Author's response to reviews

Title: Intermittent preventive treatment: efficacy and safety of sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine plus piperaquine regimens in schoolchildren of the Democratic Republic of Congo. A study protocol for a randomized controlled trial

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Author's response to reviews: see over
Subject: submission of a manuscript: "Intermittent preventive treatment: efficacy and safety of sulfadoxine-pyrimethamine and sulfadoxine-pyrimethamine plus piperaquine regimens in schoolchildren of the Democratic Republic of Congo. A study protocol for a Randomised Control Trial"

Dear editor,

Malaria is a major parasitic disease that affects 243 million individuals and causes more than 1 million deaths annually particularly in Sub-Saharan Africa. In intensive transmission areas like the DRCongo where individuals are permanently exposed to infectious mosquitos bites, severe disease develops in infants and young children. However, in children of 5 years of age and school-age children, the malaria infection is characterised by low recurrent parasitaemia. The prolonged carriage of malaria parasite in school-age children re-triggers the development of acquired immunity, the premunition that reduces the risk of clinical malaria and of death in school-age children. However asymptomatic malaria infections if untreated cause malaria-induced inflammation that may lead to iron deficiency anaemia. In malaria endemic countries anaemia affects approximately 85 million SSA school-aged children. Anaemia reduces the cognitive potential the school children, retards their growth, and predisposes them to other diseases.

Intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine (SP) is an efficacious public health intervention that markedly reduces clinical malaria incidence and the overall child mortality, and improves haemoglobin concentration and the nutritional states of children of age < 5 years. In addition, owing to its prophylactic effect IPT may decrease malaria transmission in vulnerable populations. However, reversely to infancy and pregnancy, antimalaria IPT has been sparsely investigated in children.

Furthermore the implementation of IPT may be challenged by the development of SP resistance that has been reported in malaria endemic areas. To minimise the risk of SP resistance SP could be combined with another antimalarial. Unfortunately, evidence about the efficacy and safety of IPT SP in mono or combination treatment in the presence of SP resistance strains selection is not yet substantiated in schoolchildren. Merely three clinical trials with restricted treatment arms and/or follow-up have so far been performed on IPT in school children of hyper endemic areas. We carried out a randomised controlled trial to assess the efficacy and safety of IPT SP or sulfadoxine-pyrimethamine plus piperaquine (SP-PQ) versus controls in schoolchildren of the DRCongo and evaluated the impact of these interventions on SP resistance.

If proven effective, IPT SP or SP-PQ would be of direct benefit for the schoolchild, contribute to malaria control at school, and facilitate community-wide the implementation of other control interventions i.e. vector control, IPT in infancy and pregnancy, and malaria primary diagnosis and treatment. Also IPT as a preventive intervention is likely the most feasible in schoolchildren because schoolchildren are usually asymptomatic to malaria infection and are consequently untreated in practice. Furthermore, the implementation of IPT is expected to be the easiest in schoolchildren as schools could be a sustainable delivery channel.

By submitting this manuscript we aim to encourage fellow researchers for further studies on IPT in schoolchildren of other settings to generalise the findings on the efficacy and safety of IPT SP. As consequence, we submit our manuscript to the Trials Journal that is one of the leaders in sharing and disseminating study protocols to a large audience.

Please, note that the research is funded by the Flemish Interuniversity Council (VLIR-UOS) (funding reference: ZRDC2012MP076) and the Research Foundation -Flanders (FWO) (funding reference: G.078.11) of Belgium. The authors of this manuscript disclaim any competing interest in the concept and the conduct of this clinical trial.
Major Compulsory Revisions

Comment 1: Sample size: This study makes a fair attempt to test two superiority hypotheses on malaria chemoprevention ((i). SP vs control; (ii) SP+PQ vs control) and one non-inferiority hypothesis (SP vs SP+PQ). The assumptions, formulae or model applied in the determination of the sample size have been either incompletely or poorly described. The statistical assumptions for non-inferiority and superiority were alluded to but it remains unclear how the numbers were worked out (at least a reference to source of formula or method used for sample size calculation).

Authors’ response: the sample determination has been described in the new version of the manuscript.

Comment 2: Randomization and Allocation concealment: The sentence “A randomization list of blocks of varying size and stratified according to the number of recruitment points in each site was provided”, is not enough. How exactly was sequence of allocation generated? How was the allocation concealed?

Authors’ response: the randomization process has been described as required by the reviewer.

Comment 3: Ethical issues: In describing the ethical considerations the authors refer to “other tests” to be performed with residual plasma. Are these other tests going to contribute to hypothesis testing and the objectives of the trial which the parents/legal guardians of these children consented to? Do these explain the collection of rather volume of blood from the children (3ml)? It would be helpful to submit the consent information sheet to the editors of the journal to reassure readers that all the ethical issues in this regard have been appropriately addressed and explained in the information given to these parents and their children.

Authors’ response: This study also aims to assess the prevalence and risk of host-related predictors for malaria (re)infections. Therefore, other tests such as detection of antibodies and cytokine assays are considered to be done at a later stage. These results will not contribute to the hypothesis testing of the trial but will bring more insight regarding host protection and susceptibility to malaria. Indeed the collection of 3ml blood is explained by further use in these other tests. The version of the informed consent that was approved by the Ethics Committee as part of the study protocol is submitted together with the manuscript for the editor and reviewer’s considerations.

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. Important terms have been vaguely described/defined and rather ambiguous. Examples are “malaria-induced anaemia”, “malaria infection status and morbidity”, “educational achievement”.

   • What exactly would the researcher describe as “clinical symptom of severe anaemia” (which is one of the exclusion criteria). • It would be crucial to clearly define exactly these terms that appear in the objective statements, hypotheses and outcome indicators mean in this particular trial context.

Authors’ response: correction is made for the terms determined by the reviewer as vague.

   • It is particularly needful to clearly explain the meaning of “Control” in this study.

Authors’ response: controls are “untreated trial participants” in this study. The description has been added in the manuscript.

2. Exclusion criteria overlap with some of the outcome indicators e.g. For instance “clinical malaria at baseline” is an exclusion criterion but also a subset of the #2 secondary endpoint.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

Authors’ response: “clinical symptoms of severe anaemia” was referred by the authors to “decompensated anaemia”. The authors agree with the reviewer that the term was inappropriately used and changed it, accordingly to the reviewer recommendations. Further the authors adjusted the discrepancies between the exclusion criteria and the objectives.
General comments

1. Authors could be more explicit in description of important study terms. It would be difficult for others to replicate the outcome assessments proposed in this study because several important terms and statistical processes have not been adequately described.

2. The planned statistical analysis could be more explicit; making specific reference to planned study outcomes.

Authors’ response: the statistical analysis is developed as recommended by the reviewer.

Yours faithfully,

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