Assessment of pharmacovigilance approaches for monitoring the safety of antimalarial drugs in pregnancy
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Chapter 1

General Introduction
Pharmacovigilance

All drugs have the potential to cause harm and their risk-benefit profiles need to be determined to maximize therapeutic outcomes.[1] Attention to the importance of drug safety monitoring was brought to light by the thalidomide tragedy in the 1960s.[2,3] Thalidomide was used as an antiemetic and sedative which was considered safe including during pregnancy. More than 10,000 malformed children with phocomelia (with limbs severely underdeveloped or absent) were born before a safety signal was identified and thalidomide was withdrawn.[4] This had a profound impact on drug regulatory processes from registration to post-marketing surveillance.[5]

Pharmacovigilance, sometimes referred to as drug monitoring or post-marketing surveillance, is defined by the World Health Organization (WHO) as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse reactions or any other possible drug-related problems”.[1] Fundamental aims are early detection of unknown safety issues, quantifying risk and risk factors associated with adverse drug reactions (ADRs) and primarily preventing unnecessary harm to patients.

Before a drug is marketed, drugs are tested pre-clinically in-vitro and in animal studies for toxicity. If a compound passes these tests it goes through a series of clinical trials (see figure 1). Drug regulatory authorities make their decision based on evidence regarding efficacy, safety and quality deemed adequate for a drug to be approved. By the time a drug is marketed, information on safety and efficacy has been derived from limited number of subjects (between 500-5000) who are typically carefully selected and followed under controlled conditions for a relatively short amount of time.[6] This limits the possibility of detecting rare adverse events (the rule of three suggests that by the time of registration, safety information is typically only available for adverse events occurring at frequencies of 0.1 to 1%[7]), or events with slow onset such as cancer or events occurring in vulnerable groups such as pregnant women, children and the elderly or people with co-morbid conditions and concomitant medications which are usually excluded from pre-registration clinical trials.

Passive surveillance through spontaneous reporting is the backbone of post-marketing surveillance. This entails identification of a suspected ADR following drug exposure by healthcare professionals, assessments of severity and causality and reporting according to standard procedures. Passive surveillance is useful for hypothesis generation and identification of new safety signals but has its limitations such as under-reporting, variable quality and completeness of the reported data, tendency for reporting of known reactions and false causality attribution.[8] Active surveillance approaches are essential to assess and evaluate the nature and rates of adverse events as they can provide denominator data. The most common pharmacovigilance active surveillance involves identifying individuals exposed to a drug of interest and following them systematically to assess for adverse events (e.g. Prescription Event Monitoring system used in the UK [9]). Other approaches using pharmacoepidemiological methods, include cohort or case control designs, are used for safety signal confirmation or characterization.[10,11] Deciding on an approach should be based on the safety specification of a product and whether the purpose of the investigation is hypothesis or signal

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1 The rule of three is commonly used in pharmacovigilance to estimate the sample size needed to detect adverse events. It is based on the assumption that there is 95% chance of observing one occurrence of an event in a population 3 times the size of the event’s rate (e.g. to pick up a rare event occurring at a rate of 1/10,000, 30,000 individuals will need to be monitored to be 95% certain of detecting this event).
generating; hypothesis strengthening or a confirmatory study, (i.e. evaluation of a known safety signal).

Figure 1 Clinical development of medicines adapted from “WHO Policy Perspectives on Medicines — Pharmacovigilance: ensuring the safe use of medicines”.[6]

Pharmacovigilance in resource constrained settings

The public health burden of ADRs and medication errors is difficult to quantify but it is likely to be worse in resource constrained settings because of weak health systems, overstretched and often inadequately trained healthcare staff, unreliable supply and quality of drugs, polypharmacy (use of multiple drugs concomitantly), concomitant use of herbal remedies as well as availability of most prescription drugs from the informal market.[12] Few low and middle-income countries have functioning national pharmacovigilance systems. Currently, less than 2% of ADR reports collated at the Uppsala Monitoring Centre of the WHO Programme for International Drug Monitoring (UMC, which collates reports from national pharmacovigilance centres globally [13]) come from low or middle-income countries.[14] Indeed, most of these countries make national treatment or prevention policy decisions with reliance on drug safety data from industrialised countries where pharmacovigilance systems and regulatory authorities are better established. However, this often comes at the expense of no or limited safety data for drugs targeting tropical diseases which are seldom encountered in these industrialised settings.

