Assessment of pharmacovigilance approaches for monitoring the safety of antimalarial drugs in pregnancy
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Citation for published version (APA):

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Chapter 9

Summary and Discussion
Post-marketing surveillance of drugs used in pregnancy is challenging, especially in developing countries where resources for pharmacovigilance are rare. There is a need to establish simple but effective systems to monitor safety of drugs given during pregnancy in resource constrained countries. Although ACTs are not recommended in early stages of pregnancy, inadvertent exposures to ACTs are unavoidable; this will occur through different channels including outpatient clinics, the informal sector, clinical trials or mass drug administration programmes because either the woman or the prescriber is unaware of her pregnancy status. Deliberate exposures will occur in situations where the benefit outweighs the potential risk, when no other effective antimalarial drugs are available and particularly in the case of severe malaria. There are currently no established systems to monitor drug safety in pregnancy in malaria endemic countries. The aim of this thesis was to develop and evaluate pharmacovigilance systems in resource constrained settings to provide a better estimate of the risk-benefit profile of ACTs in pregnancy.

In Chapter 2 the published evidence with regard to the safety of artemisinin compounds when administered during pregnancy was reviewed through systematic literature searches. At the time of the review (November 2006), fourteen relevant studies (nine descriptive/case reports and five controlled trials) were identified. Overall there were reports on 945 women exposed to an artemisinin during pregnancy, 123 in the first trimester and 822 in second or third trimesters. The limited data available suggested that artemisinins are effective and safe when used in late pregnancy, although rare adverse events could not be ruled out. There was insufficient evidence to effectively assess the risk–benefit profile of artemisinin compounds for pregnant women, particularly with respect to exposure in the first trimester of pregnancy. This was in line with the WHO recommendation following informal consultations convened in 2006 to assess the safety of artemisinin compounds in pregnancy, highlighting the need to set up pharmacovigilance systems to document first trimester exposure to ACTs.

In Chapter 3 we provided an estimate for the number of pregnancies living in areas with malaria transmission in 2007. Updated maps of *P. falciparum* and *P. vivax* transmission were combined with gridded population data and growth rates to estimate total populations at risk of malaria in 2007. The numbers of pregnancies was derived from country-specific demographic data from the United Nations, combined with estimates for stillbirths and induced abortions derived from contemporary published reviews and estimates of spontaneous abortions based on an established formula (using the number of live-births and induced abortions). We estimated that in 2007, 125 million pregnancies occurred in areas with *P. falciparum* and/or *P. vivax* transmission of which approximately 60% resulted in live births. Estimates from Africa (32 million) were similar to previous estimates by WHO (25–30 million) but estimates for non-African regions was much higher than previously estimated (95 million vs. 25 million). These estimates of the number of pregnancies at risk of malaria provided a first step towards a spatial map of the burden of malaria in pregnancy. Recently Walker et al estimated the risk of placental infection and low birthweight attributable to *Plasmodium falciparum* malaria in Africa taking into account heterogeneity in transmission and parity-dependent effects.[1] They report that 12 million pregnancies resulting in live-births would have been exposed to malaria infections without malaria protection (i.e. through insecticide treated nets or IPTp) resulting in 900,000 low birthweight babies. They projected that the majority of placental infections (65%) would occur early in the first trimester of pregnancy. Considering that only about two thirds of pregnancies result in live-births the number of pregnancies potentially exposed to infection could be up to 18 million. It is difficult to predict what proportion of such
infections would lead to treatment with an antimalarial as in areas of high transmission most malaria infections remain asymptomatic particularly in multigravidae. Nevertheless even if only a small proportion were to seek treatment, millions of pregnancies could be exposed to antimalarials each year and many in the first trimester of pregnancy.

