Reviewer's report

Title: Medication exposure during pregnancy: a pilot pharmacovigilance system using health demographic surveillance platform

Version: 5  Date: 27 May 2014

Reviewer: Stephanie Dr Dellicour

Reviewer's report:

Pharmacovigilance in pregnancy is an important and neglected area, particularly in developing countries, which is needed to maximize therapeutic outcomes for the pregnant patient and her unborn baby. This is particularly important in the light of the undetermined safety profile of the artemisinin class of antimalarials in this vulnerable group. There is therefore an urgent need to set up sustainable pharmacovigilance systems to monitor the safety of antimalarials as well as other drugs used in the tropics. This paper could provide interesting information regarding methods for monitoring the safety of drugs in such settings. However more detail on the methodology as well as implementation challenges and successes is needed for this paper to be useful for future research.

- Major Compulsory Revisions

1. The authors need to clarify the aim of this paper- it is not clear whether the aim of this publication is to report on methodology and feasibility of using a DSS platform to do pharmacovigilance surveillance in pregnancy or to assess potential teratogenicity/safety issues of drugs used in the tropics by pregnant women. The authors report on page 7 of the discussion, that “A more detailed assessment of antimalarial exposure, taking into account the type and time of exposure during pregnancy will be reported elsewhere” and that this papers focuses more on the feasibility of the methodological approach. This is not clear throughout the paper (for example in the abstract it is noted: “e aim of the present study was to assess medication exposure during pregnancy, and its relation to pregnancy outcome using a Health Demographic Surveillance System (HDSS) platform “).

2. In light of the previous comment, the method section of this paper is very important and need to be fleshed out as not enough detail is provided on the methods and implementation issues. This seems to be the most important aspect of this paper for others to learn from this study. More specifically:

2.1. Under “Study site and HDSS platform”: please provide more information on the epidemiology of malaria, HIV and burden of other prevalent disease in the area to put potential medication use in context.

2.2. Under “Study design and population”:

2.2.1. Provide information on how pregnancy were detected as this is highly relevant- was self-reported or by use of a pregnancy test?
2.2.2. Please describe the follow up procedures- who did the follow ups (nurse/community interviewers)? Where did the visit take place? Were these visits part of the routine DSS visits or were these study specific visits?

2.2.3. Was there any incentives for the participants to go to the health facility during pregnancy and/or for delivery? How were pregnancy outcome detected, notified and followed up?

2.2.4. More information on the “medical record log” is needed-in terms of completeness /data quality control and assessed, compliance, issues in implementation (how did this work for illiterate participants? Any issues of keeping this log book and whether this was actually used every time the participants sought healthcare?)

2.2.5. How were congenital anomalies assessed? Who was doing the assessment and what training did they get? What happened to the cases with suspected anomalies- were they referred?

2.2.6. How was gestational age assessed?

2.2.7. Was there any quality control methods used for data collected on illnesses, medication, dates and pregnancy details?

2.3. Under “Primary endpoints”: Please provide definition of your primary endpoints miscarriage and stillbirth and what gestational age cut off you used for these endpoints.

2.4. Under “Statistical analysis”:

2.4.1. Provide information on how you chose the covariates for the adjusted models (i.e. which other covariates did you assess for potential confounding?)

2.4.2. Did you consider potential confounding by indication?

3. For analysis looking at pregnancy loss (miscarriage and stillbirth) the use of survival analysis accounting for the time of pregnancy detection through left truncation is more appropriate than logistic regression. See reference: P. Howards et al. Conditions for Bias from Differential Left Truncation Am J Epidemiol 2007;165:444–452.

4. In the result section (including the result section in the abstract): there is a need to be cautious with the interpretation of the analysis looking at antimalarial and antibiotic exposures in pregnancy. I would recommend stating the level of risk that this study was powered to exclude rather than stating that there was no significant association since the number of exposures (particularly in the 1st trimester which is of most concern) are small. Furthermore, it would be most informative to see the analysis stratified by exposures occurring in 1st trimester and 2nd/3rd trimester (as pooling the risk estimates could bias towards the null if there was indeed a embryo-toxic effect restricted to 1st trimester exposures).

5. Discussion please include a section on the limitations of the current study and consider the points below:

5.1. Information on drug exposure: mean gestational age at enrollment was 14
weeks and information on drug used prior to enrollment was self-reported by the participants. Please discuss potential limitation in the reliability of dates of exposure and completeness of this information. This has important implication as the most drug safety concerns for pregnant patients relate to exposure in the 1st trimester of pregnancy (during organogenesis as you describe in your introduction).

5.2. Congenital abnormalities: you noted the need to follow up infants later in life to have more comprehensive detection of abnormalities. Please provide more information on the type of follow up needed.

5.3. Gestational age measurement error and impact on exposure ascertainment.

- Minor Essential Revisions

6. Under “Introduction” P.3, “There are few studies in sub-Saharan Africa which have attempted to assess prevalence of drug use in pregnancy and its relation to pregnancy outcome.” Provide references for all these studies.

7. Under “Study design and population” P.4, please spell out the FDA drug categories as not all readers will be familiar with this.

8. Under “Results” p.5: please provide the mean gestational age (and standard deviations) at time of pregnancy detection for participants detected at the community level versus health facility.

9. Under “Results” p.6: be consistent in the terminology use for pregnancy loss and replace the word “abortions” by “miscarriages”. Please also check the spelling for “spinal bifida” it should be “spina bifida”. There are a few more typos and English errors to be corrected- the authors are recommended to thoroughly reread the manuscript.

10. Under “Discussion” p.8: The reported background rate of 3% for major congenital malformation includes defects of genetic aetiology and cardiovascular defects. As far as I understand this study was not equipped to detect such defects and the estimated rate of congenital abnormalities detectable at birth by surface examination has been estimated to be close to 1% which is not dissimilar to what was observed in this study.

11. Under “Discussion” p.8: Please note that the paper “Probabilistic record linkage for monitoring the safety of artemisinin-based combination therapy in the first trimester of pregnancy in Senegal. Drug safety 2013” recommends probabilistic record linkage only in specific settings where medical record keeping are of high standards (such as health insurance systems or agricultural estates which provide free care and have economical interest in good record keeping for budgeting purposes).

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being
published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests. I am co-investigator of a similar pharmacovigilance study for antimalarial drugs in pregnancy using an HDSS platform in western Kenya which was completed in 2013.