PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Weekly miscarriage rates in a community-based prospective cohort study in rural western Kenya
AUTHORS	Dellicour, stephanie; Aol, George; Ouma, Peter; Yan, Nicole; Bigogo, Godfrey; Hamel, Mary; Burton, Deron; Oneko, Martina; Breiman, Robert; Slutsker, Laurence; Feikin, Daniel; Kariuki, Simon; Odhiambo, Frank; Calip, Gregory; Stergachis, Andreas; Laserson, Kayla; ter Kuile, Feiko; Desai, Meghna

VERSION 1 - REVIEW

REVIEWER	Arri Coomarasamy and Helen Williams Arri Coomarasamy Professor of Gynaecology, University of Birmingham, United Kingdom Helen Williams Research Associate, University of Birmingham, United Kingdom
REVIEW RETURNED	15-Jan-2016

GENERAL COMMENTS	Thank you for this interesting paper! You may like to consider our comments below: Page 5 lines 5-6: More importantly than for academic interest, the physiological and psychological effects upon patients and their families are potentially life-changing. Page 5: It may be relevant to note that there are significant challenges to the estimation of miscarriage rates in more developed settings too. Page 5: There is potential for improvement to the order of paragraphs and sentences in the "background", to provide greater clarity about (a) measurement challenges inherent to the nature of the outcome and (b) particular measurement challenges in less developed settings. Page 5 line 18: It would be helpful to clarify your definition of "clinical pregnancy" within the context of this study, since non-specialist understandings vary. Page 6 lines 14-19: How is the local rate of parasitaemia in children under five - or even HIV prevalence - particularly relevant to this study? Perhaps you could explain the link or remove. Page 6 line 50: Please clarify how pregnancy was confirmed. Pages 6-7 ("gestational age assessment"): This paragraph could be

	reported much more concisely and with less repetition. Pages 6-7: We wonder if a diagram of the patient recruitment and follow up pathway could be useful: the different routes to recruitment and the number and timings of data collection points are rather hazy. Page 7 lines 46-48: More explanation of left truncation could be helpful. Page 8: The rate of LTFU/exclusion is high, not least because this paper selectively reports miscarriage only although other outcomes were collected from the total cohort. Please see our general comment below. Page 8 line 33: So 80% of miscarriage outcomes were captured more than a week after the end of pregnancy, with median timing 24 days (and up to more than 19 months) afterwards? How did you ensure accurate records of the timings of pregnancy end? Please could you explain and justify? Page 8 line 40, and page 9: The mean gestational age at time of pregnancy detection was 13.3 weeks (median 12.1 weeks). Yet we know that more than 80% of miscarriages occur before 12 weeks. This raises the question of whether or not the data you collected is really fit for purpose to estimate the rate of miscarriage. Your total miscarriage rate of less than 8% is indeed much lower than the rates of miscarriage observed in study after study where the setting is better suited to surveillance (typically 1 in 4 or at least 1 in 5). Page 8: We understand there were 89 (7.9%) miscarriages among the 1,134 pregnancies included in the analysis. Please could you clarify how the cumulative probability of miscarriage is calculated as 18.9%? Page 9 line 41: Why do you consider it surprising that pregnancy testing was acceptable to the population? Page 9 line 49: How does this particular study show that particular attention should be given to adolescent girls? Perhaps you could explain the link or remove. Page 10 line 22: How are HIV and malaria particularly relevant to miscarriage? Perhaps you could explain the link or remove. Page 16: Your Table 2 is slightly confusing: what is the message? It is an unnecessarily large and complex table to merely demonstrate that weekly miscarriage rates decline steadily with increasing gestation (which is well known already). Page 18: Your CONSORT diagram suggests that participants who were lost to follow up nevertheless also contributed to outcomes. How so? Generally: The manuscript could be considerably more succinct. Generally: You followed pregnancy outcomes but with a focus on miscarriage only (in this manuscript). Your word count could be better used and the general medical interest of the study could be improved by reporting and discussing other outcomes such as live

	births, stillbirths and congenital malformations too. It is questionable whether the results discussed here are sufficiently substantive to warrant a manuscript dedicated solely to them. We hope you consider these comments to be useful.

