Author's response to reviews

Title: Cyclical iron supplementation to reduce anemia among Brazilian preschoolers: a randomized controlled trial

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Author's response to reviews:

Reviewer's report
Title: Cyclical iron supplementation to reduce anemia among Brazilian preschoolers: a randomized controlled trial
Reviewer: Katarzyna Kordas

Major comments:
1. in paragraph 2, when discussing the fact that weekly iron supplementation is as efficacious as daily in reducing anemia prevalence, only 1 reference is cited. There is more work on this and some of it is contradictory to the view presented here. It would be important to acknowledge this. How much of this work has been done in children?
Reply: Other references were included

Minor comments:
1. In paragraph 1, sentence 2, revise as "It affects populations not only in developing but also highly-industrialized nations."
Reply: the sentence was changed

2. In paragraph 3, "Alternative strategies" are mentioned in the first sentence. Please explain what this means. Alternative to what?
Reply: We agree this was vague and made the necessary corrections

3. In paragraph 3, it is stated "although there is no prescribed, ideal interval between supplementations". What does this mean? That the regimen proposed by the ACC/ASN is not well tested? Also, this is the reason why this study is
being conducted. It is important to really highlight this as a gap in our knowledge and the motivation for the study.

Reply: Again this was vague and the necessary corrections were made with a better description of our ideas

METHODS
1. In paragraph 3, it is stated "all children stayed at the daycare centers fulltime". Does this mean they lived there or that they attended daycare full time? The word "stayed" makes this unclear.

Reply: this was corrected

2. In the same paragraph, please describe the typical meals the children received in the daycare.

Reply: A typical menu was described although all the alternatives would require too much space

3. Finally, describe how the schools were chosen. Why was the study conducted in this city? Please describe the setting in more detail and state whether ID/anemia is suspected or documented (provide references to published work as applicable).

Reply: all these points were tackled

4. On the second page, where the dosage and timing of supplement administration are described (first full paragraph), please explain who administered the supplement and where, as well as who evaluated compliance.

Reply: this was corrected

5. Pg 2, paragraph 3, please describe in more details how anthropometry was conducted. Who did the measurements, how they were trained/standardized if more than one person did this.

Reply: again these points were included in the paper

6. Coulter counter and cyanomethemoglobin method are mentioned for measuring hemoglobin levels. Were both methods used at the same time? Why? Where was this analysis done? What quality control measures were used? %CV?

Reply: This was corrected – the equipment uses this technique

7. For statistical analysis, it is mentioned that ANOVA was used to compare
means for three or more variables. You mean three or more groups?

Reply: This was removed from the study – the original work was more comprehensive (PhD thesis)

RESULTS
1. In 2nd paragraph, it is mentioned that both groups were "homogenous". You mean comparable? Were they comparable on hemoglobin? this is not mentioned.

Reply: The reviewer is correct and this was changed

2. Throughout, when reporting height, hemoglobin, etc. use only 1 decimal value.

Reply: The authors decided that it is better to leave with 2 dp

3. In paragraph 3, "some side effects" were mentioned (nausea in parenthesis). If nausea is the only side effect experienced, then do not say "some" but state that three children experienced nausea.

Reply: The other common possible side effects were mentioned

4. In paragraph 4, the percentage of anemic children decreased from 20.2 to 5.0%. Say "the overall percentage" to make sure it is clear that all children are considered together.

Reply: this was corrected

Reviewer's report
Title: Cyclical iron supplementation to reduce anemia among Brazilian preschoolers: a randomized controlled trial
Reviewer: Therese Dowswell

Thanks for sending me this very good manuscript to review.

First, the authors address an important public health question; anaemia in young children is a problem throughout the world and examining the best way to administer iron to reduce anaemia while avoiding side-effects is relevant to health care providers in many settings. The question is well defined. The methods (RCT) are appropriate and well described. The analysis methods are described and seem appropriate. The data appear sound. The authors state that there were no significant differences in the age, weight etc of children in the two groups, nevertheless, I thought the paper could have been improved by the addition of a table setting out the background characteristics of participants. This
would be helpful so that readers could compare characteristics of children in the two randomised groups and it would also allow readers to consider the extent to which findings can be generalised to other settings and populations. (I suggest this could be a discretionary revision).

Reply: the table was included

I would also like the authors to clarify whether they collected information about side-effects in a systematic way - were school staff asked to record possible side-effects or to record where absence from school could be due to side effects. At the moment all we know is that 3 children experienced nausea over the study period. The fact that children may suffer fewer side effects with intermittent (eg weekly) supplementation is one of the main justifications for recommending this type of regime. I suggest that the provision of more information on side effects should be an essential minor revision. If information on side effects was not collected this may be a limitation of the study.

Reply: This information was included in the study

The authors use appropriate up to date references and the paper is well-written. The abstract accurately conveys the findings (a very minor point - I would avoid using dashes just before numbers in the results section of the abstract as this could suggest a negative value).

Reply: we corrected this point

I enjoyed reading this paper on an important topic.

Level of interest: An article of outstanding merit and interest in its field

Reply: Thank you very much for the encouragement

Reviewer’s report
Title: Cyclical iron supplementation to reduce anemia among Brazilian preschoolers: a randomized controlled trial

Reviewer: Ekhard Ziegler

This manuscript reports the results of a trial comparing two regimens of iron supplementation of preschool children. Both groups received the same amount of supplemental iron, but one received it in weekly doses whereas the other (cyclical) received it in two supplementation periods each lasting 20 week days, separated by 4 months. The manuscript needs improvements in a number of
areas, including English diction.

1. Supplemental iron: We must know what the concentration of ferrous sulfate was, whether it was flavored, what volume of the solution was given, how it was measured (syringe?), how it was given to the children? Was it given on an empty stomach?

Reply: All these points were included in the latest version

2. Hemoglobin: We must know how blood was obtained (venous or capillary)

Reply: this was stated

3. Subjects: There were apparently 252 children in the 4 day care centers. Of these 110 participated and we need to know how you got from 252 to 110. We need to know how many were excluded because of infections, because they took iron supplements or because they had hereditary anemia (sickle cell disease?). And how many parents declined to let their children participate? What are “infections” – viral colds? parasitic infestations?

Reply: this was corrected – infections meant any type of infection but as mentioned in the study no parasitic infections were identified.

4. Statistics: It is not evident where ANOVA was used.

Reply: we agree and this was removed – this was part of a more comprehensive work (PhD thesis)

5. Results: This reviewer would like to suggest that the results regarding prevalence of anemia be incorporated into the table. In the table, “variation” should be changed to “difference” or “change”.

Reply: anemia was included and variation was changed

6. Abstract: It needs to convey to the reader in succinct form the essentials of the study and its results. What is missing now is who the study population was. It must state exactly what was done. For example, “the weekly group received 30 mg elemental iron sulfate” needs to be changed to say that this dose of iron was given weekly. In the results, increases in hemoglobin are given as “¬¬ 0.27 g/dL” which would be understood by most readers as a decrease.

Reply: All this was corrected

7. Discussion: Maybe you want to say the reason why iron supplementation did not completely eradicate anemia is that not all anemia is caused by iron
deficiency. “Adhesion” should be changed to “adherence” or “compliance”; “school” should be changed to “daycare”

Reply: all these points were included