While there is increasing access to medicines to combat HIV, malaria and tuberculosis in the tropics, systems are needed to assess the risk-benefit balance of these much-needed interventions.[15] Drug safety monitoring cannot rely on passive spontaneous reporting systems for ADRs due to the limitations mentioned above. Targeted pharmacovigilance approaches are required in situations where no systematic recording of drug exposure and suspected ADRs exist particularly where health resources are limited. Passive surveillance has been proposed at selected sentinel sites where healthcare professionals are trained and incentivised to report suspected severe ADRs to specific drugs of interest.[16] Building on existing infrastructure and surveillance systems or studies would provide more cost-effective ways to collect reliable and timely data. Demographic surveillance sites
are increasingly being considered for use as platforms for post-marketing surveillance. Such sites monitor vital events (births, deaths and migration) through regular censuses of a pre-defined population (typically 2 to 4 times per year), most also have links to clinical and treatment data from local health facilities. They have well-defined and characterized populations, and are valuable to monitor public health interventions where health information systems are weak as they provide denominator data, a framework to identify specific groups (such as pregnant women or children) outside the healthcare setting as well as human resources and infrastructure for research.\cite{17} Five African sites that are part of the International Network for the Continuous Demographic Evaluation of Populations and Their Health (INDEPTH) are conducting Phase IV studies to monitor antimalarial effectiveness and safety in “real life” settings.\cite{18} Antimalarial safety is being monitored through a Spontaneous Adverse Events Reporting System (passive surveillance) and Cohort Event Monitoring (CEM; active surveillance). The spontaneous reporting system is being strengthened in the selected sites ensuring health workers are sensitised and familiar with the ADR reporting procedures. CEM protocols involve active follow up of patients prescribed antimalarials on days 3 and 7 following treatment and systematic recording of all clinical events during that time. This enables the characterisation of known ADRs in terms of incidence as a denominator is available (which is not the case for systems based on spontaneous reporting) and identification of risk factors as well as detection of unknown safety signals. Another approach is to capitalize on planned studies, such as those conducted by the Malaria in Pregnancy Consortium (MiPc) and the ACT consortium (ACTc) which have set up a centralized safety database collating ADRs collected across studies using standardized reporting procedures and tools.\cite{19,20} Such systems could then be extended to other drugs and expanded to additional sites through new collaborations.

**Drug safety in pregnancy**

Special considerations apply to the assessment of drug safety in pregnancy, particularly for drugs used to treat diseases that are only endemic in resource constrained settings. Most drugs are marketed with limited information on their safety when used during pregnancy. Pre-approval studies have inherent limitations in determining the safety of drugs used during pregnancy. Animal reproductive toxicology studies have ambiguous predictive value for human teratogenesis due to variations in species-specific effects \cite{21} and pregnant women are routinely excluded from pre-licensure clinical trials for fear of harming the mother or the developing fetus.\cite{22,23} Physiological changes associated with pregnancy limit the inference of pharmacokinetic and pharmacodynamic data from non-pregnant subjects.\cite{24} Consequently, most drugs are not recommended for use during pregnancy due to the lack of information on their risk-benefit profile. Yet drugs are widely used by pregnant women. Medication often cannot be avoided for chronic diseases, such as asthma, epilepsy, malignant diseases, HIV, or other illnesses which may harm the mother and the unborn baby if left untreated. Furthermore, many women are likely to be inadvertently exposed to drugs at the most vulnerable time of embryo development early in gestation before pregnancy status is recognised. Healthcare providers, pregnant women and policy-makers need valid information in order to make informed decisions about the use of drugs during pregnancy.
Pharmacovigilance approaches for drugs used in pregnancy