REVIEWER	Sohinee Bhattacharya University of Aberdeen, Scotland, United Kingdom
REVIEW RETURNED	10-Feb-2016

GENERAL COMMENTS	This interesting article describes the cumulative incidence of miscarriage in a rural Kenyan population with high background prevalence of malaria and HIV. Miscarriage rates are notoriously difficult to estimate even more so in LMIC where early detection and reporting of pregnancy is extremely rare. This well written report is a welcome addition to the sparse literature on the topic. The study utilises women recruited for a pharmacovigilance project. There are a few minor concerns, which if addressed should make the article imminently publishable: 1. As the study population was drawn from a separate pharmacovigilance project and from a wider disease surveillance area, the authors need to discuss how representative the study population was to the rest of Kenya and other African populations. 2. Is there any information on contraceptive use in the population at the time of recruitment? 3. Gestational age measurement: How was disagreement between LMP and USG dates handled? I am not clear as to who had the pregnancy tests done - was it only those who had reported a missed period? If not, and all recruited women had pregnancy tests done every 3 months which is what lines 46 - 49 (page 5) suggests, it is surprising that the mean gestational age at detection of pregnancy was ~13 weeks. 4. Table 1 : mean gestational age at detection? of what? pregnancy? miscarriage? The authors may like to consider disaggregating "other pregnancy outcomes" into live birth, stillbirth etc. or removing that column as it is not the comparison group. 5. I am a little confused as to why Cox proportional hazards model was used for continuous variables? what was the reference category? The p-values in a number of variables are placed against the missing value rows - this causes confusion as readers are apt to think that this is the reference category. 6. As above, the authors may want to consider using a multivariable model to calculated adjusted hazard ratios for miscarriage including the factors identified as significant on univariate analysis.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Arri Coomarasamy and Helen Williams
Institution and Country: Arri Coomarasamy - Professor of Gynaecology, University of Birmingham, United Kingdom; Helen Williams - Research Associate, University of Birmingham, United Kingdom.
Competing Interests: None declared
Please leave your comments for the authors below
Thank you for this interesting paper! You may like to consider our comments below:
1. Page 5 lines 5-6: More importantly than for academic interest, the physiological and psychological effects upon patients and their families are potentially life-changing.

Thank you for reminding us of this important point, the following sentence has been added to the introduction: “Miscarriage is the most common adverse pregnancy outcome with aggravating emotional consequences for affected individuals and families.”

2. Page 5: It may be relevant to note that there are significant challenges to the estimation of miscarriage rates in more developed settings too.

We agree, and in fact the challenges listed in the second paragraph of the introduction relates to all settings (developed and developing countries). In response to the next comment, this is now clarified.

3. Page 5: There is potential for improvement to the order of paragraphs and sentences in the "background", to provide greater clarity about (a) measurement challenges inherent to the nature of the outcome and (b) particular measurement challenges in less developed settings.

The second paragraph of the introduction has been rearticulated as follows:

“Miscarriage is a challenging endpoint to ascertain and accurate rates of miscarriage difficult to estimate. There are methodological complexities of conducting studies to assess miscarriage rate [10] which relate to the difficulties in identifying a representative sample of pregnancies at time of conception; the confirmation of suspected pregnancy and the determination of the exact timing of pregnancy loss. To accurately capture all pregnancy losses in a population, a study needs to be able to identify pregnancies from the time of conception and follow them prospectively. Early pregnancy losses, which occur before a pregnancy is usually recognised (i.e. <5-6 weeks gestation), can only be detected by frequently repeated highly sensitive pregnancy tests.

Few studies have been designed to detect such early pregnancy loss and ascertained pregnancies close to the time of conception by enrolling participants that are planning to conceive and consent to regular pregnancy tests [7-9, 16-18]. Since a significant proportion of pregnancies are unplanned[19], data from these studies may have limited generalizability. Other studies recruiting women from antenatal clinics miss pregnancy loss occurring before initiation of antenatal care (ANC) and may also be prone to selection bias as women presenting early for antenatal care may represent higher risk pregnancies than women presenting later[13]. The assigned timing of miscarriage is usually based on the time of clinical recognition of pregnancy loss however fetal death may have occurred weeks before [11].

