## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Prevalence and determinants of anaemia in children aged 6 to 59 months in Africa: a protocol for systematic review and meta-analysis |
| **AUTHORS** | Simo, Larissa Pone; Agbor, Ndip Valirie; AgborNdip, Ettamba; Ekaney, Domin Sone M; Mbeng, Emmanuel Njang; Linonge, Christie Etom; Neba, Kilton Nforchu; Kemah, Ben-Lawrence Ayong; Mbanya, Dora |

## VERSION 1 – REVIEW

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| **REVIEWER** | Jobert Richie Nansseu<br>Department of Public Health, Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I, Yaoundé, Cameroon |
| **REVIEW RETURNED** | 30-Jun-2019 |

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| **GENERAL COMMENTS** | General comments<br>There are some typos and grammatical errors that should be corrected<br>I think that the reference should be indicated/placed just before or after a punctuation, depending on the journal requirements.<br>Strengths and limitations<br>I suggest rewording the first point; for eg: “This will be the first SR and MA depicting the burden of anaemia in under-5 aged children living on the African continent”. This is more directive and specific…<br>Introduction<br>Last sentence of the 1st paragraph: I think it should read “…whose prevalence was…” considering that prevalence is singular.<br>I also think that the last sentence of the second paragraph should be in the past, as the authors present estimates for 2011.<br>Data presented in the second paragraph are old. Are there not more recent data??<br>Last sentence of the 3rd paragraph: It should read “…for high prevalence rates of anemia…”<br>The first sentence of the last paragraph is hard to read and understand. Please rewrite it to make it clearer; in addition, perhaps do you need to recall the SDG 3.2 you have mentioned so that the reader can easily fix how your study will inform attainment of that specific goal.<br>Objective/review question<br>Unless it is a specification/request from the journal, I think there is useless repetition between your objective and review question.<br>Why they authors don’t think of exploring the driving factors of anemia in this study? I think this would be an interesting add-on value of their review.<br>Methods<br>Criteria |

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| | Is it not to be considered, control arm of RCTs, if eligible?<br>What do the authors mean by hemoglobin measurements? I think this should be clearly stated<br>“Children below five” does not equal “children aged 6-59 months”. The authors should be consistent with their definitions throughout the manuscript.<br>Why excluding the 0-5 months? This should be made clear for the reader<br>Why was the cut-off of 30 participants chosen to exclude case series?<br>Letters, commentaries and other types of articles are they not part of exclusion criteria? What about case-control studies? RCTs?<br>The authors do not say how they are going to manage duplicated studies/data.<br>All forms of haemoglobinopathies prompting exclusions should be enumerated.<br>Nothing is said in inclusions/exclusions about the study population with regard to place of study: are you including children of African origin residing inside Africa, outside Africa, or both? Note that a child can be inside Africa but not be of African origin: how do you intend to discriminate these children?<br>Another way of doing things could be to include all studies which have identified anemia in 6-59 years infants, and group them according to the definition used and diagnostic test. Further, perform subgroup analyses for each of these groups of studies. The issue is that if studies which have used the “below 110g/l” definition are lower than others, it could result in a picture different from the true burden of the condition…I hope the authors understand my point.<br>Search strategy<br>Your search strategy in pubmed should include the date limits.<br>You should also manually search the references of relevant review articles, not only full texts of articles you included in the review<br>Data extraction<br>It should be made clear that the process is to be conducted by two independent authors.<br>The terms mild, moderate and severe anemia are not defined at all.<br>Data synthesis<br>The Cohen’s should not only be used to assess agreement between authors for study inclusion, but also for data abstraction and risk of bias assessment<br>A sensitivity analysis could be conducted only for studies with low risk of bias, to see if the estimates differ from the overall estimate driven from all studies included in the meta-analysis<br>What difference the authors do between school-based and community-based studies?<br>In line with a previous suggestion, you could add definition of anemia as a criteria for subgroup analysis.<br>Why consider only p less than 0.1 for multiple meta-regression? Why not p less than 0.25? |

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| **REVIEWER** | RAKESH PS<br>Amrita Institute of Medical Sciences<br>India |
| **REVIEW RETURNED** | 25-Jul-2019 |

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| **GENERAL COMMENTS** | Dear Authors,<br><br>Nice protocol. But kindly consider the followiing |

