KNOWLEDGE, ATTITUDES AND PRACTICES ON MALARIA IN NEONATES AMONG GENERAL PRACTITIONERS IN DISTRICT HOSPITALS IN KIGALI CITY

A QUALITATIVE STUDY

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DECLARATION

I, Theodonata Tuyisenge, declare that this dissertation contains my own work except where specifically acknowledged.

Dr Theodonata TUYISENGE

Signed……..

Date: March 31st, 2019

DEDICATION

To God the Almighty,

To my husband Vincent and my son Beni,

To my parents, brothers and sisters.

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I am grateful to my Lord who gave me the life, knowledge and strength to be able to accomplish this work.

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ABSTRACT

Background: Malaria during pregnancy can lead to adverse effects on the mother, fetus and neonate. Neonatal complications include intrauterine growth restriction, low birth weight, prematurity, intrauterine fetal demise, increased risk of anemia and increased risk for malaria during the first month of life. Cases of malaria in neonates have been previously reported in Rwanda with lack of specific guidelines on care to be provided to a neonate exposed to malaria. This study aimed at assessing the knowledge, attitudes and practices of general practitioners working in urban area on neonatal malaria.

Methods: Qualitative data was collected through the use of semi structured interviews with 12 general practitioners working in maternity and neonatology wards at district hospitals located in Kigali City. The interview guide focused on the knowledge, attitudes and practices of general practitioners vis-à-vis diagnosing and managing malaria in neonates exposed to malaria in utero. A thematic analysis was applied to analyze data.

Results: Thematic analysis revealed ten themes. Most of interviewed general practitioners revealed to know both congenital and acquired neonatal malaria. For neonates born from mothers who had malaria during pregnancy or labor, participants would monitor vital signs, especially fever. Respondents consider malaria in neonates who have fever, jaundice, anemia, hepatosplenomegaly or any neonate whose sepsis is not responding to antibiotics. Participants would exclusively use blood smear to investigate for *plasmodia*, and consider investigating for sepsis for any neonate suffering from malaria and vise-versa. Some respondents define severe neonatal malaria the same as severe malaria in the older children, while others think that all cases of neonatal malaria should be severe. Artesunate was mostly reported to be used to treat neonatal malaria with some reporting the use of artemether-lumefantrine. Respondents consider giving antibacterials to neonates suffering from malaria. Discussants reported to educate families of neonate recovering from malaria on the diagnosis, management, breastfeeding and prevention strategies; and consider giving a follow up plan for reassessing the baby. Different websites, national and World Health Organization's guidelines and experienced clinical personnel were reported by participants to be consulted for information on malaria.

Conclusion: The study showed the awareness of neonatal malaria existence, different opinions in classifying and managing neonatal malaria. Our study suggests a strong need in the guidelines for management of neonatal malaria, especially at district hospitals.

Key wards: neonate, malaria, congenital malaria, general practitioner.

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LIST OF ABBREVIATION

ACT: Artesiminin-based combination therapy
CHUB: Centre Hospitalier Universitaire de Butare
CHUK: Centre Hospitalier Universitaire de Kigali
CNS: Central Nervous System
CRP: C-reactive protein
FBC: Full blood count
GP: General practitioner
IUGR: Intrauterine growth restriction
LBW: Low birth weight
PCR: Polymerase chain reaction
PI: Principle investigator
RDT: Rapid diagnostic test.
TORCH: Toxoplasmosis, Other (syphilis), Rubella, Cytomegalovirus, Herpes simplex virus
WHO: World Health Organization

CHAPTER 1: INTRODUCTION

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected female Anopheles mosquitoes. Plasmodium species are parasites responsible of causing malaria [1]. *Plasmodium falciparum* is responsible for most malaria-related deaths globally [1]. Ninety-eight percent of malaria cases in Rwanda are due to Plasmodium falciparum [2].

Malaria is an acute febrile illness. Patients with weak immunity present symptoms at seven days or more (usually 10–15 days) after the infected mosquito bite [1]. If not treated within 24 hours, *P. falciparum* malaria can progress to severe illness, often leading to death. The symptoms of malaria in young children includes lethargy, poor feeding and cough [3]. Uncomplicated malaria is defined by the presence of symptoms with positive parasitological test but with no features of severe malaria [3]. Patients whose malaria is severe, present with one or more of the following symptoms: coma, metabolic acidosis, severe anemia, hypoglycemia, significant bleeding, jaundice, shock, hyperparasitemia, acute renal failure or acute pulmonary edema [3].

Light microscopy and rapid diagnostic test (RDT) are two methods routinely used to diagnose malaria [3]. The gold standard test for malaria is microscopic examination of Giemsa stained blood smears [4,5]. The microscopy detects parasites when there is a concentration of above 20 parasites per microliter. Patients who are acutely ill are likely to have parasitemia which is detectable by microscopy [6]. RDT detects parasite specific antigen [3]. RDTs are able to detect more than 100 to 200 parasites/microliter and do not report the parasitemia or life cycle stages present. RDTs should be used to complement blood smears [6]. A patient whose symptoms strongly correlate to malaria and the first blood smear is negative; a series of blood films analysis should be repeated at every 6 to 12 hours along with an RDT. If both blood smear and RDT are negative, malaria is less likely to be the diagnosis [3]. Polymerase chain reaction (PCR) is used primarily as a research tool and it typically detects as low as 1 parasite/microliter [6].

Rational therapy of malaria is indispensable in order to avoid drug resistance and expenses to alternative, sometimes more expensive medications [4]. According to the 2015 World Health Organization (WHO) guidelines for malaria treatment, a combination therapy of at least two effective antimalarial drugs with different mechanisms is recommended for treating all episodes of malaria in order to protect current and future antimalarial medicines [3].

Prevalence of malaria in pregnant women is higher than in non-pregnant women of the same age, living in same geographic area [7]. Malaria infection is more common in primigravidae women than in multigravidae women [8]. In a study done in 2001 to assess the burden of malaria in pregnancy and its contribution to infant mortality in sub-Saharan Africa, Steketee and colleagues found that infection due to *Plasmodium falciparum* during pregnancy contributes to 2-15% cases of maternal anemia (400,000 cases of severe maternal anemia), 8-14% cases of low birth weight (LBW) and 3-8% of infant mortality (75,000-200,000 infant deaths annually). These

complications are more likely to happen in the first and second pregnancy [9,10]. Maternal anemia and placental malaria lead to prematurity and low birth weight. These complications are associated with higher morbidity and mortality in infancy [11].

Infants born from women who had malaria during pregnancy may suffer from consequences of gestational malaria, placental malaria or congenital malaria [12]. The adverse outcomes of malaria during pregnancy include intrauterine growth restriction (IUGR), low birth weight (LBW), prematurity, miscarriage, intrauterine fetal demise, increased risk of anemia during infancy and increased risk for malaria during the first month of life [12–15].

According to the 2014-2015 Rwanda Demographic and Health Survey, malaria remains a major cause of morbidity and mortality in Rwanda [16]. Its prevalence was 2% among children aged 6-59 months (versus 1% in 2010). Children age 48-59 months had higher prevalence of malaria (3%), compared to those aged 9-11 months. Malaria was more prevalent in rural areas than in urban areas (3% versus less than 1%). The WHO world malaria report of 2017 revealed that Rwanda had the worst increase in malaria cases from 2015 to 2016 (an increase of around 800,000 cases) [17] and in WHO world malaria of 2018, the trend has changed with a decrease of 430 000 fewer cases in 2017 compared with 2016 (although cases in 2017 still represent a more than 10-fold increase compared with 2011) [18].

A newborn infant, or a neonate, is a child aged less than 28 days. Reports on case series [19,20] had revealed that neonatal malaria exists in Rwanda and a number of challenges are associated with its clinical recognition, diagnosis and management [19]. In this study, we were interested to know how general practitioners are coping with difficulties vis-a-vis the diagnosis and management of malaria in the neonate age group as highlighted by our literature review.

