Author’s response to reviews

Title: Sulphadoxine-pyrimethamine plus azithromycin for the prevention of low birthweight in Papua New Guinea: a randomised controlled trial.

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Author’s response to reviews: see over
Point-by-point response

We would like to thank the reviewers for their prompt response and thorough review.

1) Comments from senior editor

In addition, we would appreciate a short statement, within your current ethics statement, that clarifies the rationale and the ethical consideration for your RCT in PNG despite no recommendation from WHO for use of SP-IPTp outside of Africa. You have mentioned this in your original cover letter that accompanied your initial submission to the journal. If you could also mention this in a couple of sentences within your manuscript, that would be great.

Response: We have included the following in the ethics statement:

“Because there is currently insufficient evidence to support a general recommendation for the use of IPTp-SP outside Africa, and because SP alone is often ineffective against Plasmodium vivax, which causes around 40% of malaria infections in PNG, we compared SPAZ IPTp to a single course of SP and chloroquine (CQ) to eliminate infection.”

2) Reviewer 1

No comments.

3) Reviewer 2

a) Acknowledging the fact that efficacy/effectiveness of SP-IPTp depends on levels and degrees of SP-resistance, description of the study area in relation to this aspect should have been upfront instead of briefly touching on it under discussion. In this regards, I suggest most contents of lines 487 to 494 be re-located to the heading of line 143 (Trial design, setting and participants).

Response: We have added the following to the relevant section in the methods.

A previous survey of molecular markers of SP resistance in children from the study area demonstrated absence of ‘high’ and ‘super’ resistant P.f. and a low prevalence of dhps 540 (20%).

b) Admittedly, the loss to follow up rate is high. A through description and/or presentation of the characteristics of participants who were lost to follow up is essential. Presumably, efforts were made by the team to establish reasons for loss. For example: if many participants decided to quit the study because they experienced adverse events, current reported findings may have underestimated the true picture of adverse events. Basing only on the fact they (loss to follow up) had similar baseline characteristics at enrollment is not strong enough!
Response: We agree with the reviewer that high (non-differential) loss to follow-up is concerning and this major limitation is highlighted in both the abstract and the discussion. Supplementary tables 1 and 2 detail (1) the characteristics of women lost to follow up vs. included in the analysis of the primary outcome and (2) lost to follow up by treatment arm. Importantly, the latter table reveals no important differences in loss to follow-up by treatment arm.

Of those women for whom a pregnancy outcome (stillbirth/live birth) could be established (81% of women included a baseline, n = 2,247) reasons for non-inclusion in the ITT birthweight analysis are highlighted in the trial flowchart. Most women with a live birth had to be excluded from the birthweight analysis because they presented more than a week later to the health centre to have their infant assessed (and a weight measured). They were more likely residents of rural communities (as were all women not included in the BW analyses, Supp Table 1). Travelling in rural PNG is challenging and likely explains why many women did not make it on time to one of our delivery centres. Sub-analyses of this trial included birthweight imputations for these women.

The number of women who were withdrawn by the study team, or formally asked to be withdrawn themselves, is provided (with reasons) in trial flowchart. Tolerability of the intervention appeared to be very similar (and high) for both treatment arms.

We were unable to establish pregnancy outcome (or reason for leaving the study) for 17% (474/2775) of women randomized to treatment (lost contacts). We do not know why these women were lost to follow-up. As you rightly suggest, a number of reasons may be important, which could include outmigration (common in PNG), adverse effects (treatment defaulters), economic reasons, or severe adverse events, amongst others. The trial was supported by a team of 2 community liaison officers, 25 community reporters, and 1-2 nurses which, on a weekly basis, attempted to establish the pregnancy outcome and reasons for non-attendance for those women who did not present to one of our study sites within one month of estimated delivery. ALL women for whom we know what happened are included in the trial flowchart, safety analyses, and if applicable, birthweight analyses. For women that are lost contacts reasons for non-attendance could not be established, and we did not want to speculate as to why they did not come back. All we can show is that numbers did not differ between trial arms, and neither did their baseline characteristics.

We have added the following to the Methods section:

A team of community liaison officers, reporters, and nurses was dedicated to the follow-up of women who did not present for delivery at a participating health centre within one month of the estimated delivery date in order to establish pregnancy outcome.

We have added the following to the limitations section (pertaining to loss to follow-up).

Furthermore, the reasons for not presenting for delivery remain unknown for 474 women, which may include adverse events.
c) A clear description for the management of study participants who became sick from malaria is required, including treatment regimen used, and the time lag before rejoining the study.

Response: We have added the following to the methods section:

Anaemia and malaria were treated with iron/folate supplements and albendazole, and quinine (in first trimester, 300mg, two tablets orally three times daily for 7 days) or artemether-lumefantrine (in second and third trimesters, 20/120mg, four tablets six times over three days), as per national protocol [25]. Women treated for malaria had their study medication administration rescheduled two weeks later.

- Similarly, there is need to state how concomitant treatments using drugs with antimalarial activity and/or self-medication with similar medicaments were handled and/or controlled for??

Response: We did not control for this and believe this is not necessary in the context of a randomised controlled clinical trial. Self-reported antimalarial use in the index pregnancy and prior to enrolment was similar between trial arms (Table 1)

- Furthermore, there is need to know drugs used to treat STI and how such managerial approaches were harmonized to avoid interferences with drugs under study.

Response: STI swab results only became available after delivery. Swabs were transported to a Goroka, PNG, where they were processed and analysed. Lack of staff meant that turnover of samples was comparatively slow, precluding provision of results to women prior to delivery. Participants were informed as soon as the result became available, and referred to the STI clinic for treatment. As treatment was given after delivery it could not have acted as a confounder for the primary outcome analysis.

- Separately, in line with GCP, the managerial approach for SAEs needs a mention without going into specifics!

Response: We added the following to the relevant section of the methods:

The study clinician on-call was alerted by the nursing team upon detection of a possible SAE, whereby cases were clinically evaluated and reported shortly thereafter, but allowing for a maximum time frame of 24 hours for reporting of cases detected at distal study sites.

d) It is unclear whether loss to follow includes defaulters or true losses. The two need differentiation as they will have different repercussion on the findings.

Response: Please see response to point b). 474 women were lost contacts (or true losses). For them reasons behind non-attendance are unknown.

e) Study enrollment exclusion of age <16 years would mean inclusion of minors (in
most settings), as adult age in most communities/countries starts at 18 yrs. Assuming this is true for PNG, what was the consenting process for the minors?

**Response:** The legal age of consent regarding heterosexual activity as well as marriage for PNG women is 16. Pregnancy studies were given approval by the PNG ethics committees because by law they were legally allowed to become parents.

We have added the following to the Methods section.

**The legal age of consent for PNG women is 16 years.**

f) An objective way of assessing drug compliance/adherence should have been deployed. It is clearly established that what is said by participants is not what they may have really done. The issue of lack of funds for drug assays could be argued for and against!

**Response:** We agree that this is a limitation. Ideally, DOT of all doses of each treatment course would have been undertaken. Given the AZ regimen used (4 doses over 2 days), this was neither logistically feasible for the study team or for most participants (who often resided at considerable distance from the health centre). The first dose of each treatment course was taken under supervision (including all SP tablets, and 1 g of AZ in the intervention arm).