PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Estimating the relative contribution of parasitic infections and nutrition for anaemia among school-aged children in Kenya: a subnational geostatistical analysis
AUTHORS	Pullan, Rachel; Gitonga, Carol; Mwandawiro, Charles; Snow, Robert; Brooker, Simon

VERSION 1 - REVIEW

REVIEWER	Dr Peter Gething Research Fellow Department of Zoology University of Oxford, UK I declare I have no competing interests
REVIEW RETURNED	14-Sep-2012

GENERAL COMMENTS	The authors present an analysis of spatial variation in the prevalence of anaemia in Kenya, and in the contribution of malaria and hermit infections to these rates whilst adjusting for a range of socioeconomic and nutritional co-factors. Data from extensive school surveys are used and analysis is via a spatially explicit Bayesian hierarchical model. The study is well designed, appropriately powered, and meticulously written and presented. The findings are of biological (the multiplicative impact of the different parasite species) and operational (the implications of heterogeneity in PAF for school-based intervention packages) interest. I have no major criticisms of the work and believe it represents a useful contribution to knowledge around this key cause of childhood morbidity that is likely to be of interest across a broad swathe of practitioners. Some more minor comments and/or edits: P4: 56: “innovate” should be “innovative” P5:21: “schoolstool” should be “schools, stool..” P5:25. Maybe explain explicitly what classes 2-5 represent in terms of age ranges? P5:31: Maybe specify that microscopy corrected means all RDT positives had subsequent slide readings. P7: 26: Is there a reference for a “clustered sandwich estimator”. P7:57: ‘PAF’ is used here without being defined previously in the text (although it is in the abstract) P9: first para: I would have liked to see more credible intervals presented in parentheses to accompany the various predicted values discussed. P11:17: Missing *of* ..? P11: first Para: “Results provide a vital decision-making tool for cost-

	effective targeting the delivery of integrated, packages of interventions tailored to each province, with the aim of reducing anaemia in schoolchildren." Can the uathors elaborate a little here: how, more specifically, might the results translate into a specific targeting tool? P12:24: "Our results also provide some indication that whilst existing school-feeding programmes in Kenya do appear to be targeted to those at most need, they are currently ineffective at tackling anaemia in this population." Can you support this observation? Surely this would require longitudinal rather than cross-sectional data – it could be that anaemia was much worse prior to the programme? P12:37: delete 'does'. Figure 3: I could not see this referenced in the text? I'm not sure how much this graphic adds to the results and would consider omitting or moving to the annex.

REVIEWER	Harold Alderman Senior Research Fellow International Food Policy Research Institute USA no conflict of interest
REVIEW RETURNED	01-Dec-2012

THE STUDY	There is a web appendix that lays out the details of Baysian kriging for anyone who desires more information (and can follow the details). But it would not be a bad idea to proide a few lines on the intuition behind the approach given the novelty. [That novelity is indicated as one of the primary innovations of the paper]
GENERAL COMMENTS	The authors indicate that they do not have data on menarche which would be necessary to addess the increasing risk of anemia for adolescent girls. But they have included a separate analysis of girls aged 14 with relatively little disucssion of whether the risk factors differ. They have also indicated that i) on average boys have lower Hb compared to girls and ii) Hb increases with age (page 9). But they may be able to include an interaction to measure if it increase as fast with age for girls as boys. Otherwise, the discussion of table 3 might mention that the study does not have the power to address this question (that is, mention the issue of adolescents in this section as well as the discussion). Is there any data on school enrollment? Again, the discussion highlights a potential bias given a plausible correlation of anemia and attendance. Actually the correlation of anemia and enrollment might be as large or larger. In any case, some information on enrollment [and its association with food security?] might allow the reader to infer whether this bias is likely minor or not. That is, does the school based sample fairly represent the community as a whole? I think the direction of any bias is not in dispute. I suspect there is data on enrolment that overlaps the geographic distribution of the sample. I am less optimistic that there is age specific enrollment that disaggregated. but even in the absence of such disaggregated data, it is plausbile that the sample of 14 year

	old girls is more susceptible to selection bias due to school drop out than the sample of 7 year old boys. The discussion might reflect on this. Finally, the citation of reference 41 is missing the journal name.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Some more minor comments and/or edits:

P4: 56: “innovate” should be “innovative”
P5:21: “schoolstool” should be “schools, stool..”
-- Changes made.