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| | 1. There might be country wide major surveys which included anemia, which might not appear in electronic databases.Will that be included?<br><br>2. Putting WHO criteria of 11mg/dl may exclude some major studies. If the study has enumerated the categories clearly, why should we exclude that?<br><br>3. In Risk of bias table, total is adding to 9, while in scores 8-10 is mentioned as high bias.<br><br>4. Which are the acceptable and validated tests you will consider. Please pre define it<br><br>5. Taking time since inception- there mght be gross variations in anemia prevelance. For prevalnec recent studies might be more useful. Is there a plan to capture for various time periods?<br><br>6. If a study is done among hospital attendees or among children with chronic diseases- will you include that? Think of excluding the same and include only community based studies. Or at least plan for a sub group analy |

**VERSION 1 – AUTHOR RESPONSE**

Jobert Richie Nansseu (Reviewer 1)

General comments.
Reviewer's comment: There are some typos and grammatical errors that should be corrected. I think that the reference should be indicated/placed just before or after a punctuation, depending on the journal requirements
Authors' response: Thank you for your comment. The references have been placed before the punctuation marks. We have also read through the manuscript and typos have been addressed accordingly.

Reviewer's comment: Strengths and limitations
I suggest rewording the first point; for eg: "This will be the first SR and MA depicting the burden of anaemia in under-5 aged children living on the African continent". This is more directive and specific…
Authors' response: Thank you for your comment. This section has been corrected. The statement now read: "This will be the first systematic review and meta-analysis to estimate the burden of anaemia in children aged children 6-59 months living on the African continent."

Introduction
Reviewer's comment: Last sentence of the 1st paragraph: I think it should read "…whose prevalence was…" considering that prevalence is singular. I also think that the last sentence of the second paragraph should be in the past, as the authors present estimates for 2011. Data presented in the second paragraph are old. Are there not more recent data?? Last sentence of the 3rd paragraph: It should read "…for high prevalence rates of anaemia…" The first sentence of the last paragraph is hard to read and understand. Please rewrite it to make it clearer; in addition, perhaps do you need to recall the SDG 3.2 you have mentioned so that the reader can easily fix how your study will inform attainment of that specific goal.
Authors' response 3: Thank you for your comment. This section has been updated. We have added

more recent estimates provided by the World Bank (Please see paragraph 2/lines 7-8).

Objective/review question
Reviewer's comment: Unless it is a specification/request from the journal, I think there is useless repetition between your objective and review question. Why they authors don't think of exploring the driving factors of anaemia in this study? I think this would be an interesting add-on value of their review.
Authors' response: Thank you for your comment. This section has been corrected. Also, the authors agree with the reviewer's suggestion and will narratively summarise the determinants of anaemia due to the anticipated wide varieties of risk factors of anaemia and how these factors were defined (or categorised) in various studies.
Methods-Criteria
Reviewer's comment: Is it not to be considered, control arm of RCTs, if eligible?
Authors' response: Thank you for your comment. They will be considered for inclusion. We have updated the inclusion criteria.

Reviewer's comment: What do the authors mean by hemoglobin measurements?
Authors' response: Thank you for your comment. This sentence has been clarified. It now reads: "Studies which diagnosed anaemia based on haemoglobin estimation using a complete blood count or hemoglobinometer."

Reviewer's comment: I think this should be clearly stated "Children below five" does not equal "children aged 6-59 months". The authors should be consistent with their definitions throughout the manuscript.
Authors' response: The authors agree with the reviewer. We have edited throughout to indicate that we will be working with children from 6 to 59 months of age.

Reviewer's comment: Why excluding the 0-5 months? This should be made clear for the reader.
Authors' response: Thank you for your comment. Children 0-5 months will be excluded because we assume that for most of these children, the minimum iron requirement is gotten from breastmilk which contains an easily absorbable form of iron. Iron deficiency anaemia is the most common cause of anaemia in children. After this period (0-5 months), breastmilk becomes insufficient as the infant's daily iron requirement increases; thereby putting these infant's from 6 months and older at greater risk of becoming anaemic.

Reviewer's comment: Why was the cut-off of 30 participants chosen to exclude case series?
Authors' response: Thank you for your comment. To better estimate the prevalence of anaemia in children aged 6-59 months at population, we are considering a minimum sample size of 30 participants per study to apply the assumptions of the Central Limit Theorem.

Reviewer's comment: Letters, commentaries and other types of articles are they not part of exclusion criteria? What about case-control studies? RCTs?

Authors' response: Thank you, we listed articles that will be considered for inclusion. Nevertheless, letters to the editor, commentaries and case-control studies will be excluded. We have updated the inclusion and exclusion criteria according to the reviewer's comments.