Studies of miscarriage in low and middle income countries face additional challenges as most miscarriages occur without any contact with the formal healthcare system and are not registered. As pregnant women usually present for antenatal care late in pregnancy (with an estimated 11%-54% of women initiating ANC in the first trimester [20-22] and most presenting late in the 2nd trimester), health facility based recruitment and data collection strategies are inappropriate. In such settings the study of miscarriage requires a community based approach taking into account the different cultural and superstitious beliefs that may affect pregnancy disclosure and detection [22-24]. Furthermore reliable data on gestational age is difficult to obtain as ultrasound scans are rarely available and date of last menstrual period may not be reliable in settings with limited literacy [25, 26]. There is also a higher risk of misclassification of induced abortions as spontaneous abortions as the former are illegal in most of these settings.”

4. Page 5 line 18: It would be helpful to clarify your definition of "clinical pregnancy" within the context of this study, since non-specialist understandings vary.

As per the definition used by Wang et al 2003, clinical pregnancy refers to a pregnancy that lasts over 5 weeks since LMP (i.e. suspected on the basis of amenorrhea) which is usually when a pregnancy is clinically recognised. This has been clarified as follows: “Studies from industrialised countries report rates of miscarriage in clinically recognised pregnancies (i.e. from five-six gestational weeks following the last menstrual period (LMP), the common gestational age for pregnancy recognition) that vary between 11% and 22%”

5. Page 6 lines 14-19: How is the local rate of parasitaemia in children under five - or even HIV prevalence - particularly relevant to this study? Perhaps you could explain the link or remove.

These are important background information to put findings into context. The study area is within one

of the poorest regions of Kenya and has one of the highest HIV prevalence and malaria incidence nationally. HIV and malaria are known risk factors for miscarriage and therefore important to interpret representativeness of the study findings. We have removed the information on parasitaemia in children but retained this information for adults. The following sentence has been added under limitations page 10: “Lastly, as HIV and malaria are known risk factors for miscarriage [39, 43, 44, 48] and were highly prevalent in this area, this may influence generalisability of study findings to areas with differing disease burden.”

6. Page 6 line 50: Please clarify how pregnancy was confirmed.

This is now clarified on page 6 as follows: “Any participant with a detected pregnancy was referred to the antenatal clinic at the referral health facility, Lwak Hospital, where trained study nurses confirmed the pregnancy through ultrasound or examination and auscultation for gestations >24 weeks and offered free ANC.”

7. Pages 6-7 ("gestational age assessment"): This paragraph could be reported much more concisely and with less repetition.

Gestational age assessment is very important for the study of miscarriage as it affects the estimated time under observation as well as the accuracy of time of pregnancy loss. We feel this deserves explanation given the different methods used in this study.

8. Pages 6-7: We wonder if a diagram of the patient recruitment and follow up pathway could be useful: the different routes to recruitment and the number and timings of data collection points are rather hazy.

The timing of data collection on risk factors has been clarified as follows in the methods page 6: “Demographic characteristics was collected through interviews at ANC or at the time of pregnancy outcome follow up if the participant was not seen at ANC.”

We have also added a new figure (now fig 2) showing the number of pregnancies detected by the different strategies and the mean gestational age at the time of detection over the recruitment period of the study.

9. Page 7 lines 46-48: More explanation of left truncation could be helpful.

The explanation of left truncation has been moved from the background to the methods section page 7: “Crude rate estimates (i.e. dividing the number of miscarriages by the total number of pregnancies under study) are appropriate when it is possible to detect and enroll pregnancies from the time of conception. Most miscarriages occur early in pregnancy prior to clinical detection of pregnancy [10]; the rapidly decreasing risk of miscarriage across the first trimester of pregnancy highlights the influence of gestational weeks at time of pregnancy detection in study or program settings on the estimated miscarriage rates. Therefore rate estimates should account for left (early pregnancy) truncation and , as far as it is possible, for the actual number of pregnancies under observation at each specific gestational week [11-13].”

10. Page 8: The rate of LTFU/exclusion is high, not least because this paper selectively reports miscarriage only although other outcomes were collected from the total cohort. Please see our general comment below.

The rate of loss to follow up was 6% (85/1453 shown in Figure 1), this is not considered high for prospective cohort studies. As we used the lifetable method to determine the rate of miscarriage which takes into account all pregnancies under observation with the use of right-censoring at the time of either the end of the “at-risk period” for miscarriage (defined as <28weeks) or loss to follow up or induced abortion. 319 pregnancies were not included with the majority (n=219) because they were no longer at risk of miscarriage as they were recruited after 28 weeks of gestation.