There are several methodological challenges to the study of safety of drugs in pregnancy, including those common to overall pharmacovigilance methods such as the need for large sample sizes to minimise the possibility that the observed association between a drug and a rare outcome occurred due to chance; the possibility of confounding by indication which implies studies should take into account the contributing risk of the underlying maternal illness; the general lack of background rates needed to put signals into context and the potential self-referral bias introduced by voluntary reporting.[25,26] Special considerations are also required for assessment of outcome and drug exposure. Monitoring drug safety in pregnancy necessitates systematic recording of pregnancy outcomes, examining the newborns and possibly following up the infants to detect anomalies not detectable at birth. Where deliveries occur outside health facilities, as is the case in many rural settings in low and middle income countries and particularly for early pregnancy loss, systems need to be put in place to capture all pregnancy outcomes. Ascertainment of drug exposure requires reliable information on the drug and gestational age at the time of exposure. This is important as the impact on the fetus from drugs used in pregnancy depends on the stage of pregnancy at the time of exposure as different tissues and organs have specific developmental timelines.[27,28] These methodological considerations are described in detail in chapter 4 based on the case of artemisinin combination therapies used for the treatment of malaria.

Passive surveillance (i.e. spontaneous reports of suspected ADRs) for detecting drug with potential embryo-fetal adverse effects relies on judicious clinicians to make the association between a drug exposure in pregnancy and an adverse event which will often occur months and sometimes years later (for congenital anomalies not detectable at birth). In resource constrained settings, such an approach has limited use due to under-ascertainment of outcomes such as miscarriages and birth defects in communities where birth anomalies are considered taboos, as well as the general lack of awareness around pharmacovigilance and the need to report suspected ADRs.

Pregnancy exposure registries, a type of cohort design, are the most common approach to monitor drug safety in pregnancy in industrialised countries (e.g. the Antiretroviral Pregnancy Registry[29] or the Antiepileptic Drug (AED) Pregnancy Registry[30]). The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommend pregnancy exposure registries for products that are likely to be used during pregnancy or by women of reproductive age, particularly if there have been case reports of adverse pregnancy outcomes following exposure, drugs in the same pharmacological class are known to pose risk during pregnancy or pre-clinical animal data suggests potential teratogenic risk.[31,32] A pregnancy exposure registry involves active identification and recruitment of pregnant women exposed to a drug or class of drug of interest and following these women throughout pregnancy. This approach has many advantages such as active enrolment and pregnancy outcome ascertainment to minimise loss to follow up, centralised and prospective ascertainment of exposed pregnancies which reduces biases. Drawbacks of most pregnancy registries are the limited sample size to detect moderate effects, the lack of outcome validation and standardisation of birth defect assessments.[27] To overcome the sample size requirement pharmacoepidemiologic studies using existing databases are often used in high income countries. Cohort studies use large databases such as medical insurance claim databases (e.g. the Medicaid database in the US[33]), electronic medical records (e.g. GPRD in the UK[34]), or data from teratology information services (e.g. the Motherisk Program in Canada[35]). Birth defect registries and case-control surveillance systems are also used to assess associations between medications and
congenital malformations (e.g. the Birth Defects Study by Slone Epidemiology Centre[36]). Applicability of these methods in low and middle income countries is unknown.

