a sentence to the Introduction highlighting this and citing this paper

2. As a minor point there needs to be a capital N in New Zealand in the appendices.

We have corrected the capitalization, thank you for your reminder.

Reviewer 3 - E. Jacqz-Aigrain

1. Please add that initial judgments will be made independently first … and precise the competences of the reviewers: initially students or trained pediatricians or pharmacists …

Thanks for your suggestions. We have added that initial judgments would be made independently first by two students and reviewed by a pharmacist. Modified version as follows:

The studies will initially be independently selected by two reviewers (WYL and XCP, students) upon reading of the title and abstract of the articles. Once relevant articles are screened in, a complete analysis of the full-text articles will be performed by the previously defined selection criteria. , independently by two authors. Any disagreements will be resolved by discussion with a third reviewer (LNZ, a trained pharmacists) if needed.

2. Are the authors thinking of discussing causality of the events (in particular when including case reports and small series of cases)?

We will use WHO—Uppsala Monitoring Centre system to evaluate the relevance of suspected ADRs and azithromycin in case report studies. We verified the protocol to make it more accurate, as follows:

WHO—Uppsala Monitoring Centre system will be adopted to evaluate the relevance of suspected ADRs and azithromycin in case reports.

3. Is an analysis of potential risk factors planned? if yes, which variables will be collected for this : age, context of administration, associated treatment….that may be included and available in the reports ?

We will add an analysis of potential risk factors in this study. Considering the relevance and availability of data, we will collect age, sex, weight, administration route, rationality of indication, rationality of dose, and rationality of course of treatment. We have modified as followed in the protocol:

Logistic regression models will be used to identify univariable and multivariable risk factors for AEs .We will include all significant variables in univariable logistic regression analysis. The multivariate analysis will be performed with the variables with $P < 0.05$ ($P < 0.05$ will be considered to be statistically significant) and calculate the OR and the 95% CI of the study factors. All significant variables are as follows: (1) age; (2) sex; (3) body weight; (4) administration route; (5) rationality of indication; (6) rationality of dose; and (7) rationality of course of treatment.