11. Page 8 line 33: So 80% of miscarriage outcomes were captured more than a week after the end of pregnancy, with median timing 24 days (and up to more than 19 months) afterwards? How did you ensure accurate records of the timings of pregnancy end? Please could you explain and justify?

This is indeed a limitation and may have introduced error in gestational age at the time of pregnancy loss which was reported by the participants. Very few women sought care at a health facility following miscarriage and in most instances study staff were only made aware of the pregnancy loss either at one of the 3 monthly home visits or when scheduled to follow up at the estimated time of delivery. Follow ups had to be arranged at the participant's home at their convenience and this sometimes required several attempts. The trained study staff enquired about dates of events (rather than gestational weeks or months) and used calendars with locally relevant events (school holidays, rainy season, planting/harvest season etc) to enhance recall. We have added the following sentence under limitations: "There could have been error in the estimation of gestation at the time of miscarriage since this was largely self-reported sometimes months after the event."

12. Page 8 line 40, and page 9: The mean gestational age at time of pregnancy detection was 13.3 weeks (median 12.1 weeks). Yet we know that more than 80% of miscarriages occur before 12 weeks. This raises the question of whether or not the data you collected is really fit for purpose to estimate the rate of miscarriage. Your total miscarriage rate of less than 8% is indeed much lower than the rates of miscarriage observed in study after study where the setting is better suited to surveillance (typically 1 in 4 or at least 1 in 5).
We acknowledge that our estimates for the week specific rates of miscarriage in early gestation lacks precision as reflected by the wide confidence interval (discussion 3rd paragraph page 9). Please note that the overall risk of miscarriage was 18.9% as estimated by the life table approach (described in methods page 7). The crude proportion, in this study the 7.9% as reported above, could only be considered as the miscarriage rate in studies that recruit women from the day of conception (see explanation on left truncation in the methods page 7). As this is not the case in this study it is not a true representation of miscarriage rate. Our findings are similar to a prospective study in China where 25% of pregnancies ended in early pregnancy loss (before 6 weeks of gestation) and the proportion of clinically recognised pregnancies (>=6 weeks since LMP) ending in miscarriage was 8% (Wang et al 2003 "Of 618 total conceptions, 373 (60.4%) ended as live births, 49 (7.9%) as spontaneous abortions, 152 (24.6%) as EPL"). Previous studies using the life-table methods have reported risk of miscarriage between 13 and 20% which is in line with what we found here.

13. Page 8: We understand there were 89 (7.9%) miscarriages among the 1,134 pregnancies included in the analysis. Please could you clarify how the cumulative probability of miscarriage is calculated as 18.9%?
The life table methods enable more accurate calculations of the risk of miscarriage due to the issue of left truncation. In life tables, risk estimates are calculated for each gestation weeks and then aggregated to determine the risk estimate for the entire pregnancy. This method accounts for variations in the gestational ages when the women were first recruited in the study and variations in the time when women exit the cohort due to loss to follow up or induced abortions. This is important as women remaining pregnant will eventually be recruited into the study, those who miscarried before enrolment are missed which leads to under-ascertainment of the true miscarriage rate. Reporting the number of pregnancies entering each gestational week and the corresponding estimated risk, as provided in table 2, helps readers understand how the cumulative risk is derived. Therefore risk derived using the life table method, as opposed to simple proportions, provide better estimates in situations where the pregnancies are not uniformly observed from the time of conception. This has been described in detail before (Modvig et al, Avalos et al). We added the following sentence to the discussion page 9: "However, this represents a more accurate estimate of the risk of miscarriage than the crude prevalence of 7.9% as pregnancies were not observed from the time of conception and entered the study at different gestational age."

14. Page 9 line 41: Why do you consider it surprising that pregnancy testing was acceptable to the population?
The following text was added to the discussion page 9 for clarification: "Women in this setting are

usually reluctant to disclose their pregnancy status due to cultural and superstitious beliefs about pregnancy disclosure. This has been recognised as one of the reasons for delay in seeking antenatal care[22, 24]. Women are worried about gossip, witchcraft particularly in the early stage of pregnancy, being accused of boastfulness and embarrassment in case of later pregnancy loss. For unmarried and/or young girls, pregnancy is not disclosed due to fear of social repercussions. Before initiation of the study, no information was available on the acceptability of pregnancy tests in a similar rural community; our formative research indicated very few women were even aware such tests existed."