CHAPTER 2: LITERATURE REVIEW

Full search description

We searched PubMed and the Cochrane database using the search strings in Table 1. We identified 114 relevant articles in PubMed. We did not find any articles in Cochrane. A secondary hand-search was performed of the reference lists of the relevant papers and found two additional relevant papers [15,21]. Two further complementary articles were found by a search in Google scholar [19,22] and no paper found in Cochrane database. An automated email update was set up on PubMed during the process of writing this literature review to ensure no new articles were missed.

Table 1: Search terms (MeSH terms in italics)

	(Congenital malaria)
OR	((Congenital OR *Infectious Disease Transmission, Vertical* OR vertical transmission) AND (*malaria OR plasmodium OR paludisme OR falciparum))*
NOT	*(vivax OR ovale OR antibodies OR HIV OR complement OR* toxoplasmosis*)*
FILTERS	Humans, English, Child: birth-23month. (387 items without filers).
Inclusion criteria	Infants with congenital malaria or risk of congenital malaria and papers describing *plasmodium falciparum*
Search date:	January 12th, 2017; October 24th, 2017 and March 3rd, 2019

Definition of congenital malaria

Congenital malaria is defined as the presence of asexual stages of malaria parasites in cord blood smear at delivery or peripheral blood smear of the baby in the first 7 days of life, irrespective of clinical symptom [13,23–26]. Congenital malaria is due to the transmission of malaria from the mother to the fetus just before or during delivery [13].

In endemic areas, congenital malaria may be difficult to differentiate from acquired neonatal malaria (which is due to an infected mosquito bite after birth). Acquired neonatal malaria can occur within first 28 days-of-life [13]. Infants who have congenital malaria usually present symptoms between 10-30 days postpartum. In some cases, clinical features can be present in 1 day old baby or they can be delayed for weeks to months. Thus, the definition of congenital malaria is still controversial [23].

Epidemiology of congenital malaria

The prevalence of congenital malaria was underestimated for a long time. Speculated factors that were associated with the report of low prevalence were that the placenta is a physical barrier to maternal infected red blood cells; the enhanced immunity in endemic populations led to the passive transfer of maternal protective immunity; and the high level of hemoglobin F in fetal erythrocytes was not favorable for *plasmodium* replication [23,27].

Cross-sectional studies conducted in sub-Saharan Africa on congenital malaria within the last two decades (1990-2010) revealed that congenital malaria prevalence ranged from 0% to as high as 54% [23,24,26]. Placental malaria was strongly associated with umbilical cord parasitemia which was suggested to be responsible for the congenital malaria [23].

Our literature search did not identify data or studies regarding the prevalence of congenital malaria in Rwanda. A case report of neonates at risk for congenital malaria, admitted in the neonatology unit (whose mother tested positive during labor) at CHUK from 2013 to 2016 revealed that of a total number of 2600 neonates infant admitted in neonatology unit, 17 neonates had mothers who had malaria during labor, and among these 17, four infants (23.5%) had positive blood smear during hospitalization [20]. Thus, there was a minimum annual prevalence of 0.04%. This case series only looked at babies who were admitted in neonatology unit, probably overlooking babies who had malaria positive mothers but were not admitted to the neonatology unit. However, using this statistic, with 250,000 births per year in Rwanda, there could quite feasibly be more than 100 cases of congenital malaria per year in Rwanda. At CHUB (Centre Hospitalier Universitaire de Butare), three cases of neonatal malaria reported to be treated successfully in the neonatal unit from July to September 2014 [19].

The big variation in prevalence of congenital malaria found in different studies could be defined due to differences in the definition of congenital malaria, the endemicity of the region, the level of maternal immunity, the methods and characteristics of the diagnostic tool used and the type of specimen collected. Other postulated factors are that clinicians are not widely aware of this burden, the disease has no specific clinical features, and the onset of the illness may be as late as until 4 weeks of life [5,23,24].

Transmission

The mechanism of transplacental passage of the malaria parasite from mother to fetus is still obscure. Postulated mechanisms are the direct penetration through chorionic villi, premature separation of the placenta and possible physiologic transfusion of maternal red blood cells to the fetal circulation in utero or at the time of delivery [23,28]. Some factors have been identified to increase the risk of transmission of malaria from the mother to the fetus, including: occurrence of severe malaria during pregnancy, absence of immunity especially pregnant women travelling to endemic areas, and maternal HIV infection [23].

Maternal to fetal transmission occurs most commonly during the intrapartum period [27]. Umbilical cord blood *plasmodium* infection may also be acquired antenatally because *plasmodia* may be found in cord blood at delivery and not in maternal blood. It is also possible to find discordant strains in maternal and cord blood [27,28]. Malaria in second trimester pregnancy can possibly cause placental damage and this permits the passage of infected maternal red blood cells to the fetal circulation [29].

HIV-associated impairment of antibody responses in pregnant women may contribute to a higher transmission of *Plasmodium falciparum* to their infant. The mechanism is that the virus might increase cord blood *Plasmodium falciparum* infection by decreasing maternal anti-malarial specific antibodies [30,31].

Clinical presentation

As previously mentioned, symptoms of congenital malaria arise 10-30 days postpartum [23]. Only 34% of parasitemic newborns would present symptoms within 3 days-of-life [24]. Many patients with congenital malaria will present with fever, anemia and splenomegaly. Other signs and symptoms that may be present are hepatomegaly, jaundice, regurgitation, loose stools, and poor feeding. Occasionally, patients may have drowsiness, restlessness, and cyanosis [23,25,32]. Malaria in the newborn may present as cholestatic jaundice alone [33].

Congenital malaria is commonly mistaken for neonatal sepsis or other congenital infections such as the TORCH infection. Neonatal sepsis is a life-threatening condition that must be considered, however a good index of suspicion and a careful physical examination are recommended in cases where malaria could be the cause [34]. In malarial endemic areas, clinical features of congenital malaria cannot easily be differentiated from those of neonatal sepsis. Therefore, any neonate with sepsis should be investigated for malaria. Furthermore, malaria should be ruled out in babies born from mothers who had fever in 2 weeks prior to the delivery [28,35]. This practice is infrequently done because of insufficient resources in many countries with high malaria prevalence [28].

Investigations

Diagnosis of congenital malaria is made by the microscopic identification of organisms on Giemsa-stained smears of peripheral thick or thin blood smears. This technique is associated with many pitfalls as such as: artifacts are often mistaken for parasites; young gametocytes of *Plasmodium falciparum* are often mistaken for *Plasmodium vivax*. Thus, single smear without parasites is not sufficient to rule out malaria and molecular tests such as the PCR has been used as a supplementary tool to provide more precise diagnoses [5,23]. Narrow sensitivity of blood film microscopy in detecting congenital malaria (comparatively to molecular tests) has been noted in different studies conducted in Africa [26].

Different studies had used umbilical cord blood to investigate congenital parasitemia (malaria). In babies whose cord blood was positive for malaria, it was rare to find it on microscopy of their samples taken at birth or in the few hours after birth [28].

Findings from a recent study in Western Kenya indicated that microscopy was able to reveal the prevalence of placental and cord blood *plasmodium* infections in 17.2% and 0% samples respectfully. This was compared to the results of real-time polymerase chain reaction (PCR) in the same study which showed 33.1% from placental samples and 10.8% from cord blood. In this study, the diagnosis of malaria in neonates using the microscopic technique was frequently missed [31]. As congenital malaria clinical features are similar to those of other neonatal infection, the authors in this study recommend that repetitive blood smear may be required to confirm the diagnosis [34].

PCR has been proven to be more sensitive than a blood smear for the detection of congenital malaria. However, evidence is still lacking whether a positive PCR result indicates active infection [24,36]. Therefore "caution is needed to interpret results based on PCR detection as parasite macromolecules and not live parasites crossing the placental membrane may give a positive PCR result in cord blood" [28].

Rapid diagnostic tests (RDT) are the most widely used diagnostic tests for malaria; they are easy to use, affordable, and reliable. Therefore, they can be used at peripheral levels. The validity of RDT for the diagnosis of congenital malaria is not yet proven [24]. RDT false positive results for diagnosing congenital malaria (control done by PCR) have been detected in prevalence studies conducted in Burundi and Burkina Faso [24,26]. In the study conducted in Burkina Faso, congenital malaria infections cases with high cord blood parasitemia tested negative on RDT and cases that tested positive on RDT were not associated with high parasite burden in cord blood with one false positive. In both studies from Burundi and Burkina Faso, RDT false positive cases were from neonates born from mothers with high peripheral smear parasite count. Therefore, positive cord blood RDT may be due to transplacental transfer of maternal antigen instead of an active congenital infection [24,26].