In Chapter 4, we estimated that the probability an embryo will encounter artemisinins during the critical six-week period (weeks 6 to 12 post-LMP) through accidental exposure is 12% for areas where adults receive on average one treatment with three days of artemisinin-based combination therapy per year. This assumed that the likelihood of infections was similar throughout pregnancy. In light of the modelling study by Walker et al, this probability is likely an underestimate. This information is useful to grasp the scale of the problem related to malaria in pregnancy and the potential for exposures to antimalarials in pregnancy. In this chapter we further described the methodological considerations for the systematic assessment of pregnancy outcomes and congenital malformations in women exposed to antimalarials early in pregnancy, as well as approaches to capture drug exposure information, choice of comparison groups and sample size concerns. We proposed a targeted prospective pharmacovigilance approach enabling timely assessment of the risk-benefit profile of antimalarials through the establishment of an international antimalarial pregnancy exposure registry. The WHO recently published a description of methods for pregnancy exposure registries in resource constrained settings which provides valuable tools for standard methods of data collection facilitating pooled data analysis.[2]

A complementary approach to pregnancy exposure registries is illustrated in Chapter 5, which describes the findings from a pilot study to assess the feasibility of record linkage using routinely collected healthcare data as a means of monitoring the safety of ACTs in early pregnancy. This study used data from paper-based registers (2004–2008) from a mission-run dispensary in Mlomp, south-western Senegal. Data from the outpatient clinics and delivery registers were linked based on a probabilistic matching approach as no unique identifier was available. The findings from this feasibility study suggest that record linkage using routine healthcare data is feasible in resource-constrained settings with a relatively well defined catchment population. Tapping into readily available data sources of sites adequate for record linkage could greatly contribute to the high numbers needed to provide adequate reassurance for ACT use in the first trimester of pregnancy, in terms of stillbirths and major congenital malformations. However, in these settings assessment of the risk of miscarriage and specific birth defects, such as congenital heart defects, would require dedicated studies. Sites amenable for record linkage studies need to have reliable and comprehensive medical records for treatment, pregnancy and maternity services. This requires a high proportion of health facility deliveries and limited availability of the drug of interest outside the central health facility record system (and therefore not captured in the health records). A prime example of such sites is the Shoklo Malaria Research Unit (SMRU) clinic which has already contributed significantly to what is known about ACT risk-benefit profile in the first trimester of pregnancy.[3] The unique set-up of the SMRU allows it to serve a stable refugee population where many pregnant women receive weekly antenatal care, pregnancies can be identified early, the gestational age assessed at every contact, the health-care provided, and drug exposure and birth outcome recorded centrally. Other potential sites with comprehensive and reliable healthcare records include agricultural estates providing free healthcare for their workers, refugee camps or use of health insurance data where coverage is high and homogeneous.
In Chapter 6 we investigated contextual information on perceptions of adverse pregnancy outcomes in an area of high malaria transmission in western Kenya. Through ten focus group discussions we explored the perceptions, beliefs and health-seeking behaviours of women from rural western Kenya regarding congenital anomalies and miscarriages. We found that lack of information regarding causes of adverse pregnancy outcomes such as miscarriages and congenital anomalies could lead to stigmatisation of the mother and further hamper health seeking behaviour. This could have devastating consequences for children born with a malformation who are sometimes hidden from society and don’t have access to care that could improve their quality of life. Although women reported that care is usually sought in case of complications following a miscarriage, delaying care until symptoms are pronounced could adversely affect recovery and the woman’s health. These findings highlight the need for education about the potential cause of adverse pregnancy outcomes and better information on where care is available. The qualitative data gathered through these focus group discussions was informative to understand the socio-cultural context around pregnancy and pregnancy outcome. It was also interesting to understand that although some women were aware of the potential danger of medicines used in pregnancy, drugs considered safe in medical practice were being reported as potentially dangerous. Mostly a risk was perceived when drugs were used without or not following clinician recommendations. This emphasised the need for education materials for both community and healthcare providers regarding the consideration for the choice of treatment in pregnancy.