Malaria in pregnancy

Epidemiology and burden
Malaria is a major public health problem affecting an estimated 3.4 billion people worldwide (half of the world’s population) which live in areas at risk of malaria. In 2012, an estimated 207 million cases of malaria occurred globally, resulting in over half a million deaths.[37] This life threatening disease is preventable and treatable through proper use of antimalarial drugs, insecticide treated bednets and indoor residual spraying of insecticides. Since 2000, a significant decrease in malaria mortality rates have been observed due to the vast increase in the financing and coverage of malaria control programmes.[37]

Pregnant women and children under five are most at risk of malaria. Malaria in pregnancy (MiP) can have devastating consequences for the mother and fetus, including severe maternal anaemia and mortality, miscarriage, intrauterine growth retardation and low birthweight (LBW), preterm birth and stillbirth.[38,39] It is estimated to cause as many as 900,000 low birth weight births, and 100,000 infant deaths every year. Furthermore, up to a quarter of maternal mortality in endemic countries could be attributable to malaria.[39,40,41,42,43]

Prevention guidelines
WHO recommends two approaches for the prevention of MiP in areas with stable malaria transmission (where the population is exposed to a fairly constant, high rate of malaria infected mosquito bites [>10 per person per year]): intermittent preventative treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) at each antenatal clinic visit following quickening and the use of insecticide-treated bed nets (ITNs) to protect pregnant women from the bites of infected mosquitoes.[44,45] Coverage with these prevention strategies remains very low. In 2007 it was estimated that only about 39% and 25% of pregnant women in sub-Saharan Africa used ITNs and received at least two doses of IPTp, respectively.[46]

Treatment guidelines
Pregnant women, when infected, require rapid diagnosis and case management with safe and effective antimalarial drugs to prevent progression to severe disease or death, or to prevent asymptomatic infections from becoming chronic leading to fetal growth restriction and malaria-related maternal anaemia.[38,39] Established antimalarials like chloroquine and SP are no longer recommended for the case management of malaria illness due to drug resistance of the parasite. Artemisinin-based combination therapies (ACTs) are now the recommended treatment for uncomplicated malaria in sub-Saharan Africa.[47] Artemisinin derivatives have been used for centuries in China but they have only been deployed for use as ACTs since 2001.[47,48] Based on the level of drug resistance to the partner medicine, the following fixed-dose combination ACTs are recommended: artesunate plus lumefantrine; artesunate plus amodiaquine; artesunate plus mefloquine; artesunate plus SP and dihydroartemisinin plus piperaquine.

In the first trimester of pregnancy an ACT is indicated only if an alternative antimalarial is not immediately available, or if treatment with 7-day quinine (without, or combined with, clindamycin) fails or there is uncertainty of compliance with the 7-day quinine regimen. The recommendation for treatment of pregnant women with severe malaria includes parenteral artesunate because it is
faster acting than parenteral quinine and is associated with improved survival in patients with severe malaria.[49,50,51]

**Antimalarial safety in pregnancy**

**Antimalarials considered safe throughout pregnancy**

Antimalarials recommended for pregnant patients must be safe for the mother and her unborn baby. There is insufficient information on the safety of most antimalarials in pregnancy, particularly for exposure in the first trimester. A retrospective study in Thailand, reported the deleterious effect of even a single episode of malaria in the first trimester and its association with an increase in the risk of miscarriage, emphasising the need for safe and efficacious drugs in this critical period.[52]

This is further supported by a recent modelling study reporting that up to two thirds of placental infections occur by the end of the first trimester.[43] Antimalarial medicines considered safe in the first trimester of pregnancy are quinine (with or without clindamycin), chloroquine, proguanil and more recently mefloquine although this is based on limited evidence. As mentioned above, chloroquine is no longer recommended for treatment of *falciparum* malaria. Proguanil and chlorproguanil although deemed very safe in pregnancy, have limited value in resource constrained settings as the current formulations available are either too expensive (atovaquone-proguanil) or carries the risk of acute haemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency (which has a prevalence of up to 30% in some African countries[53]) when in combination with dapsone. This combination is no longer available since its marketing authorization holder withdrew it from the market in 2008.[54] Animal studies (in rodents, dogs and primates) did not find quinine to have embryo-fetal toxicity except one study which reported congenital malformations in 5% of pups born to rats receiving quinine.[55,56,57] There was no evidence of embryo-fetal toxicity in published human data. Quinine is often thought to have abortifacient properties at high dosage.