Treatment of confirmed cases of congenital and/or early neonatal malaria

Established specific protocols for the clinical management of congenital or neonatal malaria are still not available in Rwanda or globally. The authors of this study contacted members of the Rwandan Neonatal Working Group and members of the WHO malaria group and confirmed that newborns are considered in the category of children weighing less than 5kg. In the current 2015 WHO malaria treatment guidelines, there is no specific information regarding the diagnosis and management of malaria in the subgroup of neonates (including premature and very low birth weight).

Non evidence-based suggestions recommend that severe cases of congenital malaria should be managed with intravenous quinine or with intravenous artesunate [23].

In a congenital malaria prevalence study done in Nigeria, 62.1% of neonates who had parasitemia obtained spontaneous clearance of parasites without using antimalarial medications [37]. Some studies suggest that congenital malaria is infrequently associated with clinical disease [23].

A study done in China comparing the efficacy of artesunate versus quinine in the treatment of congenital malaria observed that the total effective rates were 92.31% and 83.33%, respectively, and the clearance rates of plasmodium were 92.31% and 78.57% [23].

Artesiminin-based combination therapy (ACT) containing sulphadoxin-pyrimethamine is not recommended during the first 6 weeks of life because of the immaturity of the neonatal enzyme system [3]. Primaquine should be avoided in the first 6 months of life because no data on its safety in this age group are available. Primaquine also causes hemolysis in a fetus with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency [3]. Otherwise, there is no evidence of specific serious toxicity of other ACT. However, additional efforts should be made to establish their safety profile. ACT offers greater efficacy and tolerability in children compared with quinine [3,23,32].

The WHO recommends treating children weighing <20kg who have severe malaria with a higher parental dose of artesunate (3mg/kg/dose) than in children >20kg (2.4mg/kg/dose). The reason for differentiating the doses is to ensure equivalent drug bioavailability in both groups [3].

Infant weighing <5kg with uncomplicated malaria are recommended to be treated with ACT at the same dose as in children weighing >5kg (strong recommendation). But WHO states that it is still lacking sufficient evidence for confidence in current treatment recommendation in infants weighing <5kg. This is due to the fact that in most clinical studies, this subgroup was not considered different from older children. The target dose for Coartem tablet (20mg artemether/120mg lumefantrine) is 5-24mg/kg body weight of artemether and 29-144mg body weight lumefantrine. Monotherapy use is not an appropriate and/or optimum approach to the treatment. Pediatric formulations should allow accurate dosing without needing to break and/or dissolve tablets and should promote adherence by their acceptability to children [3].

In Rwanda, the Pediatric Clinical Treatment Guidelines of 2012 recommend use of artesunate 2.4 mg/kg/dose as first-line drug in the treatment of severe malaria. Intravenous quinine is the second option when artesunate is not available. Artemether-lumefantrine is indicated in the treatment of simple malaria but it is contraindicated in children weighing <5kg. The guidelines provide the option of using quinine 10mg/kg/dose 3 times daily for 7 days. In the Rwandan neonatal guideline there is no specific standard regarding the management of malaria in newborns [2]. Cases managed at CHUB in 2014 were treated with intravenous artesunate 2.4mg/kg/dose for 7 days, none of them received ACT [19].

In Tanzania, quinine is the drug of choice in treating congenital and acquired neonatal malaria in all cases of malaria with infants weighing <5kg [38]. In Kenya, Mwaniki et al. used intravenous quinine in treatment of children who tested malaria positive during their prevalence study from 2002 to 2009 [39]. In Burkina Faso, a recent study aimed to detect the prevalence of congenital malaria; neonates who tested positive were treated with artesunate-amodiaquine or artemether-lumefantrine according to national guidelines [26].

Problem statement

Recently, Rwanda has seen a significant increase in the rate of malaria [17]. It is also known that pregnant women are more likely to have malaria than non-pregnant women [16]. Therefore, there is a fear that cases of congenital malaria may continue to rise in Rwanda and that this may have an impact on neonatal mortality which is currently 20 deaths per 1000 live births [16].

The incidence of congenital malaria globally, and in Rwanda, is still not accurately known. But the evidence shows that cases of malaria in newborn infants exist in Rwanda [19,20].

There are a number of challenges related to the investigation and management of malaria in newborns and available information related to every issue:

1. Clinical features for congenital or acquired malaria are similar to those of common neonatal illnesses. No suspicion index mentioned in current WHO guidelines for treatment of malaria and the current Rwandan neonatal protocol.
2. Some features like signs of respiratory distress, prostration, hypoglycemia and jaundice that are stated by WHO as signs of malaria severity may be due to prematurity or other common illnesses of newborns. Hyperparasitemia is uncommon in congenital malaria.
3. WHO recommends considering severe malarial anemia when hemoglobin is ≤5gr/dl or hematocrit is ≤15% in children ≤ 12years of age [3]. These values may be very low to be considered in neonates who usually have high hemoglobin concentration.
4. Light microscopy of blood smears and RDT recommended by WHO in confirming malaria frequently miss congenital malaria cases. PCR that has a higher sensitivity in confirming this disease is expensive and recommended to be reserved for research purposes. There are no recommendations from current WHO guidelines for malaria treatment regarding using cord blood in detecting congenital malaria.
5. The WHO recommend use of ACT as first line in management of malaria in children and provides specific recommendations of how to use them in children weighing <5kg. It is not clear if newborns (including preterm babies with LBW) are considered in the same category (for instance, we do not know if premature neonates with very low birth weight are considered in the same category as infants weighing <5 kg).There is a wide range of artemether-lumefantrine dose which is recommended in children weighing <5kg. Given the available formulation of this drug (tablets), it would be difficult use it in preterm neonates with LBW.

Research aim

This study aims to deduct the knowledge, attitude and practices of general practitioners (GP) working in district hospitals regarding neonatal malaria in Rwanda.

Research objectives

This study has the following objectives:

1. To evaluate GPs knowledge and attitudes on clinical approaches to the neonate exposed to malaria and to identify the clinical features in the neonate that GPs consider as suggestive of malaria.
2. To assess if and how GPs classify malaria in a neonate (i.e. simple or severe) and inquire about medications (type of drug, dose, route and duration) they use in treating malaria in different categories of neonates (preterm, term, low birth weight).
3. To determine the education and follow up plan provided by GPs to the families or mother with a neonate confirmed to have malaria.

CHAPTER 3: RESEARCH METHODOLOGY

Reporting:

Reporting of the current study proposal was verified in accordance with the COREQ and SRQR checklist [40,41].

Study design:

This was a qualitative research study employing semi-structured face-to-face interviews.

The purpose of qualitative research is to understand the perspectives/experiences of individuals or groups and the contexts in which these perspectives or experiences are situated [41]. This phenomenological framework attempted to understand the ideas, situations and problems from general practitioners experience in treating malaria in neonates.

Qualitative design - Interviews [40]: This study used face-to-face, semi-structured interviews in order to gain the experience of GPs in taking care of neonates who have the potential for malaria. Twelve interviews were conducted with GPs working in neonatology services at Muhima, Kacyiru, Kibagabaga and Kacyiru District Hospitals. Interviews focused on how GPs clinically suspect, investigate and manage a newborn with probable malaria.

Qualitative research paradigm: A phenomenological approach was taken. This approach describes the meaning for several individuals of their lived experiences of a concept or a phenomenon. In this study, the principal investigator interpreted the experiences described by GPs of treating malaria in newborns (interpretative paradigm), described and reflected upon this experience.

Study sites

Four district hospitals from Kigali City were involved in this study. These hospitals are Kibagabaga Muhima, Masaka and Kacyiru Hospitals.