In Chapter 7 we described healthcare provider and drug dispenser adherence to and knowledge of national guidelines for treatment of uncomplicated malaria in pregnancy. We conducted a cross-sectional study from September to November 2013, in health facilities and randomly selected drug outlets in an area of high malaria transmission in western Kenya. This study highlighted knowledge inadequacies and incorrect prescribing practices in the treatment of malaria in pregnancy, particularly in the first trimester. As the first line treatment for malaria, artemether-lumefantrine, is not recommended in the first trimester of pregnancy, all women of childbearing age should be assessed for potential pregnancy. Such pregnancy enquiries were only observed in 44% of cases in health facilities and 7% in drug outlets, although 93% and 49% reported routinely assessing for potential pregnancy respectively. A reason for this could be that prescribers and dispensers do not feel adequately prepared to enquire about potential pregnancy and/or the lack of access to pregnancy tests. Prescription of the correct drug at the correct dosage was observed in 32% of all cases in health facilities and 0% in drug outlets for first trimester cases. Knowledge was moderately higher for health facility staff (56%) and remained nonexistent in drug outlets staff. The reason for the discrepancy between what is reported and what was observed should be further explored. Exposure to artemether-lumefantrine in first trimester occurred in 16% and 51% of cases in health facilities and drug outlets, respectively; none were a result of quinine stock-out. Overall, SP was prescribed as treatment in 11% of all cases and the vast majority of all women prescribed quinine were given an insufficient supply. Provider knowledge in both settings was poor and was reflective of the low levels of correct case management observed in practice. Such incorrect prescribing practice can have serious consequence for the pregnant patients not only by the risk posed by using a drug of undetermined safety for the unborn baby (ACTs) but also in terms of adverse consequences due to the inability to clear a malaria infection when treated with an ineffective drug (SP) or incomplete drug regimen (as seen with quinine). The latter also contributes to emerging parasite resistance to these drugs. This study provided insights on the high potential for ACT
exposure in pregnancy in this setting but more broadly revealed a need for better dissemination of guidelines for case management of malaria in women of childbearing potential with the need to include both formal and informal sectors.

In Chapter 8 the findings from a prospective cohort study on the risk of inadvertent exposure to ACTs in the first trimester of pregnancy and its association with miscarriage in Western Kenya were presented. Community-based surveillance was used to identify early pregnancies among women of childbearing age under health and demographic surveillance in western Kenya. Multiple data sources (including outpatient records, longitudinal household level morbidity surveillance data and study specific pregnancy follow up questionnaires) were combined to ascertain ACT exposures in pregnancy. Out of the 1,126 pregnancies included in the analysis, there were 42 (4%) confirmed ACT exposures in the suggested artesinin embryo-sensitive period (6-12 weeks post LMP) and 75 (7%) confirmed exposures in the first trimester. This study showed that pregnancy detection in the first trimester (before most women present for ANC) was feasible through community based testing in this setting. We provided the first estimates for the rates of miscarriage stratified by gestational week in this area and found that the cumulative probability of miscarriage was 19% in this population during the period that women were under observation (up to 28 weeks of gestation). Compared to pregnancies without reported malaria and antimalarial treatment, those with a confirmed ACT exposure in the suggested artesinin embryo-sensitive period did not have a statistically significant different hazard of miscarriage [HR=0.85 95% CI (0.22-3.33)]. There was also no statistical difference for the confirmed exposures in the first trimester as a whole, although the effect estimate suggested a potential increase in risk [HR=1.60 95% CI (0.70-3.68)]. As noted from the upper bound of the confidence interval, we could not rule out a 3.7 fold increase in miscarriages linked to ACT exposure in early pregnancy. In line with what was observed in the cross-sectional survey on prescribing behaviours (chapter 7), very few women in their first trimester of pregnancy were treated with the recommended treatment, quinine (n=34 with 22 exposed to both quinine and ACTs). This hampered our ability to compare pregnancies exposed to ACTs in the first trimester to those exposed to a safe drug. Although an increased risk of miscarriage could not be discarded, the results are consistent with recent findings reported from the Thai-Burmese border and provide further reassurance regarding the use of ACTs in early pregnancy.[3] Findings from pooled data analysis combining data from this study and 2 other sites that were part of the Malaria in Pregnancy Consortium, assessing risk of miscarriage, stillbirth and major congenital malformations are forthcoming and will provide further insights on the risk-benefit profile of ACTs.