The author of a commonly cited publication from 1908 reports the beneficial effect of quinine as “It may be laid down as an almost invariable rule that if in a pregnant woman suffering from malarial fever uterine action has begun, the quinine will probably hasten the abortion; but that if uterine action has not begun, it will not start it, but will, on the contrary, probably be the means of saving the pregnancy”.[58] A recent observational study in Tanzania reported an increased risk of pregnancy loss in women exposed to quinine in the first trimester[59] however it is not clear whether the observed effect could be explained by the underlying malaria infection, especially because of the potential for poor compliance with the 7-day quinine regimen given the poor tolerability of quinine due to cinchonism (a syndrome which includes symptoms of ringing of the ears, blurred vision, headache, nausea and dizziness) and hypoglycaemia.[60,61] Mefloquine has been recommended as a prophylactic for pregnant travellers by WHO and CDC. Recently after review of existing evidence the FDA and CDC changed their recommendation for the use of mefloquine in pregnancy both as a prophylactic and for treatment.[62] Mefloquine has an acceptable reproductive toxicity profile in animal studies at standard doses and data on 1000 first trimester exposures suggests no increase in risk to adverse pregnancy outcomes. Although 1 retrospective study found an increase in the risk of stillbirths associated with mefloquine treatment doses in pregnancy this finding has not been confirmed by subsequent studies.[60,61,63] The result of a multi-centre randomised controlled trial in over 4000 second and third trimester pregnant women did not find an increased risk of stillbirth with two or three 15 mg/kg treatment doses of mefloquine compared to SP when used as IPTp. However tolerability was low, even when 15 mg/kg
was given as a split dose over two days, with 30% of pregnant women reporting vomiting and dizziness which could limit the use of mefloquine for IPTp.[64]

**Antimalarials contraindicated in the first trimester of pregnancy**

SP, which has limited use due to increasing drug resistance, is still used for the prevention of malaria in pregnancy through IPTp in most areas with high malaria transmission. As an anti-folate it is not recommended in the first trimester of pregnancy due to risk of neural tube defects.[65] Animal studies found embryotoxicity at high doses including cleft palate in rat models.[66] Documented use in over two thousand pregnancies in the second and third trimester of pregnancy found no evidence of embryotoxicity.[60,61] Amodiaquine is considered safe in pregnancy although there are neither documented data on exposure in the first trimester of pregnancy nor animal reprotoxicology studies.[67,68] Lumefantrine is only available as an ACT in combination with artemether which is contraindicated in the first trimester of pregnancy (see below) and data from animal studies did not show any embryotoxic effect.[60,61] Piperaquine, which is also only available as an ACT, has a safety profile expected to be similar to that of chloroquine. Animal reprotoxicology studies of piperaquine found no safety concerns except that gestation was prolonged in exposed rats.[69,70] The few studies on the use of the combination dihydroartemisinin-piperaquine in second and third trimesters of pregnancy reported favourable outcomes for pregnant women.[71,72,73] Further trials are underway with women in their second and third trimesters.[74,75,76,77,78]