Reviewer's comment: The authors do not say how they are going to manage duplicated studies/data.
Authors' response: Thank you for your comment. We updated the inclusion criteria to indicate that "For duplicate publications, only the most recent, comprehensive publication with the largest sample

will be included.”.

Reviewer’s comment: All forms of haemoglobinopathies prompting exclusions should be enumerated.

Authors’ response: As mentioned under the exclusion criteria/point 2: “Studies conducted in a population with haemoglobinopathies like as sickle cell anaemia”. We are not sure if the author wants us to list every possible haemoglobinopathy.

Reviewer’s comment: Nothing is said in inclusions/exclusions about the study population with regard to place of study: are you including children of African origin residing inside Africa, outside Africa, or both? Note that a child can be inside Africa but not be of African origin: how do you intend to discriminate 0these children?

Authors’ response: Thank you. We will consider only children residing in Africa. We will only exclude a study if it is conducted among a different race residing in Africa.

Reviewer’s comment: Another way of doing things could be to include all studies which have identified anaemia in 6-59 years infants, and group them according to the definition used and diagnostic test. Further, perform subgroup analyses for each of these groups of studies. The issue is that if studies which have used the “below 110g/l” definition are lower than others, it could result in a picture different from the true burden of the condition…I hope the authors understand my point.
Authors’ response: Thank you for the suggestion. We will only consider studies which used the WHO criteria to defined anaemia; please see Methods/inclusion criteria/Point 3. However, we will perform subgroup analysis according to the diagnostic test as the reviewer suggested.

Search strategy
Reviewer’s comment: Your search strategy in pubmed should include the date limits. You should also manually search the references of relevant review articles, not only full texts of articles you included in the review.
Authors’ response: Thank you. We have updated the date limit of our search in our search strategy and included it in Table 1.

Data extraction
Reviewer’s comment: It should be made clear that the process is to be conducted by two independent authors.
Authors’ response: Thank you for your comment. This has been highlighted under data item and extraction/line 1.
Reviewer’s comment: The terms mild, moderate and severe anaemia are not defined at all.
Authors’ response: Thank you for your comment. The cut-offs to define mild, moderate and severe anaemia have been defined in the methods. Please, see Data items and extraction/last sentence.

Data synthesis
Reviewer’s comment: The Cohen’s should not only be used to assess agreement between authors for study inclusion, but also for data abstraction and risk of bias assessment.
Authors’ response: Thank you. Interrater agreement between authors will be assessed for study inclusion, data abstraction and assessment of study quality. Please, see Data synthesis and analysis/Lines 3 and 4.

Reviewer’s comment: A sensitivity analysis could be conducted only for studies with low risk of bias, to see if the estimates differ from the overall estimate driven from all studies included in the meta-analysis.

Authors' response: Thank you. A sensitivity analysis will be performed to estimate the prevalence of anaemia using only studies with low risk of bias.

Reviewer's comment: What difference the authors do between school-based and community-based studies?
Authors' response: Thank you. We anticipate that there is a socioeconomic difference in children recruited from school and the community which might influence the prevalence of anaemia. We understand that most of the children will not attending any formal school program. If the data permits, we will analyse pre-schoolers recruited from the community from those recruited from schools to perform the subgroup analysis. Else, this aspect of the subgroup analysis will be dropped in the final review.
Reviewer's comment: In line with a previous suggestion, you could add definition of anaemia as a criteria for subgroup analysis. Why consider only p less than 0.1 for multiple meta-regression? Why not p less than 0.25?
Authors' response: Thank you for your comment. We will increase the cut-off to p value less than 0.25. This has been upgraded in the manuscript.

RAKESH PS (Reviewer 2): Dear Authors, Nice protocol. But kindly consider the following:

Reviewer's comment: There might be country wide major surveys which included anaemia, which might not appear in electronic databases. Will that be included?
Authors' response: Thank you for your comment. We are going to search both readily available electronic databases and grey literature. For grey literature search, we will scrutinise the reference list of relevant published articles. We will also search conference proceedings and platforms like ResearchGate (please, see Search strategy/L6-10). We hope to capture these surveys which will be included in our review if they meet our inclusion criteria.

Reviewer's comment: Putting WHO criteria of 11mg/dl may exclude some major studies. If the study has enumerated the categories clearly, why should we exclude that?