**ACT risk-benefit profile in first trimester of pregnancy: where are we to date?**

Since the review presented in chapter 2, more data has been published, increasing the number of documented first trimester exposures to 757 (see table 1). The evidence so far is reassuring and rules out artemisinin derivatives as major teratogens (defined as a drug that would increase the risk of major congenital malformations by 5 to 10 fold). The 757 documented first trimester exposures confer enough statistical power to detect relative risk of 2.3 or greater for overall major malformations and a RR of 1.3 for miscarriages (assuming the background rate of 0.9% for major malformations detectable by surface examination at birth and 12% for miscarriage with ratio of exposed to unexposed of 1:4 at 80% power). However for specific congenital anomalies which occur at frequencies of 1/1000 for the most common, the 757 documented exposures could only detect a relative risk of 6.6.
### Table 13. Description of documented ACT first trimester exposures.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Publication Year</th>
<th>Number of first trimester exposures</th>
<th>Reference</th>
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<td>TBB</td>
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<td>64</td>
<td>[3]</td>
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<tr>
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<td>Gambia</td>
<td>2001</td>
<td>77</td>
<td>[4]</td>
</tr>
<tr>
<td>Adam</td>
<td>Sudan</td>
<td>2009</td>
<td>62</td>
<td>[5]</td>
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<tr>
<td>Mayando</td>
<td>Zambia</td>
<td>2010</td>
<td>156</td>
<td>[6]</td>
</tr>
<tr>
<td>Rulisa*</td>
<td>Rwanda</td>
<td>2012</td>
<td>96</td>
<td>[7]</td>
</tr>
<tr>
<td>Mosha</td>
<td>Tanzania</td>
<td>2014</td>
<td>172</td>
<td>[8]</td>
</tr>
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<td>Indonesia</td>
<td>2014</td>
<td>11</td>
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<tr>
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<td>MiPc</td>
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<tr>
<td><strong>Total</strong></td>
<td>****</td>
<td><strong>757</strong></td>
<td><strong>Total</strong></td>
<td>****</td>
</tr>
</tbody>
</table>

*Rulisa et al published results from an observational study following pregnant women exposed to artemether-lumefantrine however pregnancy outcomes were not reported separately for first vs second/third trimester exposures.

Interestingly, few studies reported the effect of exposures during the suggested artemisinin embryosensitive period (only McGready et al 2012 and the study presented in chapter 8). The suggested period (6-12 weeks post LMP) was derived from the observed causal mechanism in animal models indicating that primitive erythroblasts are the primary target for embryotoxicity and these are the weeks when primitive erythroblasts are the predominant form of erythrocyte in circulation in human embryos.[10] As considering the exposure for the whole first trimester could bias effect estimates towards the null, it is important to carry out analysis to explore the associations between ACT exposures and outcomes during this period of maximum sensitivity in humans. This was performed and presented in chapter 8 where we found no trend of increase in risk to exposure in the sensitive period compared to the whole first trimester. Another point for consideration is the need to investigate congenital cardiovascular defects as this was one of the safety signals identified from preclinical reprotoxicology studies in rodents.[11,12] None of the studies were designed to assess cardiovascular defects, which require review by a cardiologist and access to specialised equipment (ultrasound for echocardiography, electrocardiogram and x-ray). Furthermore, most of the studies in table 1 were not designed to capture early pregnancy losses and adjustment for potential survival bias will need to be considered when assessing miscarriages as an end point.

Meta-analysis with individual patient data would be a useful next step for better evaluation of the safety profile of ACTs in the first trimester of pregnancy. This will need to take into account heterogeneity in data collection methods and different levels of certainty regarding potential exposure misclassifications. Review of current evidence by the WHO Technical Expert Group (TEG) on malaria chemotherapy will be a first step in deciding if more and what type of data is needed to inform the Malaria Policy Advisory Committee (MPAC) which provides independent advice to the WHO for the development of policy recommendations.

Safety is not an absolute property of a drug and it will depend on the appropriate use of the drug considering indication, dosage, efficacy and suitability for the patient. A balance between risk and benefit needs to be determined. In the case of ACTs, the deleterious effect of malaria infection in the first trimester of pregnancy and the benefit of rapid and effective treatment needs to be taken into consideration. Recent publications highlight first trimester malaria infections are more of a problem.
than previously thought, with two-thirds of all malaria placental infections occurring in the first 12 weeks of pregnancy (without preventive interventions), the high associated risk of maternal anaemia and impact on birthweight as well as a 3-4 fold increased odds of miscarriage with malaria infections in early pregnancy in an area of low and seasonal malaria transmission.[1,3,13,14] We found that treatment with ACTs was much more common than the recommended first line treatment quinine in the first trimester of pregnancy in the study area in western Kenya. It is unclear whether this was due to inadvertent exposures because of unknown or undisclosed pregnancies, because of lack of knowledge regarding the national treatment guidelines or whether this was a deliberate choice because quinine was out of stock or that an ACT was considered a better option for these women. Poor tolerability to quinine and common low compliance to the long 7-day regimen are known problems.[15,16] There is a clear need for improved recommendations regarding treatment of malaria in early pregnancy but also a need to investigate suitability of quinine for case management of uncomplicated malaria in pregnancy.