**Artemisinin derivatives in early pregnancy**

Although ACTs are highly effective in treating malaria the safety of artemisinin derivatives during early pregnancy remains to be determined. Animal reprotoxicology studies showed that artemisinin derivatives have embryotoxic effects in all species studied (i.e. rat, rabbit and monkey) at low dose ranges.[79,80] Pre-clinical studies showed that the mechanism of embryotoxicity was through insult to immature red blood cells (primitive erythroblasts) causing severe anaemia in the embryo and leading to either embryolethality or malformations, skeletal (shortened or bent long bones and scapulae, misshapen ribs, cleft sternebrae and incompletely ossified pelvic bones) and cardiovascular (ventricular septal and vessel defects).[79,81] These studies also predicted that the main window for insult to the fetus will occur early in pregnancy (between 4 and 10 weeks post conception).[79] This is the period when the nucleated, metabolically active primitive erythroblasts predominate in the blood. However, the exact moment when humans are most sensitive is unknown as the primitive erythroblasts are gradually replaced by enucleated mature erythrocytes (which are less sensitive to the effects of artemisinins) over several weeks. Information regarding risks associated with the use of antimalarials in pregnancy in humans is sparse. Although the limited data on human exposures is reassuring for first trimester exposures 2, further information is required.[61,82,83] With the widespread deployment of ACTs, the potential for inadvertent exposure early in pregnancy is high when neither the physician nor the patient is aware of the pregnancy.

It is essential to study the risks of artemisinins and ACT drugs in early pregnancy, and that vigilant attempts are made to establish systems for the systematic collection of pregnancy-drug exposure data. It is unknown how best this can achieved in resource constrained malaria endemic countries. The specialized nature of the reliable assessment of drug exposures, pregnancy outcome and

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2 At the time of the first review in chapter 2 there were 123 documented exposures this number is now close to 760 as discussed in the last chapter of this thesis.
malformations is not easily achievable from routine surveillance systems such as national pharmacovigilance programmes, where they exist, and will require sentinel sites with enhanced active surveillance or dedicated studies, good record keeping and follow-up systems, and training of staff to examine newborns.

**Thesis Aim and Outline**
The aim of this thesis is to develop and evaluate such targeted pharmacovigilance systems to assess the safety of the ACTs in early pregnancy.

This thesis is divided into two components: desk-based reviews (chapters 2-4) and field-based studies (chapters 5-8) with the overall aim to assess pharmacovigilance approaches to provide better estimates of the risk-benefit profiles of ACTs used in early pregnancy.

**Objectives and outline**

1) Review existing evidence on human exposure to ACTs in pregnancy with the emphasis on first trimester exposures (chapter 2)
2) Derive global estimates of the number of pregnancies at risk of malaria based on a contemporary map of malaria transmission and demographic data for pregnancy and fertility rates to provide an estimate of the scale of the problem posed by MiP (chapter 3)
3) Describe the methodological considerations for setting up antimalarial pregnancy exposure registries in resource constrained settings (chapter 4)
4) Assess the feasibility of record linkage using routinely collected healthcare data as a pragmatic means of monitoring antimalarial safety in early pregnancy. A study involving extraction of data from health records from a dispensary in south-western Senegal is reported (chapter 5)
5) Explore community perceptions of miscarriage and congenital anomalies. Findings from 10 focus group discussions carried out in western Kenya are described which provide insight for studies of pregnancy outcomes in similar rural African settings (chapter 6)
6) Assess prescribing behaviour and knowledge of malaria treatment guidelines for pregnant women among healthcare providers and drug outlet dispensers in an area of high malaria transmission. The results from a cross-sectional survey in rural western Kenya are presented providing insight on the scale of ACT prescribing in early pregnancy (chapter 7)
7) Assess the risk of miscarriage associated with exposure to ACTs in the first trimester of pregnancy. The findings from a prospective cohort study of women of childbearing age in Western Kenya are presented (chapter 8)
8) Draw conclusions on the potential of the proposed pharmacovigilance approaches for drugs used by woman of childbearing age and pregnant women in resource constrained settings based on all the evidence presented in this thesis (chapter 9)

**Description of study sites**

**Senegal**
The study described in chapter 5 took place in a private mission dispensary based in Mlomp, a village of approximately 8,000 inhabitants in the District of Ouussouye, Casamance, south-western Senegal. The dispensary offers outpatient, antenatal clinic (ANC running once a week), and maternity (since 1968) services. The dispensary is well attended, offers high quality services and is equipped to perform simple laboratory tests including microscopy evaluations of malaria slides. Dispensary
registers for antenatal care, delivery, child welfare clinics and a general register for outpatient visits have been meticulously kept since 1993. Nearly all pregnant women attend ANC and health facility deliveries have increased from 50% in 1961 to 99% in 1999. [84,85] The district hospital is situated in Oussouye (the closest town) about 10km away with limited public transport option and the regional hospital is in Ziguinchor (about 50km away).