15. Page 9 line 49: How does this particular study show that particular attention should be given to adolescent girls? Perhaps you could explain the link or remove.
The sentence has been removed.
16. Page 10 line 22: How are HIV and malaria particularly relevant to miscarriage? Perhaps you could explain the link or remove.
Both HIV and malaria are known risk factors for miscarriage (Brocklehurst P et al 1998, Temmerman et al 1992 and McGready et al 2012 LID). The study area has one of the highest HIV prevalence and malaria incidence in Kenya, making this highly relevant for interpreting the findings. As addressed in comment 5 above, the following sentence has been added in the discussion: "Lastly, as HIV and malaria are known risk factors for miscarriage [39, 43, 44, 48] and were highly prevalent in this area, this may influence generalisability of study findings to areas with differing disease burden."

17. Page 16: Your Table 2 is slightly confusing: what is the message? It is an unnecessarily large and complex table to merely demonstrate that weekly miscarriage rates decline steadily with increasing gestation (which is well known already).
Table 2 shows the detail of week specific events enabling the calculation of miscarriage risk in different gestational age periods for a rural African setting, which is one of the main objectives of this paper. This is relevant to compare with estimates reported in studies carried out in different regions and for other researchers in the field as described by Modvig et al. Table 2 also enables the reader to understand the difference between the crude estimate of 7.9% miscarriage versus the more accurate risk estimate of 18.9% derived using the life-table method. It also illustrates the lower numbers recruited early in gestation and the less reliable estimates derived for these early weeks.
18. Page 18: Your CONSORT diagram suggests that participants who were lost to follow up nevertheless also contributed to outcomes. How so?
That is correct; all observed pregnancy-weeks prior to the cut off of 28 weeks contributed to the analysis and were censored according the time of exit which was either gestational age at last study visit for cases loss to follow up, gestational age at induced abortion or 28 weeks which ever came first. Please see explanation to comment 9.

19. Generally: The manuscript could be considerably more succinct.
The manuscript is ~ 3600 words and according to many of the comments, some additional explanation is required for clarity. It is not clear whether this comment refers to a specific section of the manuscript which should be removed.
20. Generally: You followed pregnancy outcomes but with a focus on miscarriage only (in this manuscript). Your word count could be better used and the general medical interest of the study could be improved by reporting and discussing other outcomes such as live births, stillbirths and congenital malformations too. It is questionable whether the results discussed here are sufficiently substantive to warrant a manuscript dedicated solely to them.
To our knowledge no study so far has been able to characterise the risk of miscarriage in Kenya, or even in sub Saharan-Africa. Although this study has limitations as described in the discussion, it provides the first estimates for miscarriage and weekly rates for such settings which in our opinion is highly valuable information for researchers and program managers. Data for other pregnancy outcomes are being reported elsewhere and are beyond the scope of this specific paper on miscarriage.

We hope you consider these comments to be useful.

Reviewer: 2
Reviewer Name: Sohinee Bhattacharya
Institution and Country: University of Aberdeen, Scotland, United Kingdom
Competing Interests: None declared
Please leave your comments for the authors below
This interesting article describes the cumulative incidence of miscarriage in a rural Kenyan population with high background prevalence of malaria and HIV. Miscarriage rates are notoriously difficult to estimate even more so in LMIC where early detection and reporting of pregnancy is extremely rare. This well written report is a welcome addition to the sparse literature on the topic. The study utilises women recruited for a pharmacovigilance project. There are a few minor concerns, which if addressed should make the article imminently publishable:

1. As the study population was drawn from a separate pharmacovigilance project and from a wider disease surveillance area, the authors need to discuss how representative the study population was to the rest of Kenya and other African populations.
We have no reason to believe that the study context, neither the Pharmacovigilance project nor the enhanced morbidity surveillance, could have influenced the rates of miscarriage described in this study. Neither studies included interventions or procedures that would affect the risk of miscarriage. Therefore we feel that the described rates are representative of the larger population in this area. It is however important to keep in mind the high disease burden in this region which limits the generalisability of the findings to Kenya as a whole or other regions of Africa with a different burden of disease. The following sentence has been added in the discussion: “Lastly, as HIV and malaria are known risk factors for miscarriage [39, 43, 44, 48] and were highly prevalent in this area, this may influence generalisability of study findings to areas with differing disease burden.”

