

Summary

Malaria is one of the most important infectious diseases worldwide. In Africa, which bears the greatest burden of this disease, control efforts have shown some successes without any prospect on elimination; in Rwanda however the recent years have registered great success in reducing malaria.

Malaria is transmitted to humans by a female *Anopheles* mosquito that injects the malaria parasites called *Plasmodium* into humans during mosquito feeding. It is the parasite that causes the disease as it multiplies in the red blood cells (erythrocytes) of the patient. The most frequently occurring and most dangerous form is *Plasmodium falciparum*. There are no exclusive typical signs and symptoms for malaria; the commonest clinical presentations however are: fever, headache, arthralgia, malaise. Sometimes symptoms are even less specific. The disease is lethal if not treated well but can be cured if promptly detected and treated. During pregnancy diagnosis of malaria can be much more difficult as signs and symptoms of malaria may not be present. This can happen when the parasite infected erythrocytes accumulate and sequester in the placenta leading to maternal anemia and problems to the intra-uterine fetus including abortion, still birth, growth retardation, low birth weight and sometimes congenital malaria. Although much is known about malaria in pregnancy in areas where malaria is highly endemic much less is known on malaria in pregnancy in areas which recently shifted from high to low endemicity. Pregnant women require special attention in malaria control but the topics that are frequently addressed in highly endemic areas such as the occurrence of low birth weight and in utero effects as well as proper and safe treatment should be re-assessed in areas where malaria elimination is at the horizon.

There are several ways to control malaria and these include prevention from being bitten by the infected mosquito by sleeping under mosquito nets and by indoor residual spraying and, if these fail and one gets sick, to seek immediate diagnosis and treatment with a highly active antimalarial drug.

In **Chapter 2** of this thesis we conducted a household survey in Ruhuha sector in Bugesera district to determine the proportion of malaria among people presenting with fever at the health center and eventually follow them to their homes to see how many of their household members carry malaria parasites without symptoms.

It was found that among patients consulting for fever at Ruhuha health center 22.9%, or one in every five, had malaria and that the prevalence of parasitaemia among household members 5.1% was, even with coverage of bed nets and indoor residual spraying of 97.1% and 98.2% respectively.

This indicates that there are people in the community who are infected with malaria but do not have symptoms (yet) but are able to transmit the disease to other household members or households. Health seeking behavior of the community is therefore an important factor in disease

control especially if a person can have disease without serious symptoms. It also showed that malaria tends to cluster around index cases, which offers options for more targeted surveillance.

In **chapter 3** we studied factors affecting health facility utilization among women in Bugesera district and we found that possession of health insurance, greater financial autonomy among women, more recent interactions with the health system, and previously delivering at a health facility were some of the factors stimulating women to use health facilities.

In the last few years, the government of Rwanda embarked on malaria control measures that lead to reduction of over 70% of malaria incidence in the whole country.

In **chapter 4** we studied the impact of malaria on pregnancy outcomes and we found that no effects of malaria incidence on pregnancy outcomes such the frequency of low birth weights, abortions and still birth. This is probably the result of the reduced endemicity of malaria in Rwanda and the country wide availability of low threshold prompt diagnosis and treatment. During the reduction of malaria endemicity, malaria specific immunity declines, pregnant women develop symptoms soon after infection and seek help. Promptly installed treatment prevents chronic placental infection. The low endemicity, low level of acquired malaria specific immunity and accessible health care facilities are the main arguments why intermittent presumptive treatment (IPT) of malaria is not implemented in Rwanda.

In **chapter 5** we studied the effect of acute malaria on pregnancy whereby we closely monitored pregnant mothers who developed malaria compared to those without malaria. The fetus was monitored by ultrasound and cardiotocogram (CTG) and maternal vital signs (pulse rate and blood pressure) were also closely monitored to measure the effects of malaria to both mother and fetus during acute malaria compared to those without.

It was found that maternal vital signs remained persistently higher (prolonged tachycardia) compared to the control group even after treatment with artemether-lumefantrine (AL, Coartem®) and effective parasite clearance. Fetal heart rate normalized immediately after treatment. These findings confirm that, in Rwanda, malaria in pregnancy presents as an acute febrile disease with no longstanding effects on the fetus.

But, even though no effects could be observed in the -fetus when looking with CTG- it was not known if the same is true for other effects that the treatment could have on the outcome of the pregnancy. AL is the only drug recommended in Rwanda to treat uncomplicated malaria albeit not registered for this indication. It has been used safely and effectively in the non-pregnant population but there was no clear evidence that treatment would have no effect on fetal development when the pregnant women uses it.

In **Chapter 6** we therefore conducted a pharmacovigilance study of AL in pregnancy. We followed over two thousand women (1,072 who had malaria and took AL and a comparison group of 978 pregnant women who had no malaria and hence no AL during pregnancy). We did not find any statistically significant difference between the two groups when comparing birth weight, birth outcome or birth defects and can therefore conclude that there are no frequent safety concerns for the use of AL during pregnancy.

In conclusion, it appears that malaria in Rwanda is not a major contributor to adverse outcomes of pregnancy anymore from a public health perspective but it can still give problems in individual patients, also in areas of low malaria transmission. This thesis shows that for individual cases the current treatment options are safe and sufficient but it remains of utmost important to closely follow pregnant women. Although most of malaria infected women will develop symptoms and seek help, active monitoring during pregnancy is important especially when their household members contract malaria parasitaemia should be treated. Only this special attention for the individual pregnant women, which is different from the IPT approach in other sub-Sahara countries, will ensure that malaria will not again cause the severe effects that it has in high endemic areas.