Kacyiru and Kibagabaga Hospitals are both public hospitals located in Gasabo district, with Kacyiru located in Kacyiru sector and Kibagabaga located in Kimironko sector. Masaka District Hospital is a public hospital of Kicukiro district, located in Masaka sector. Muhima Hospital is public hospital located in Nyarugenge district, Muhima sector.

Study population (Participants)

Inclusion criteria: All general practitioners working at Kacyiru, Muhima, Masaka and Kibagabaga district hospitals were eligible for our interview. The participants' clinical working language was Kinyarwanda plus French or English.

Exclusion criteria: Excluded GPs were those who neither worked in maternity nor in neonatology.

Recruitment:

This study used a purposive sampling method. The principal investigator worked with the clinical directors at each district hospital to identify GPs working in maternity and neonatology wards, and their schedule. Selected participants are GPs who were on day shift when the PI arrived at the target district hospital. GPs were approached for recruitment by telephone, having gained the phone numbers from the hospital and the interview time was planned according to their availability.

Saturation and sample size:

Saturation is defined not in terms of theoretical development, but simply when information from analysis produced "little or no change to the codebook" [42]. After every interview, data were transcribed/coded and a thematic analysis undertaken prior to the next interview. This continued until our codebook did not change (i.e. saturation). Once saturation was achieved, two further interviews were conducted to ensure that saturation has been reached. Guest et al. (2006) stated that 6-12 participants are normally sufficient to gain saturation in the majority of qualitative projects [42,43]. During this study, saturation was reached after conducting twelve interviews.

Interview guide (questionnaire):

An interview guide (see appendix) written in English and French (as preferred by the subject) was developed specifically for this study. The questionnaire was revised by supervisors for content validity. Supervisors were pediatricians experienced in neonatal medicine or qualitative methods. The interview guide was piloted on one year-1 postgraduate Internal Medicine resident (without recording and/or transcription) to ensure good understanding of the questions and to produce the initial themes and codebook. This subject was chosen due to their proximity in experience to a GP. The questions were well understood and no alterations to the questions were required during this piloting.

To obtain a good interview data, the purpose, general outline and the duration of interview were communicated to the participating GP at the beginning of every interview. Consent forms were signed as well; the interview started with recall questions and the assessor did her best to be attentive and non-judgmental.

During the interviews, if the subject did not initially understand the question posed, the interviewer (PI) would adapt the wording of the questions, without changing meaning. Participants were encouraged to move between languages, if it enabled them to better express their responses.

Ethical considerations and approval
Ethical approval:

This study was approved by the Institutional Review Board (IRB) of the school of Medicine at the University of Rwanda (Approval notice: No 354/CMHS IRB/2018), all involved district hospital Directors, the Rwanda Biomedical Center (Ref: No 1643/RBC/2018), the National Health Research Committee (Ref: NHRC/2018/PROT/045) and the Minister of Health (No 20/9714/DGPHFIS/2018).

Risk for participants

The principle of beneficence entails maximizing benefits and minimizing harms to research subjects. All research is associated with a certain degree of risks. Risks are categorized as physical, social, emotional, legal and financial. It is our judgment that this study process did not incur any significant risks to the participants.

Physical risks: None noted

Social risks: Participants may be reluctant to report previous cases of neonatal infection with bad outcomes for fear of judgment or professional outcomes. This risk was mitigated by all responses being kept confidential.

Emotional risks: Neonates with malaria may have poor outcomes (including death). Some participants may find it distressing to recall these events. However, the cases are not eccentric in the usual day-to-day clinical practice encountered by GPs.

Legal risks: None noted.

Financial risks: The mean time for interview was 10 minutes and 54 seconds (10:54). This could have incurred financial loss to the participant, however the interviews were done in working hours therefore, this risk is minimal and participants were free to decline entry to the study.

Confidentiality: All information that can lead to the identification of any participant was made anonymous during transcription and all process of data analysis.

Funding & Sponsors: This project had no available funds. No funding has been sought or gained for the study. The transport, communication and printings were paid by the principal investigator.

Incentives for subjects: Subjects did not receive any incentives for their participation in this study.

Potential conflict of interest: None

Consent form

A consent form for participating in the study and voice recording acceptance was signed before every interview (see appendix). The consent form has been piloted for understanding by a year -1 Postgraduate in Internal Medicine.

All participants were preliminarily informed that the results of this study may be used by health care policy makers in the development of pediatric clinical treatment guidelines. Interviewees were also informed that there is a possibility that the results of this may be published in national or international journals.

Data collection and processing

Setting of data collection: Data were collected at hospital sites, in GP offices or another quiet room. All interviews were conducted during working hours of week days. No other persons were present during the interviews except the interviewee.

Repeat interviews: repeat interviews were not performed.

Researcher/Interviewer: The principle investigator (PI) is a female, fourth year resident in pediatrics and child health. The project was undertaken as the research memoire for her MMed in pediatrics. She is fluent in Kinyarwanda, French and English to degree level. She has no previous experience of qualitative research and was therefore given one-to-one training in interview techniques from her supervisors. She has received training in research as part of her MMed in pediatrics.

Relationship with participants: The PI had no personal or professional relationship with any of the participants. Participants had no prior knowledge regarding the researcher and therefore were given information on the goals of the researcher and the reasons for doing the research in the information sheet.

Data collection process: The purpose of the study was explained by every participant, a consent form was then signed by participants, and then they filled with the demographic information. The face-to-face interview was then conducted using an interview guide. At the end of the interview, the participant was asked if she/she needed to provide a feedback in the transcripts and thanked for the participation to the study.

Ensuring good quality data:

Minimizing bias: To minimize the investigator bias, a protocol specific for data collection and analysis in this study was developed and respected, any alteration of data was avoided, and different supervisors reviewed the data and helped to draw conclusions.

Validation by subjects: Participants were given the option of having their own transcript sent to them (via email) to ensure correct transcription. All participants declined to review their transcripts. Participants were not given the opportunity to provide feedback on the findings of coding and analysis as it was beyond the scope of the resources of the project.

Duration: The recorder had a timer and the duration of each interview is known. Interviews lasted between 7 and 19 minutes. Data were collected from November to December 2018.

Recording: Interviews were recorded using digital voice recording. Two digital voice recorders (Two mobile phones) were used during interview in order to minimize the risk of losing data due to recorder malfunctioning. The interviews were stored electronically on a password protected laptop.

Field notes: Field notes were taken during the interview and used during analysis.

Transcription: After each interview, data was transcribed verbatim directly into Microsoft Excel [43,44]. This was performed by the PI or by a trained research assistant who is competent in Kinyarwanda, and English (by degree) and then double checked by the PI. One interview was undertaken in French and was transcribed and translated by the PI.

Translation: One interview was administered in French, a translation was performed by the PI (she has a certificate of French knowledge provided by National University of Rwanda). No back-translation was performed as it was beyond the feasibility and financial availability of the study. The advantage of the PI undertaking all the translation work was that it allowed for additional immersion in the qualitative data.

Software: Interviews were transcribed, translated, coded and analysed in Microsoft excel.

Coding: A code can be thought of as a label; a name that most exactly describes what this particular meaning unit is about. A code is usually one or two words long [45]. An initial code book was created prior to starting questionnaires based on the pilot interview. New codes and themes were then added as interviews progressed. A theme is seen as expressing an underlying meaning [45].

Data security: Transcriptions and translations are kept confidential by keeping the responses in a password-protected personal laptop of the PI and supervisors. No participant identifiable data was kept in the digital recording file. Pseudonyms (false names) were used in transcripts whenever the participant mentioned any name.

Thematic analysis

Analysis was done using Excel. A Thematic analysis was undertaken. The following steps were taken during data analysis [46,47]:

Step 1. Familiarizing with the data: Transcribing data, reading and re-reading the data, noting down initial ideas.

Step 2. Generating initial codes: Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.

Step 3. Searching for themes: Collating codes into potential themes, gathering all data relevant to each potential theme.

Step 4. Reviewing themes: Checking if the themes work in relation to the coded extracts and the entire data set, generating a thematic 'map' of the analysis

Step 5. Defining and naming themes: Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.