Before a change in the treatment policy for malaria in the first trimester of pregnancy is recommended, there will be a need to monitor and address poor compliance with current malaria treatment guidelines for early pregnancy. We found poor awareness of contra-indication of ACTs in early pregnancy among healthcare providers, drug outlet dispensers and women in the community (chapters 6-7). Clearer guidelines emphasising the need for pregnancy assessments of all women of childbearing age seeking treatment for malaria should be developed. Pregnancy testing in the community was found acceptable in our study which suggests that pregnancy tests offered by trained healthcare professionals could be feasible. There are at least 2 RDTs which combine malaria and pregnancy in one test, and one has an acceptable performance profile as reviewed in the last round of malaria diagnostic product testing reported by WHO.[17] These could be considered for use in female patients of childbearing potential. Implementability (including training, costs and availability) of pregnancy tests at point of care would need to be determined. In all situations a woman’s privacy and the confidentiality of her pregnancy status should be preserved by handling records carefully and choosing a suitable place for pregnancy assessments. This is particularly delicate when dealing with minors and adolescent girls who might be reluctant to disclose their pregnancy. This requires an objective, accepting and professional attitude from the healthcare provider.[18] The purpose of the pregnancy assessment should be made clear to the client such that it is to ensure the adequacy and safety of the treatment. Pregnancy assessments should be considered in all antimalarial dispensing scenarios with women of childbearing potential. This includes drug outlets, both formal and informal, and community based strategies for case management of malaria. Furthermore, there is renewed interest in mass drug administration for malaria elimination which will need to consider strategies for management of potential pregnancies. The lack of pregnancy assessment in women of childbearing potential has important implications for risk management programmes for other medications contraindicated in pregnancy in this setting.

**What are the prospects for sustainable pharmacovigilance systems for pregnant women in resource constrained settings?**

No single method can capture all desired data needed to make appropriate risk benefit assessments of a drug used in pregnancy. A combination of different methods and data sources is the only feasible approach to gather the most complete picture of potential developmental toxicity of a drug. The different approaches presented in this thesis have their own strengths and limitations but provide complimentary information. Common challenges include the need to obtain reliable and
accurate exposure data. In their retrospective analysis, McGready et al included fewer than 100 well-documented early exposures to artemisinins after review of 25 years of data including over 48,000 pregnancies.[3] We found only 25% of first trimester ACT exposures could be confirmed (chapter 8) and the sensitivity of women’s self-report at the time of pregnancy follow up interviews was estimated at 37% (based on confirmed exposures by the 2 other data sources, see chapter 8 Appendix). This indicates that studies or surveillance systems cannot solely rely on women self-report for antimalarial drugs, particularly if the recall period stretches over several months. Secondly, it is very challenging to account for confounding by indication (i.e. the fact that the disease for which the drug is being indicated, itself causes adverse pregnancy outcomes) in settings where self-medication of febrile episodes is common and where few women are treated with quinine.[19,20] Furthermore, due to the nature of these observational studies, it is not possible to account for factors influencing antimalarial treatment choice by healthcare providers and patients. If more severe cases are usually treated with one type of drug rather than other, this could confound the association between exposure and adverse pregnancy outcome. Inclusion of internal unexposed controls is necessary (as opposed to using background rates which is commonly done with pregnancy exposure registries in high income countries) as there is a lack of data on background rates of most adverse pregnancy outcomes (particularly miscarriages and birth defects) in most malaria endemic areas. Nevertheless, the use of internal unexposed controls allows a more appropriate comparison and provides the potential to control for the underlying disease provided there is enough variability in the different class of antimalarials used. Randomised controlled trials are considered the “gold standard” for generating reliable evidence in clinical research and could address these methodological challenges. Depending on the forthcoming findings from pooled data analysis, a randomised controlled trial comparing ACTs to quinine for confirmed malaria in the first trimester of pregnancy may be warranted to provide the level of reassurance needed for policy change. Whereas, a clinical trial was considered unsuitable during the last WHO consultations to review evidence on the safety of artemisinin derivatives in pregnancy in 2006 due to the limited data on first trimester exposure in humans, we may have reached the point of equipoise. Equipoise is defined as a state of genuine uncertainty regarding the comparative merits of different therapeutic choices and considered essential for the ethical acceptability of clinical trials.[21] WHO guidelines for the treatment of uncomplicated malaria in the first trimester of pregnancy state that an ACT is indicated if there is uncertainty of compliance with a 7 day quinine regimen.[22] In areas where treatment with ACTs already predominates quinine in the first trimester, a randomised controlled trial should be considered ethical.