P5:25. Maybe explain explicitly what classes 2-5 represent in terms of age ranges?
-- We have added an additional sentence to describe the captured age range:
“This captures children aged 4 to 16, although 80% of included children were aged between 8 and 13.”

P5:31: Maybe specify that microscopy corrected means all RDT positives had subsequent slide readings.
-- We have added a clarification: “Plasmodium infection in the peripheral blood based on microscopy-corrected malaria rapid diagnostic test (RDT) results, whereby slides were subsequently read for all RDT positives”

P7: 26: Is there a reference for a “clustered sandwich estimator”.
-- A reference has been added.

P7:57: ‘PAF’ is used here without being defined previously in the text (although it is in the abstract)
-- This has been corrected.

P9: first para: I would have liked to see more credible intervals presented in parentheses to accompany the various predicted values discussed.
-- BCIs have now been added where appropriate throughout the results section.

P11:17: Missing *of* ..?
-- This has been corrected.

P11: first Para: “Results provide a vital decision-making tool for cost-effective targeting the delivery of integrated, packages of interventions tailored to each province, with the aim of reducing anaemia in schoolchildren.” Can the authors elaborate a little here: how, more specifically, might the results translate into a specific targeting tool?
-- We didn’t elaborate on this in great detail to remain within word limits, and because we felt it was relatively self explanatory. However, we have elaborated and added a brief example:
“For example, school-feeding programmes in Coast, Eastern and Rift Valley Provinces may want to consider including iron-rich food stuffs, whilst programmes in Nyana and Western Provinces omitting malaria control initiatives may not see desired improvements in childhood anaemia.”

P12:24: “Our results also provide some indication that whilst existing school-feeding programmes in Kenya do appear to be targeted to those at most need, they are currently ineffective at tackling anaemia in this population.” Can you support this observation? Surely this would require longitudinal

rather than cross-sectional data – it could be that anaemia was much worse prior to the programme?
-- The thinking behind this supposition is that levels of anaemia were unlikely to vary systematically between included and non-included schools in districts with school feeding prior to the intervention, based on the observed spatial heterogeneity. However, we do acknowledge that the evidence provided here is not sufficiently strong to support this statement, and so it has been removed.

Figure 3: I could not see this referenced in the text? I'm not sure how much this graphic adds to the results and would consider omitting or moving to the annex.
-- Figure 3 was mistakenly referred to as figure 2 in the text, this has now been corrected. We believe that presentation of outlier schools does help to clarify the multilevel methods used, and so have chosen to retain the figure.

Reviewer 2

There is a web appendix that lays out the details of Baysian kriging for anyone who desires more information (and can follow the details). But it would not be a bad idea to proide a few lines on the intuition behind the approach given the novelty. [That novelity is indicated as one of the primary innovations of the paper]
-- We agree, and have included a brief definition of Bayesian kriging, as follows:
Bayesian kriging (25) , a geostatistical interpolation method that accounts for the error introduced by estimating the semivariogram model (a function of the variability in outcome against the distance separating observation points), was used to interpolate a distribution of possible values for each indicator to survey school locations. This was done by incorporating the full posterior distribution of the Bayesian semivariogram model, estimated using the Bayesian statistical software WinBUGS version 14.1 (Medical Research Council Biostatistics Unit and Imperial College London).