Step 6. Producing the report: The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

CHAPTER 4: RESULTS

Participants' demographic information:

Twelve general practitioners (GPs) were recruited from four district Hospitals (Kacyiru, Kibagabaga, Masaka and Muhima). Three GPs were recruited from each site. One eligible GP declined to participate in the study due to time constrictions. The mean duration of interview was 10 minutes 54 seconds.

Table 2 : Demographic information

ID	Age (years)	Gender	Graduation from medical school	Experience in working as a GP at DH (months)	Experience of work in neonatology (months)	Ever received neonatal malaria cases
1	33	M	2015	36	36	Yes
2	30	M	2016	24	24	Never
3	29	F	2016	24	24	Yes
4	28	F	2015	36	36	Yes
5	25	F	2017	10	10	Never
6	30	F	2015	36	8	Yes
7	42	M	2008	131	9	Yes
8	33	M	2014	36	36	Yes
9	28	M	2017	15	12	Never
10	31	F	2014	48	36	Yes
11	43	M	2013	60	18	Never
12	28	M	2015	36	36	Never
Mean	**31.7**		**NA**	**41**	**23.8**	**NA**

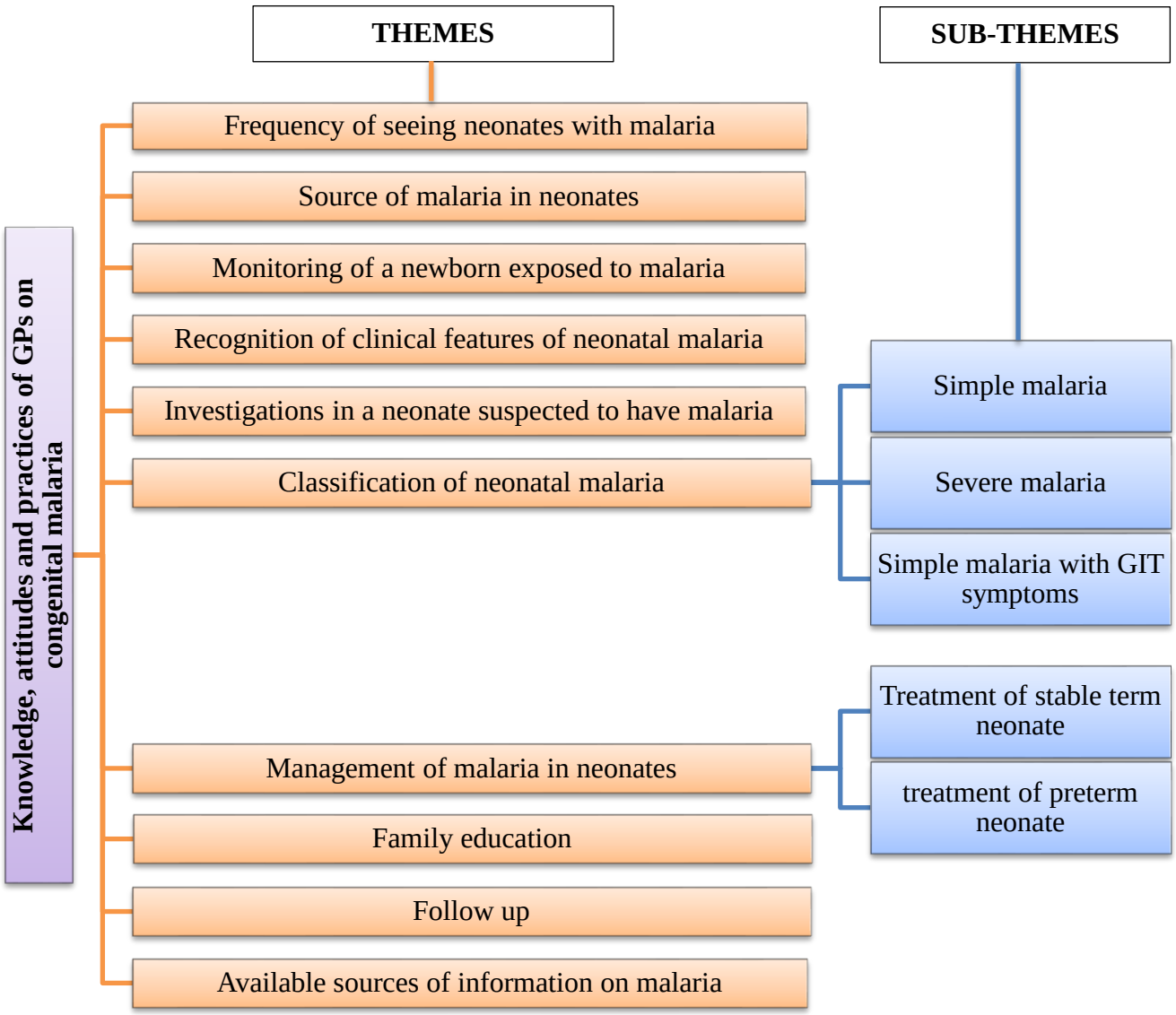
Among 12 participants, seven were male and five were female (Table 1). Their age ranged between 25 to 43 years (mean age of was 31.7 years) and the average duration of working as a GP at district hospital was 41 months. The average time of working in neonatology was 23.8 months (lower duration: 8 months, higher duration: 36months).

Knowledge, attitudes and practices of general practitioners on congenital malaria

A total of ten themes were identified during the thematic analysis (Figure 1). These includes knowledge on the source of malaria in neonates, monitoring a neonates exposed to malaria, recognition of clinical features of neonatal malaria, investigations for a neonate suspected to have malaria, classification neonatal malaria, management of malaria in newborns, family

education, follow of a neonate recovered from malaria, previous GP's experience in malaria and available source of information on malaria.

Figure 1: Thematic tree



Theme: Previous experience in treating neonatal malaria

Despite preventative measures, cases of neonatal malaria continue to be seen by Rwandan GPs. Our participants were asked how often they treated cases of neonatal malaria and most of them replied that they had seen these cases during their working experience.

> "*One to two cases per month*" (Interview 3, female)

> "*The cases of malaria in a newborn are not frequent. In my life here at district hospital, I have seen like two cases, two cases with malaria in newborns in the period of one year [of employment], I have seen only 2 cases of malaria*" (Interview 7, male).

There was a variation in the number of cases of neonatal malaria managed by different general practitioners from seeing these cases on monthly basis to never see any such case during the period of 5 years of working at hospital. Respondents reported to more frequently see these babies in pediatric wards when they come back from home few days after birth.

Fewer GPs had never seen a case of neonatal malaria. Their mean level of experience was 29.2 months compared to 51.8 months for those GPs who had seen cases.

> *"For the 10 months I have been working as a doctor, I have never received a neonate with malaria"* (Interview 5, female).

Some participants reported that they think they never see these patients because neonates who have already been discharged home from the nursery and subsequently need admission are typically referred to a tertiary hospital.

Theme: Knowledge on the acquisition of malaria in neonate

Participants were asked the ways a neonate can acquire malaria and according to their responses, interviewed GPs revealed that they were aware that a neonate can acquire malaria in the neonatal period, especially when the mother had malaria during pregnancy, but also that a neonate can acquire malaria from a mosquito bite.

> *"I think, maybe, it can be acquired from mosquito, bitten by mosquito, but also, from the mother, placental, something like that. If the mother was having malaria, it can pass from the placenta, but it rare"* (Interview 7, male).

> *"Ahh [thinking], maybe congenitally from the mother, but also as other patients, from mosquito's which are infected by parasites. It is also possible"* (Interview 10, female).

Knowing both possibilities of acquiring malaria can enable GPs to consider this diagnosis in sick neonates even in the absence of positive maternal malaria history.

Some participants could only recall that neonates exposed to malaria are the ones that are at risk of suffering from neonatal malaria. They were unaware of the risk of mosquito transmission in the neonatal period.

> *"A neonate can get malaria from her mother. Thus, a mother who is pregnant, at the last days of her pregnancy, during the last hour of delivery, she may have malaria. If it is not well treated there is a risk to contaminate her newborn"* (Interview 1, male).

The knowledge on possibilities of congenital malaria in cases of maternal malaria is a good step in early investigation of malaria in cases that these newborns are sick as mentioned by one participant.