Most teratogenic safety signals have been identified by astute clinicians through reporting of case series of abnormal pregnancy outcomes to exposed mothers.[23] Although this is less than ideal and often takes several years for the signal to be detected, the potential of such reports shouldn’t be ignored. However this requires awareness of pharmacovigilance and special considerations for treatment of women of childbearing potential. We found this to be low among healthcare providers and drug dispensers in our study area and this probably is not unique to rural western Kenya. Integration of pharmacovigilance topics into university and professional curricula for all health disciplines has been proposed.[24] The recent establishment of UMC Africa (a WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance for Africa) in Ghana provides an opportunity to share specific tools and education materials for pharmacovigilance methods for pregnant women.[25]
Identification of sentinel sites able to capture reliable data on drug exposure and pregnancy outcomes through a standard protocol as proposed in chapter 4 and recently by WHO would be essential for safety signal detection and characterisation.[2] Such an approach could be used for the evaluation of a wide variety of medications that are used during pregnancy and estimation of the risk of the spectrum of adverse pregnancy outcomes. However depending on the recruitment strategy, assessment of miscarriages might not be feasible without introducing dedicated efforts to detect these. Enrolling pregnant women attending for antenatal care is an interesting option, as close to 90% of pregnant women in sub-Saharan Africa attend antenatal clinics at least once.[26] However as many women present for their first ANC visit after completion of the first trimester (the average is around 22 weeks gestation), such an approach limits the possibility of studying early miscarriages as an outcome. For this reason, prospective community-based studies (as presented in chapter 8) are needed for detection of early pregnancies or systems to incentivise women and/or community health workers to refer pregnant women to present to ANC early should be explored. Health and demographic surveillance sites make attractive candidates as they provide a framework to identify women of childbearing age and usually have some level of health facility surveillance set up. This is exemplified through the implementation of prospective observational cohorts to field-test active surveillance systems for identifying exposures to antimalarials during early pregnancy and for monitoring pregnancy outcomes in three health and demographic surveillance sites in Africa (Burkina Faso, Mozambique and Kenya as presented in chapter 8) as part of the Malaria in Pregnancy consortium (MiPc).

Major limitations of traditional pregnancy exposure registries and prospective cohort studies include costs and length of time required to achieve a desirable sample size. As an alternative, record linkage studies using routine healthcare data provides a cost-effective and relatively rapid means of assessing the embryotoxic effect of a drug. Record linkage studies require minimal staff and resources particularly in settings with electronic medical records. However, this necessitates sites with comprehensive data on drug exposure and pregnancy outcomes. To minimize exposure misclassification, it is essential to select sites within a relatively stable population where healthcare is provided in a central location with a high proportion of health facility deliveries and limited availability of the drug of interest outside the central health facility system. Sites where this approach could be implemented effectively are few, and further study should assess suitability of private agricultural and other industrial estates, mines and refugee camps as well as data from health insurance schemes in malaria endemic countries.