Malaria occurs year-round and peaks during the rainy season (July to December) in this area. A recent study showed that malaria transmission intensity in southern Senegal has been decreasing significantly in the past 15 years.[86] The area is rural, there is no running water or electricity and rice cultivation is the main economic activity. Mlomp has been under yearly demographic surveillance by the French National Institute of Demographic Studies (INED) since 1985.[87] Several research studies on malaria and malaria chemotherapy have been conducted in the study area.[88,89,90,91]

This setting, with a relatively enclosed population and comprehensive records on malaria episodes, treatment and pregnancy outcomes, provided a good opportunity to pilot utilisation of routine healthcare data for monitoring antimalarial safety in pregnancy.

Figure 2. Study site in south-western Senegal (study presented in chapter 5).

Kenya

Studies described in chapters 6 to 8 were conducted within the Health and Demographic Surveillance System (HDSS) in western Kenya under a long-standing collaboration between the Kenya Medical Research Institute (KEMRI) and the US-based Centers for Disease Control and Prevention (CDC).[92,93] The HDSS operates a quarterly survey covering an area of about 700 km² and 225,000 people living in 385 villages. Data on pregnancies, births, deaths, cause of deaths via verbal autopsies and migrations are collected.[94] This is an integrated field site designed to manage the longitudinal follow up of residential units, households and individuals. The field operations also involve surveillance of paediatric out-patient visits in peripheral health facilities, and monitoring of paediatric in-patient visits at two District Hospitals. In addition, household socioeconomic and
educational status surveys are conducted annually to complement the morbidity and demographic data. Extensive laboratory facilities have been established to support diagnostic work in parasitic and bacterial diseases as well as HIV; basic immunology and molecular biology research in these areas is also conducted. The centre has conducted a number of large studies and trials (e.g., the large community-based, group-randomised, controlled trial of permethrin-treated bed nets (ITNs) carried out between 1996-1999, the Phase 3 trial of the RTS,S malaria vaccine and a Phase 2B trial of a tuberculosis vaccine, among others).

Malaria transmission is perennial and holo-endemic, although transmission has been greatly reduced following provision of free ITNs.[95,96] The prevalence of malaria among individuals over 15 years of age ranged between 10–20% in the period 2006 to 2008. [KEMRI/CDC, unpublished observations] There is a high rate of HIV infection (in 2008: 15.4% overall: 20.5% among females and 10.2% among males while the National HIV prevalence is around 7%).[97] The prevalence of TB in individuals over 15 years of age was 600/100,000 and geohelminth prevalence in pregnant women was recorded to be as high as 76.2%. [98,99] Consequently, the area has mortality figures that reflect this burden of infectious diseases - infant mortality rate of 111 per 1,000 live births and a life expectancy at birth of 45 years in 2008.[93] The maternal mortality ratio is 669 per 100,000 live births which is higher than the national estimate of 488 per 100,000 live births reported by the Kenya Demographic and Health Survey in 2008/2009 for approximately the same time period.[100]
13. UMC the Uppsala Monitoring Centre.
20. MiPc Malaria in Pregnancy Consortium Pharmacovigilance Activities.
64. WHO (2013) WHO Evidence Review Group on Intermittent Preventive Treatment (IPT) of malaria in pregnancy Geneva
78. Ter Kuile F (2013) STOPMiP: Intermittent screening and treatment or intermittent preventive therapy for the control of malaria in pregnancy in Indonesia. MIP Library: Liverpool School of Tropical Medicine.
87. INDEPTH (2011) Mlomp DSS.