Some GPs reported that they were ignorant regarding congenital malaria.

> *"Ahh [thinking], well, it could be from a mosquito if the mother is not very careful, I am not sure about the congenital malaria, but I think it exists"* (Interview 5, female).

Insufficient information on congenital malaria can lead to overlooking the diagnosis and cause delays that will increase the associated morbidity and mortality.

Theme: Monitoring of a newborn exposed to malaria

Participants were asked their attitudes on monitoring a neonate born from a mother who had malaria during pregnancy or labour. Their responses indicate that they would monitor the neonate's vital signs for signs of malaria, especially fever, feeding capacity and do blood smear to investigate for malaria.

> *"I want to monitor for fevers, inability to breastfeed, but, also to check for hemoglobin and platelets after 24 hours" (*Interview 4, female).

> "Y*eah, like neonates I will monitor for any fever, if she peaks fevers, I will test malaria and see*" (Interview 10, female).

This attitude enables health care providers to detect cases of congenital malaria early and leads to early treatment and improved outcome.

Some respondents reported to consider probable concomitant neonatal bacterial infection and admitted the baby in neonatology, screen for malaria and sepsis by doing blood smear and full blood count (FBC) respectively; and treated these babies with antibiotics.

> *"This neonate after birth should be admitted in neonatology intensive care unit [neonatology unit], [pause for reflection] and requests for blood smear,[pause for reflection] and treat as neonate with neonatal infection risk, give antibiotics, do blood smear blood, and blood sugar then to, to wait the results"* (Interview 3, female).

Mothers who have malaria during labor may have intrapartum fever. As this can be also a sign of chorioamnitis, general practitioners consider t to be observant for neonatal sepsis which may result from this maternal infection.

Most interviewees GPs consider that these babies may present delayed symptoms of malaria. The GPs plan to give an outpatient appointment for reassessment.

> "*If the mother was tested positive malaria during birth , we take the baby in our neonatology and we monitor the neonate, taking the blood smear and also tested the placenta if there is any plasmodium in that sample of placenta. We monitor for ahh [pause to think], we monitor about, about 3 days, we monitor the fever, we monitor the blood smear, if the baby becomes negative and there is no any indication, and we look also on the platelets of that neonate, if the platelet is decreasing for taking a full blood count and we suspect there is something wrong, if there are no abnormalities according the lab results, we discharge the patient, they come back after 1 week , the baby come back for consultation in OPD for follow up*" (Interview 11, male).

Congenital or neonatal malaria is more prevalent than previously described. The diagnosis can be easily missed if no screening measures are available in the neonatology unit located in malaria endemic regions [48].

Theme: Recognition of clinical features of neonatal malaria

Participant were asked the clinical features they consider for a neonate to have malaria. GPs responded to consider any neonate to have possible malaria if fever is not decreased by use of antibiotics, or any sick neonate whose mother had malaria during pregnancy.

> *"First of all you suspect it from the history; first of all you suspect it from the history, then also, for the baby, I think for the neonate, I think she will have persistent fevers, despite other antibiotics given and also the baby will deteriorate with time, yeah"* (Interview 12, male).

> *"For the baby with anemia, low platelets, without any history of bleeding at birth or no other signs that can indicate maybe neonatal sepsis, in that case, and if the mother has*

history of malaria[during pregnancy], in that case we start suspecting malaria in the newborn" (Interview 4, female).

The most common sign of congenital malaria is fever, with it being present in more than 90% of infected patients. Other features include jaundice, poor feeding, hepatosplenomegaly, anemia, bleeding tendency, respiratory distress, body weakness, excessive crying, tachycardia, etc. ; as also reported by our participants [13].

Participants who have not seen cases of malaria in neonates believe that these newborns suffering from malaria may have symptoms comparable to those of adults with malaria.

"I think it is the same as other children or adults and [pause], who have fever, physical asthenia sometimes they will be pale if hemoglobin is decreasing because of hemolysis ahh[pause], I am not sure about shivering, I wouldn't add it, I don't know about shivering". (Interview 5, female).

It is important to recognize that some features of malaria in adults, like shivering, may not be present in neonates [49].

Neonates who are suffering from malaria may present with complications when admitted to the health facility [50].

"But a newborn can also have convulsion, a newborn can convulsions, thus we consider, with history of malaria to the mother, with the fever, we can consider that it is also severe malaria .This is already a sign of severity" (Interview 1, male).

It is also meaningful to recognize that patients may present symptoms related to complicated malaria like convulsions, anemia and thrombocytopenia.

Participants who had never seen cases of malaria in neonates were more likely to suggest that these neonates present with convulsions, inability to breastfeed well, and fever.

"*As I didn't treat any neonatal malaria, but I think we can be based on convulsion, fever which is not related to infection or other causes in neonates, and also when the baby is not well breastfeeding and we can use blood smear to test for it*" (Interview 6, female).

It is significant to recognize that non-specific signs of neonatal illnesses may be due to malaria, especially in endemic areas. A request for a blood smear for any sick newborn may reduce mortality.

Some GPs highlighted that neonates presenting with clinical features of malaria, such as fever, should be systematically screened for malaria and other serious infections.

"Like high grade fever, temperature above 39 degrees, baby who is crying and who is not breast-feeding, and probably tachycardia, pulse will be high, will be, the heart rate

will be increased and yeah . You know, as we are living in endemic area of malaria, ehh, [pause to think], every baby who has fever should undergo blood smear test as differential to infection or sepsis, so it should be systematic blood smear test for newborn with features of fever or malaria or other things, Thank you" (Interview 8, male).

Other reports suggest that where malaria is common, any newborn with sepsis should be investigated for malaria [28].

Regarding the timing of clinical features of neonatal malaria, GPs think that malaria symptoms may present from the first day of life.

"Huh, the clinical features, is, first one is the fever. So, fever on day one or on day zero or day one [hesitating]And also when the neonate is not tolerating the feeding and also when the neonate is becoming jaundiced on day one or at the following days another one , it's when [pause], another feature it is when you give, you consider this neonate, neonate with neonatal infections risk and after five days of giving antibiotics, you see there is no response, you change for the antibiotics, there is no response, you should also think of malaria to be tested" (Interview 3, Q8, L192-198)

Generally, the clinical features of congenital malaria appears between 10 to 30 days of life [13]. Some studies suggested that the mean time for congenital malaria clinical presentation was 3 days [25,51].

Theme: Investigations of a neonate born from a mother who has malaria

Participants reported undertaking different investigations to screen for neonatal malaria and its complications. These included a blood smear, full blood count (FBC), liver function tests, bilirubin, renal function tests, electrolytes, blood sugar, C-reactive protein (CRP), and testing samples from the placenta for plasmodium pathological examination.

"I have to take full blood-count, CRP after 24 hours, and then I have to test for [pause to think] to take blood smear for this baby" (Interview 9, male).

The microscopic identification of *Plasmodium* organisms on Giemsa-stained peripheral thick or thin blood smears is the current gold standard for diagnosis of congenital malaria [52]. As congenital malaria may be a differential diagnosis for sepsis, GPs also consider FBC and CRP tests.

FBC will also help to identify malaria complications like anemia and thrombocytopenia. As jaundice is one of the signs of malaria, participants reported to test for bilirubin.

"*As I was saying, by recording vital signs especially fever or temperature, or pulse, or oxygen saturation, or if there is any sign or symptom like baby [is] not breast-feeding or*

crying too much. So, we should think about malaria and test it by blood smear, CRP or, to test for sign of infection or inflammation; if there is neonatal jaundice, we can check bilirubin and other, to see if there is hemolysis, we know that malaria causes hemolysis, so that is what I think I have to take full blood-count, CRP after 24 hours" (Interview 8, male).

An increase in bilirubin in neonates may be the usual physiological jaundice, to the hemolysis secondary to malaria or any other neonatal infection. It may be difficult to confirm that jaundice in a neonate who has malaria resulted from malarial hemolysis, hence severe malaria.

Placental malaria is suspected by one participant to be responsible for transmission in congenital malaria.