Authors' response: Thank you for your comment. To reduce bias and increase transparency of our review, we will prefer to work with internationally recommended definition for anaemia. However, since we plan to estimate the prevalence of moderate and severe anaemia, we will take these cut-offs into consideration when assessing articles for inclusion. For example, if an article does not meet the WHO criteria to define anaemia (in general or mild anaemia) but meets the criteria for moderate and/or severe anaemia, it will be considered for inclusion. We have updated our inclusion criteria with respect to this comment. Please, see inclusion criteria/point 4.

Reviewer's comment: In Risk of bias table, total is adding to 9, while in scores 8-10 is mentioned as high bias.

Authors' response: Thank you. We missed the 10th item of the tool. The supplementary table has been updated.

Reviewer's comment: Which are the acceptable and validated tests you will consider. Please pre define it
Authors' response: Thank you for your comment. We will consider studies which measured haemoglobin concentration using a Complete Blood Count or Haemoglobinometer. Please, we have updated the inclusion criteria according to this comment. Please see, Inclusion criteria/point 2.
Reviewer's comment: Taking time since inception- there might be gross variations in anaemia prevalence. For prevalence recent studies might be more useful. Is there a plan to capture for various

time periods?
Authors' response: Thank you for calling our attention to this. We will perform a subgroup analysis to look at the prevalence of anaemia before and after 2009. Please, see Data synthesis and analysis/P2/L5-6.

Reviewer's comment: If a study is done among hospital attendees or among children with chronic diseases- will you include that? Think of excluding the same and include only community-based studies. Or at least plan for a sub group analysis

Authors' response: Thank you for your comment. This is already planned and mentioned in Data synthesis and analysis/P2/L3.

**VERSION 2 – REVIEW**

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| **REVIEWER** | Jobert Richie Nansseu<br>Department of Public Health<br>Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I, Yaoundé, Cameroon |
| **REVIEW RETURNED** | 18-Sep-2019 |

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| **GENERAL COMMENTS** | I thank the authors for submitting a revised copy of their paper, and appreciate the efforts made to address the reviewers' comments and suggestions.<br>However, I have some minor comments I wish the authors to look at.<br>1- The language still needs some little polishing to remove some few grammatical mistakes<br>2- In data extraction, you say you will extract the region of Africa where the study was conducted. I ask myself if you will extract or deduce, knowing in which country the study was conducted. I am not sure the information on region of Africa is always and extensively presented in publications.<br>3- Page 5, lines 36-57: this is a very long sentence. Perhaps could you rephrase and cut up into small comprehensive sentences.<br>4- You also mention to extract coefficient of correlation for studies looking at determinants of anaemia. I wonder how the coefficient of correlation helps in identifying a determinant/risk factor...I agree with OR, RR, HR, but ask myself how the coefficient of correlation would help...<br>5- I think it is not repetitive to clearly mention that the process of methodological quality assessment will also be conducted independently by the same authors extracting the data. One could think that only one review author will be in charge of assessing the methodological quality of included studies.<br>6- In subgroup analysis, the authors have not explained why they have chosen the year 2009 as cut-point for year of publication.<br>7- In addition, they have not precised what cut-offs will be used for age grouping and why.<br>8- It would also be relevant, in my viewpoint, to indicate why the determinants will be summarized in a narrative way rather than undertaking a meta-analysis too. They have explained it in their cover letter but not in the manuscript. Another anticipatory finding is that some studies may present OR while others HR, while others HR... |

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| | 9- It is not clear to me, the inclusion criteria for studies looking at determinants of anaemia. Are the authors trying to say that they will include studies which have undertaken not only bivariate analysis but multivariable analysis, or both? |

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| **REVIEWER** | RAKESH PS<br>Amrita Institute of Medical Sciences<br>India |
| **REVIEW RETURNED** | 27-Sep-2019 |

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| **GENERAL COMMENTS** | Authors have addressed all my comments satisfactorily. |

**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below

I thank the authors for submitting a revised copy of their paper, and appreciate the efforts made to address the reviewers' comments and suggestions.
However, I have some minor comments I wish the authors to look at.
Reviewer's comment 1- The language still needs some little polishing to remove some few grammatical mistakes

**Response:** Thank you we have read through in detail to correct grammatical errors.

Reviewer's comment 2- In data extraction, you say you will extract the region of Africa where the study was conducted. I ask myself if you will extract or deduce, knowing in which country the study was conducted. I am not sure the information on region of Africa is always and extensively presented in publications.

**Response:** Thank you. We did not specify. We are going to deduce from the country where the study was conducted.

Reviewer's comment 3- Page 5, lines 36-57: this is a very long sentence. Perhaps could you rephrase and cut up into small comprehensive sentences.
**Response:** Thank you. The sentence has been shortened.