The authors indicate that they do not have data on menarche which would be necessary to addess the increasing risk of anemia for adolescent girls. But they have included a separate analysis of girls aged 14 with relatively little disucssion of whether the risk factors differ.
It should be pointed out that this was not a separate analysis, but instead that separate predictions were made – based on the same predictive model – for two age groups. Differences between the two age groups are thus attributable to i. baseline hb levels, and ii. differing distribution of risk factors in the two sub-populations. We believe that this is made clear in the manuscript:

"Given the large observed differences in mean Hb and prevalence of predictors by region and demographic group, adjusted Population Attributable Fractions (PAFs) for anaemia were estimated for two indicator demographic groups (boys aged 7 years, and girls aged 14 years) for each province in Kenya. In brief, at each model realisation we estimated the prevalence of anaemia in each of the risk groups based upon the posterior mean and standard deviation of the Hb distribution within each school. These were used to estimate (i) the relative risk of anaemia for each risk group compared with baseline risk, and (ii) the associated adjusted PAF, as described by Rockhill et al (1998). (31)"

They have also indicated that i) on average boys have lower Hb compared to girls and ii) Hb increases with age (page 9). But they may be able to include an interaction to measure if it increase as fast with age for girls as boys. Otherwise, the discussion of table 3 might mention that the study does not have the power to address this question (that is, mention the issue of adolescents in this section as well as the discussion).
-- We agree with the reviewer that adolescence and menarche perhaps wasn't investigated sufficiently; however, basic age sex interaction terms did not improve the fit of the model. This is likely due to large between-individual variation in the timing, and impact, of menarche (which was not

questioned directly). We have now noted that this interaction was investigated, but did not improve model fit, and have added a sentence to the discussion discussing the impact of adolescence:
“Basic age-sex interaction terms were also investigated, but there was insufficient evidence that these improved the overall fit of the model” [methods/analysis – second paragraph]
“An additional factor that would influence individual-level variation is the onset of menarche in girls: no specific data were collected to record this, and inclusion of a basic age-sex interaction term did not improve model fit suggesting that more detailed information is required.” [discussion – last paragraph]

Is there any data on school enrollment? Again, the discussion highlights a potential bias given a plausible correlation of anemia and attendance. Actually the correlation of anemia and enrollment might be as large or larger. In any case, some information on enrollment [and its association with food security?] might allow the reader to infer whether this bias is likely minor or not. That is, does the school based sample fairly represent the community as a whole? I think the direction of any bias is not in dispute. I suspect there is data on enrolment that overlaps the geographic distribution of the sample. I am less optimistic that there is age specific enrollment that disaggregated. but even in the absence of such disaggregated data, it is plausbile that the sample of 14 year old girls is more susceptible to selection bias due to school drop out than the sample of 7 year old boys. The discussion might reflect on this.
-- Data on enrolment at survey schools was unavailable and is, unfortunately, notoriously difficult to record accurately using such surveys. We do include discussion of this limitation, but upon the reviewer’s suggestion, have now elaborated to include discussion of the implications of regional differences. Regional data is available from the Education and Policy Data Centre (http://www.epdc.org/country/kenya). At least in 2005 (the most recent data available), reported net attendance did not differ dramatically between boys and girls over-all, although as the reviewer suggests, age-stratified data are not available.

“Although contemporary regional or school-level attendance data is not available, overall school attendance rates are known to vary geographically across Kenya. For example, in 2005 (the most recent year for which sub-national net primary school attendance figures are available) reported net attendance in Nyando District (Nyanza Province) was greater than 90% for both males and females, whilst in Turkana District (Rift Valley Province) levels were between 30-40%. If Hb levels differ systematically between non-attending and attending school-aged children, this may act to either dilute or exaggerate geographical variation in Hb levels.”
-- We have chosen not to go into further detail investigating associations between enrolment and Hb levels (or food security), firstly because the available data are ecological and we would expect to see large within-district variations in school attendance rates, and secondly because school attendance data is not sufficiently recent. School enrolment rates are known to have increased substantially between 2005 and 2009.
Finally, the citation of reference 41 is missing the journal name.
This has been corrected.