"*We take the blood smear and also tested the placenta if there is any plasmodium in that sample of placenta*" (Interview 11, male)

Doing a pathological exam on the placenta may not be easily done at district hospitals. Results of samples sent to the referral hospital might be timely extensive. It is also not clear if placental malaria directly indicates congenital malaria.

Theme: Classification of neonatal malaria

Our respondents reported that they would use adult classification signs of malaria to determine the severity of neonatal malaria. A neonate who has one of the following signs with a positive blood smear would be considered to have severe malaria: convulsions, anemia, renal failure, respiratory distress, and hypoglycemia. According to the participants, a neonate with positive blood smear plus one of the following symptoms is considered to have simple malaria; these include fever, refusal of breastfeeding, and inconsolable cry.

"… for the newborn, we can also take these adult signs, these signs that I have just said, the signs of severity in the adult, we can also observe them in the neonate but not all the signs. But a newborn can also have convulsion, a newborn can convulsions, thus we consider, with history of malaria to the mother , with the fever, we can consider that it is also severe malaria .This is already a sign of severity, and a newborn who is having anemia, who is severe respiratory distress with history of malaria, we can already consider as the severe malaria, or a newborn who is in renal failure , this is also a sign of severity, but simple malaria is when there is fever the child can refuse to breastfeed , and he can have inconsolable cries, and this can be cold simple malaria. But what I just told you, convulsion, difficulty in breathing, I mean severe respiratory distress, and he has anemia or hypoglycemia too, I had forgotten hypoglycemia too and renal failure, these are the signs of severity" (Interview 1, male).

Most of the symptoms reported by our participants regarding severe malaria match the WHO classification for severe malaria in children and adults. Refusal of breastfeeding and inconsolable

cry in neonates are generally considered as signs of neonatal sepsis (with possible meningitis). It is not clear if these signs would indicate uncomplicated disease in cases of neonatal malaria.

Table 3: Classification of severe neonatal malaria (comparison between our results and WHO criteria for severe malaria)

Items suggested by GPs	WHO classification of severe malaria
• Anaemia (<10 (gr/dl) • Acute kidney injuries • Convulsions • Hypoglycaemia • Respiratory distress/pulmonary oedema • Poor feeding • Vomiting • Shock • Age (neonatal malaria should be severe malaria) • End organ failure (liver, CNS, kidneys)	• Impaired consciousness • Prostration • Multiple convulsions • Acidosis • Hypoglycaemia • Severe malarial anaemia: Hb of ≤5g/dl in children <12 years • Renal impairment • Jaundice • Pulmonary oedema • Significant bleeding • Shock • Hyperparasitemia: [3,53]

Hb: Hemoglobin, **Hct:** Hematocrit **CNS:** central nervous system

One participant said that they would consider a different level of hemoglobin in neonates to confirm severe anemia.

> *"So, I would classify it as simple if the baby is not having severe anemia, with hemoglobin of less than 6.5 (gr/dl), ehh ok in neonate it's less than 10 (gr/dl). Then I would say it is severe if there is end organ damage like features of acute kidney injuries, if there is an involvement of the liver, CNS (central nervous system). If the neonate is in respiratory distress, I would be thinking of, there is about pulmonary edema. And as I was saying, if there are no signs of these, if there are no sign showing that kidney, lungs, brain or heart are affected, I would take it as simple"* (Interview 2, male).

WHO recommends to consider hemoglobin of 5g/dl in children less than 12 years [3]. Other recommendations suggested that in neonate with no signs of decompensation, hemoglobin of <7g/dl would be considered as severe [54] , and higher transfusion thresholds for neonates are recommended depending on the days of life and the need for respiratory support [55,56].

Some respondents reported that in any neonate with malaria, the illness should be considered severe because complications such as jaundice and anemia are more likely to occur.

"*When the blood smear is positive for this neonate, I will consider this malaria as severe because in the neonatal period the malaria, I said there is congenital and acquired malaria, so it is severe because it is the neonate. It occurs in neonate period because most of the time it causes jaundice and anemia"* (Interview 3, female).

"Huuh [thinking] I don't know, but, I think in a neonate it should be considered as severe malaria. But I don't know how to differentiate simple and severe [malaria] in neonatology" (Interview 5, female).

Neonatal jaundice may be physiological or pathological; and generally, bilirubin levels in neonates are higher comparatively to the remaining population. In case of neonatal hyperbilirubinemia in malaria endemic areas, it is important to consider malaria as a possible cause.

One participant reported the possibility of classifying neonatal malaria as simple, severe and with gastro-intestinal tract (GIT) symptoms.

"Simple it's just if there are no other signs, neurological like convulsion, seizure, this will be like severe malaria, neurologic form, if there is vomiting, diarrhea, difficult or absence of breastfeeding, it will be like malaria with GIT (gastrointestinal tract) symptoms" (Interview 8, male).

Loose stools and poor feeding are commonly reported as clinical signs of congenital malaria.

Theme: Management of malaria in newborns

Subtheme: Treatment of term stable neonate

Several participants reported using artesunate to manage malaria in neonates. (Most of them suggested a dosage of 2.4 mg/kg/dose for 7 days.

*"So in our settings we do not have, I would go for IV [intravenous] artesunate, but we don't have oral or syrup of coartem, so I will give IV artesunate. Ahh, I will calculate via ahh [pause to think] ok I would go for the dose of 2.4mg/kg per dose, not 3 (mg/kg). I do not have updated information for going, if the government adopted, I mean, Rwandan MOH approved to use 3mg/kg I am not sure, that' why. I will treat it for 7days" (*Interview 11, male).

Some participants are aware of the WHO artesunate dose recommendation in children weighing <20kg, but they prefer to prescribe it as stated in the Rwanda national guidelines for malaria treatment [53]. Their preference is to wait for these local guidelines to be updated according to the WHO malaria treatment guidelines. It is true that artesunate is given by intravenous line. Participants reported different duration for the treatment, varying from 3 to 7 days; others reported that they do not know how long they would treat neonates with malaria.

Half of the respondents reported using intravenous artesunate at the dose of 3mg/kg.

> "*Huh the treatment [for malaria] is to give IV [intravenous] artesunate so the dose will be IV artesunate 3mg/Kg at zero hour, 12 hour and 24 hours. It is IV [intravenous]. The treatment of malaria in neonate it is IV artesunate and for 7 days*" (Interview 3, female).

The use of artesunate 3mg/kg is a WHO recommendation for treating children weighing <20kg who have severe malaria g [3].

One respondent said that he would treat a term, stable neonate who has malaria as outpatient with coartem (Artemether-Lumefantrine) tablets.

> *"We can treat the baby as out-patient using coartem with tablets. For those who are below 15 kg, it will be 2 tabs per day during 3 days maximum 6 tabs: one in the morning one in the night, so 2 times a day for 3 days"* (Interview 8, male).

Artemether –Lumefantrine is one of the recommended medications of simple malaria by the WHO, but it is contraindicated in the current national guidelines for treatment of malaria in infants weighing less than 5 kg.

Some respondents reported treating the neonates (whose mother had malaria during labor) with antibiotics due to possible infection risk.

> *"And [I] treat as neonate with neonatal infection risk, [I] give antibiotics"* (Interview 3, female).

It is possible that severe malaria may be associated with septicemia, especially in children. Thus, the WHO recommends giving broad spectrum antibiotics in patients with severe malaria until bacteremia is ruled out [3]. In stable, term neonates who have malaria, it is not yet clear if they would be treated as having severe malaria and neonatal sepsis or as having simple malaria.

Subtheme: Treatment of preterm neonate

Some respondents reported using artesunate to treat preterm neonates who have malaria.

> "*Still, I will use the artesunate, but I don't know about the dosage, I think it will be modified, it can be low according [comparatively] to the term baby. I don't have much knowledge about it but I think, [pause] maybe like for me I am in the area where I don't have access to internet, I will treat her or him for 7 days*" (Interview 6, female).

Intravenous artesunate is the primary treatment in all cases of severe malaria.

Most of the respondents reported that they do not know how they would treat preterm neonates who have malaria.

> *"A preterm baby? [Interviewer: yes]. Ah, in this case, it would worth checking the protocol. I do not have an answer right now on how to manage a preterm baby. I have to check what the protocol says"* (Interview 1, male).