2. Is there any information on contraceptive use in the population at the time of recruitment?
The DHS survey showed that 33% of currently married women age 15-49 used a modern contraceptive method in Nyanza province (study area) in 2008-9, and this rose to 54% by 2014.
At enrolment we asked participants if they used any contraceptive methods, this included all women 15-49 year of age consenting to be part of the study (i.e. not restricted to married women as per DHS statistics). We found that 21% reported using any contraceptive methods. Among users, injectables were the most widely used method (77%), followed by the pill (8%) tubal ligation (8%) and implants (3%) and all other methods were used by 2% or less.
The following sentence has been added under the study site description: “The total fertility rate was 5.4 and around a third of currently married women age 15-49 used a modern contraceptive method in in the area according to a health and demographic survey in 2008-9[29].”
3. Gestational age measurement: How was disagreement between LMP and USG dates handled? I am not clear as to who had the pregnancy tests done - was it only those who had reported a missed period? If not, and all recruited women had pregnancy tests done every 3 months which is what lines 46 - 49 (page 5) suggests, it is surprising that the mean gestational age at detection of pregnancy was ~13 weeks.
Gestational age assessment was based on the most accurate measurement/method available for each participant. The order of preference is (listed under methods page 6): ultrasound scan taken before 24 weeks gestation, Ballard estimates, LMP or reported gestation at time of pregnancy loss and lastly gestational age derived from fundal height assessment. For pregnancies with ultrasound data available, gestational age was based on those findings disregarding all other methods including LMP.

All consenting women that were not visibly pregnant were offered pregnancy tests disregarding the date of their last menstruation (now clarified in the text). This was done at the time of enrolment and then approximately every 3 months. The reason why the mean gestational age was 13 weeks is due to the fact that at enrolment some women were of late gestation and enrolment occurred throughout the study period (that is eligible women moving to the area or turning 15 were recruited over the 2 year enrolment period). Furthermore the 3 monthly home visits only started 9 months into the study after the initial enrolment phase once all 33 villages had been covered. This was clarified as follows page 6: “WOCBA who consented to participate were asked if they might be pregnant and offered a pregnancy test at the time of enrolment if they were not visibly pregnant and again approximately every three months from October 2011 by village-based community interviewers.” Please also see new figure 2 highlighting the methods for pregnancy detection used throughout the course of the study and their impact on gestational age at recruitment.

4. Table 1 : mean gestational age at detection? of what? pregnancy? miscarriage? The authors may like to consider disaggregating "other pregnancy outcomes" into live birth, stillbirth etc. or removing that column as it is not the comparison group.
Thank you for the comment, we now clarified that gestational age referred to time of detection. Information on other pregnancy outcomes are being reported elsewhere and we feel disaggregating the pregnancy outcome may distract from the focus on miscarriage for this manuscript. In the cox regression model the outcome is defined as dichotomous variable (i.e. miscarriage yes/no).

5. I am a little confused as to why Cox proportional hazards model was used for continuous variables? what was the reference category? The p-values in a number of variables are placed against the missing value rows - this causes confusion as readers are apt to think that this is the reference category.
Cox proportional hazard was used as it allows to account for left truncation. This is clarified in the methods “Cox proportional hazard regression models with left truncation were fitted to estimate the effect of risk factors on miscarriage.”
Table 1 has been revised to clarify the reference categories and the missing values have been moved to a separate row for clarity.

6. As above, the authors may want to consider using a multivariable model to calculated adjusted hazard ratios for miscarriage including the factors identified as significant on univariate analysis.
Due to the high number of missing values across important risk factors, the numbers of miscarriage remaining in an adjusted model including all significant risk factors (n=17) were too small to provide any conclusive information. The aim of table 1 is to describe the characteristics of participants and demonstrate that known risk factors for miscarriage could be identified in this study. We were not looking to build a prognostic or predictive model as there were too many missing values for many important risk factors.

VERSION 2 – REVIEW

REVIEWER	Sohinee Bhattacharya University of Aberdeen, United Kingdom
REVIEW RETURNED	14-Mar-2016

GENERAL COMMENTS	The authors have addressed all concerns of the reviewers and the paper is now acceptable.