Reviewer's comment 4- You also mention to extract coefficient of correlation for studies looking at determinants of anaemia. I wonder how the coefficient of correlation helps in identifying a

determinant/risk factor...I agree with OR, RR, HR, but ask myself how the coefficient of correlation would help...

**Response:** Thank you. We agree with the reviewers. We have modified this sentence accordingly. The last sentence of Methods/Data items and extractions now reads, "*Finally, data on the measure of association (adjusted odds ratio, beta coefficient, and relative risk) of the determinants of anaemia will be extracted*".

Reviewer's comment 5- I think it is not repetitive to clearly mention that the process of methodological quality assessment will also be conducted independently by the same authors extracting the data. One could think that only one review author will be in charge of assessing the methodological quality of included studies.

**Response:** Thank you. We have modified accordingly.

Reviewer's comment 6- In subgroup analysis, the authors have not explained why they have chosen the year 2009 as cut-point for year of publication.
**Response:** Thank you. This cut-off was arbitrarily assigned. Since we have not justification for this cut-off, we have decided to remove it from the subgroup analysis.

Reviewer's comment 7- In addition, they have not precised what cut-offs will be used for age grouping and why.
**Response:** Thank you. We have excluded age from the subgroup analysis because we could not find any clinically relevant cut-off to use.

Reviewer's comment 8- It would also be relevant, in my viewpoint, to indicate why the determinants will be summarized in a narrative way rather than undertaking a meta-analysis too. They have explained it in their cover letter but not in the manuscript. Another anticipatory finding is that some studies may present OR while others HR, while others HR...
**Response:** Thank you. We have explained this in the text. Please, see last sentence under the section "Presentation and reporting of results".

Reviewer's comment 9- It is not clear to me, the inclusion criteria for studies looking at determinants of anaemia. Are the authors trying to say that they will include studies which have undertaken not only bivariate analysis but multivariable analysis, or both?
**Response:** Thank you. We will consider only studies that report adjusted measures of association. This implies that only studies that performed a multivariable analysis will be included. Studies that performed only univariable analysis with no adjustments for confounders will be excluded from the final analysis.

Reviewer: 2

Please state any competing interests or state ‘None declared’:

None Declared

Please leave your comments for the authors below

Authors have addressed all my comments satisfactorily.

**Response:** Thank you.

**VERSION 3 – REVIEW**

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| **REVIEWER** | Jobert Richie Nansseu<br>Department for the Control of Disease, Epidemics and Pandemics, Ministry of Public Health, Yaoundé, Cameroon |
| **REVIEW RETURNED** | 15-Dec-2019 |

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| **GENERAL COMMENTS** | Thank you to the authors for having sent a revised version of the manuscript, and satisfactorily addressed the large majority of our concerns.<br>The manuscript is to be accepted, though I have 2 few comments to raise<br>- Page 5, lines 53-54: When describing measures of association, the authors cite the beta coefficient, which I don't agree with, in this particular context. Indeed, I wonder how a study would use a linear regression to seek determinants for anemia which I believe is a categorical variable (yes/no, or in class hb normal/mild, moderate or severe anemia). I suggest simply canceling the brackets including the text inside, or citing the OR, RR or HR as potential measures in this context.<br>- Page 6, line 3: I think there is a mistake: it should read "separately reported"; line 18: there is a coma missing "will represent low, moderate and high". |

**VERSION 3 – AUTHOR RESPONSE**

Reviewer: 1

Please leave your comments for the authors below
Comment: Thank you to the authors for having sent a revised version of the manuscript, and satisfactorily addressed the large majority of our concerns.

Response: The authors thank the reviewer for his time, and in performing a critical review.

The manuscript is to be accepted, though I have 2 few comments to raise

Comment: Page 5, lines 53-54: When describing measures of association, the authors cite the beta coefficient, which I don't agree with, in this particular context. Indeed, I wonder how a study would use a linear regression to seek determinants for anemia which I believe is a categorical variable (yes/no, or in class hb normal/mild, moderate or severe anemia). I suggest simply canceling the brackets including the text inside, or citing the OR, RR or HR as potential measures in this context.

Response: Thank you. Totally agree with the reviewer. This section now reads “Finally, data on potential measures of association (adjusted odds ratio and relative risk) of the determinants of anaemia will be extracted”

Comment: Page 6, line 3: I think there is a mistake: it should read "separately reported"; line 18: there is a coma missing "will represent low, moderate and high".
Response: Thank you. We have corrected.