How sustainable are these approaches? There are no obvious funding mechanisms for pharmacovigilance activities. In resource constrained settings, priorities often lie with the delivery of care and pharmacovigilance programmes currently have to compete for very scarce resources.[27] However confidence in a public health programme can be seriously affected by adverse drug reactions, particularly serious adverse events affecting pregnancy outcomes (such as pregnancy loss or congenital anomalies).[28] Evidence on the safety of drugs implemented by public health programmes has the potential to increase programme success by providing guidance on reducing the risks of adverse drug reactions thereby increasing overall public trust.[29,30] The Roll Back Malaria partnership issued guidance to countries applying for malaria funding for the inclusion of pharmacovigilance component within donor-supported programmes.[31] The Global Fund to fight AIDS, tuberculosis and malaria has made provision for specific support towards pharmacovigilance which could be used to fund such initiatives for antimalarials, antiretrovirals and tuberculosis.
treatments.[32] The United States’ President’s Malaria Initiative (PMI), is one of the major donors for malaria control programmes in target countries in sub-Saharan Africa and plays a key role in the procurement of antimalarial treatment and assessment of drug safety. However, few proposals to either funding bodies included a request for funding for pharmacovigilance activities.[33] In 2011, the European Medicines Agency (EMA) approved Eurartesim (dihydroartemisinin-piperaquine) for marketing with the condition that a pregnancy registry be set up as part of the post-marketing risk management plan (among other recommendations).[34,35] This so far has resulted in the creation of a European based pregnancy registry to monitor inadvertent exposures to Eurartesim in European travellers, who rarely have access to Eurartesim, which is a treatment drug provided only to those with clinical malaria. Little progress has been made with developing a platform to monitor the safety of Eurartesim in pregnancy in malaria endemic countries where most of the exposures are likely to occur.[36] Sustainability of the proposed approaches will need political commitment and key stakeholders (including industry, governments and funders of public health programmes) buy-in to prioritise support for pharmacovigilance systems.

In conclusion, the reports presented in this thesis support the need and feasibility of implementing various pharmacovigilance approaches for monitoring safety of medicines in pregnancy in resource constrained settings. In light of the soaring number of first trimester pregnancies being exposed inadvertently and deliberately to artemisinin derivatives, an update of the last 2006 WHO review of the existing evidence is needed promptly to inform treatment guidelines for malaria in pregnancy. Observational studies on ACT exposures in the first trimester of pregnancy have provided a degree of reassurance and have not detected major teratogenicity signals in humans so far. However numbers are still limited to less than a 1000 well documented first trimester exposures, and the rule of 3 suggests that this can demonstrate a less than two-fold increase in the overall incidence of malformations.[37] Thus more research is needed, also to assess the risk of cardiovascular defects associated with ACT exposures in early pregnancy as well as studies looking at congenital anomalies detectable later in life including developmental delays. Furthermore, once enough data has accrued to provide sufficient statistical power, it will be important to carry out a sensitivity analysis of the suggested period of maximum artemisinin sensitivity in human embryos. With the accrued evidence to date and the low adherence to the recommended treatment with quinine in first trimester of pregnancy, a randomised controlled trial would be the fastest way to provide the level of evidence needed. Until adequate evidence is available to comprehensively assess the risk-benefit profile of ACTs for early pregnancy, it will be important to minimise first trimester exposures. Current options for treatment of pregnant women with malaria are few and appropriate prescribing and dispensing is critical for rational drug use. As such healthcare providers and drug dispensers should have relevant knowledge and skills regarding antimalarial drug use in women of childbearing potential. Further research is needed to investigate the best approach to implement risk management to minimise first trimester exposures including ways for appropriate dissemination of malaria treatment guidelines, as well as pregnancy assessment strategies for healthcare professionals in health facilities, drug dispensers working in the informal sector, and community health workers in areas where their mandate includes treatment of malaria in women of childbearing age. This thesis focused on treatment of malaria in pregnancy; however most of the findings are applicable to other tropical diseases in pregnancy. The case of ACTs is not unique and most of the new medicines for tropical diseases in pregnancy are not recommended for pregnancy due to lack of information.[38] Given the high burden of disease in the tropics and the extensive overlap between malaria and HIV,
it will be important to consider all concomitant drug exposures and potential for drug-drug interactions. Joint efforts are needed to tackle this paradoxical situation to enable safe and effective treatment of tropical diseases in pregnancy.

References


25. UMC-A the Uppsala Monitoring Centre Africa.