> *"For preterm neonates? [Interviewer: Yes] I don't know, I would think it is the same as term, but, I am not sure. I will have to ask"* (Interview 5, female).

Current national guidelines provide no specific information on the management of malaria in neonates. It is understandable for some health care providers to lack information about the condition.

Theme: Family education

Participants reported different elements that they would focus on when educating families whose neonate has malaria. These elements include an explanation of clinical features, diagnosis, treatment and evolution of neonatal malaria.

> *"Yes, for sure, the mother has the right to know the diagnosis of her baby and the management. Yes, we would discuss our findings in her baby, means of transmission and then we tell her the management. As we do for all mothers discharged from the hospital, we have to educate them on maternal and child health. We tell them how to take care of the baby, how to breastfeed and the advantages of exclusive breastfeeding, child and home hygiene as well as family planning. And I have forgotten, as she had malaria and as it is transmitted by a mosquito, I would educate her on prevention. And we need to teach her on what she will consider as good signs that her baby is growing well. It's just that. And, I forgot to say that we have to advise, as she is informed that she had malaria and how someone can get sick of malaria, I mean we have explained to her that the disease is transmitted by an insect, from someone who is contaminated to someone else and the disease is dangerous, especially for the small babies, and as you know, the first cause of mortality in for children under 5 sub-Saharan Africa is malaria. So we have to educate her that the most important thing is the prevention by using the mosquito net, we need to educate her that she needs to adequately use it at home"* (Interview 1, male).

It is important to educate the family on their infant's condition, the management plan and outcomes.

Respondents reported that they give an explanation of malaria prevention strategies such as modes of transmission, the use of mosquito nets and mosquito reduction strategies.

> *"If the mother brings the neonate from home, I will educate the mother to use daily mosquito [net] at home, also she can use other methods to remove the bush around home,*

and other water which can be contaminated from malaria and then also to close windows and the doors early to prevent the entry of mosquito in the house" (Interview 6, female).

Mosquito reduction strategies will lead to the decrease in risk of suffering from malaria for all family members, including mothers and children.

Respondents also described that they would give general education on topics such as family planning, breastfeeding, hygiene, early consultation in the future, vaccination, and hypothermia prevention.

"*So I will explain the mother about the diagnosis and as the malaria was acquired from the mother and also tell the mother about, educate the mother about sleeping in the mosquito net. I will tell the mother to cut the bushes around the house, to close the windows, that normal education. And then I tell the mother alarming symptoms like fever, inability to breastfeed so that she consults as soon as possible. Also encourage the mother to breastfeed because we are fearing that malaria has caused anemia so the breastmilk will boost some iron. What is your discharge plan to the family of a neonate recovering from malaria? I will educate the mother and also tell the mother about vaccination, and also tell the mother to re-consult, if no those symptoms I said, to re-consult after 2 weeks just to review the baby*" (Interview 2, male).

In every case of malaria treatment, it is important to strengthen the family education on malaria through appropriate instruction and communication.

Theme: Follow up

Most of our participants reported that they would give an appointment in the following weeks for reassessing the neonate and to undertake repeat investigations such as FBC, blood smear, liver and renal function test. One participant reported that these patients do not need follow up.

"After discharging the baby, every day we taught to the mother, if there is any sign of, any fever or any refuse of breastfeeding, any respiratory sign we can explain the mother the sighs of respiratory distress, you come immediately to the hospital but if there is no [any] of that sign you come back after one week and we do, we check clinically the baby, we examine physically and after , for [those] who were diagnosed to have malaria we can do blood smear also and full blood count" (Interview 11, male).

Treatment of malaria with artesunate may be associated with hemolytic anemia, especially in cases of hyperparasitemia. It is important to follow-up on patients treated with artesunate after 1 week of treatment, even if hyperparasitemia is not common in children.

Theme: Source of information on malaria in neonates

Our findings revealed that GPs use different resources of information to acquire knowledge on malaria. These include Rwanda National Protocol on malaria treatment, pediatric protocol, the internet, Medscape, up-to-date, neonatology protocol, ETAT, and WHO guidelines on the diagnosis and management of malaria.

> *"OK, I can use uptodate or just Medscape, those are my main references, and also I can use, so I don't have the current version for Rwanda pediatrics protocols but those also I will refer to them"* (Interview 2, male).

> *"We can use pediatric protocol from the Ministry of Health, we can also use neonatal protocol, or ETAT book, and from WHO recommendations and pediatric societies"* (Interview 8, male).

All the above options provide information on malaria in general. But they don't suggest any specific information for the diagnosis and management of congenital malaria.

Other participants reported that they seek information from their colleagues at work or from pediatricians working at their respective district hospitals.

> *"In a newborn infant, normally I check the information from the internet, from Medscape, e-medicine and also to the update from the pediatrician we work together here at [District Hospital]"* (Interview 3, female).

The guidance from experienced co-workers is of great importance for junior practitioners.

Two participants reported that they have protocol containing information on congenital malaria at their hospital.

> "*Specifically for the newborn, we get the information in our MoH (Ministry of Health) guidelines and also in the protocol of our hospital*" (Interview 11, male).

Adopting specific guidelines in every neonatology unit will help clinicians learn about neonatal malaria and apply their knowledge in the prevention of morbidity and mortality secondary to malaria in neonates.

CHAPTER 5: DISCUSSION

This study aimed to deduce the knowledge and practices of general practitioners (GP) working in urban district hospitals regarding neonatal malaria. The analysis revealed ten key themes on this topic (Figure 1).

GPs in district hospitals were chosen because they initially consult, admit patients and formulate the initial management plan. Specialists may consult later to reassess the patient, modify or supplement the plan. Nurses would to implement the plan established by treating doctors.

We included GPs who worked in neonatology wards but had never consulted a case of neonatal malaria. The reason for this is that we wanted to know their knowledge, views and assess their level of awareness about malaria in neonates and their preparedness for taking care of a newborn exposed to malaria once encountered.

Justification of qualitative methods: In qualitative health research, in-depth interviews are often used to study the experiences and meanings of disease, and to explore personal and sensitive themes (codes of the same meaning are drown together to present the findings of the study by responding to the research questions). Interviews can also help identify potentially modifiable factors for improving health care. Therefore qualitative methods were well suited to the aims of the study. Using interviewing techniques, researchers encourage participants to talk about issues pertinent to the research question by asking open-ended questions, usually in one-on-one interviews. The interviewer might re-word, re-order or clarify the questions to further investigate topics introduced by the respondent.

Previous experience on malaria in neonates

Malaria cases in tertiary neonatology units in Rwanda have previously been described in the literature [19,20]. In this study, the majority of participants confirmed that they had previously encountered such patients. There was a large variability in the number of reported cases of congenital malaria seen by the respondents. However, the diagnosis can be easily overlooked if no screening measures are available in the neonatology unit located in malaria endemic regions [48].

Knowledge on the acquisition of malaria in neonate infant

Neonatal malaria can be acquired from either the mother (congenital malaria) or from an infected mosquito bite (acquired neonatal malaria). It is not easy to establish if an individual case of neonatal malaria is congenital or acquired in areas of high endemicity [13]. This study reveals that most of participated GPs know two possible sources of malaria for a neonate. Being aware of the modes of acquisition for neonatal malaria may increase the likelihood of suspecting, diagnosing and treating malaria in neonates with presenting symptoms. It is important to know

that congenital malaria can be a differential diagnosis of neonatal sepsis in a newborn whose mother had malaria during pregnancy [50]. It is suggested that where malaria is common, it should be considered as a differential diagnosis in any newborn with sepsis [28].

Monitoring of a newborn exposed to malaria

Our findings revealed that some GPs who participated would admit exposed neonates to the neonatology unit and monitor their vital signs, request for FBC, CRP and blood smear. This is similar to practices at University of Benin Teaching Hospital when investigating the clinical characteristics of neonatal malaria [51]. Screening newborns for malaria while they are still inpatient was also reported by Agudelo-Garcia et al. in their prevalence study done in Columbia [36]. Lesi et al. [25] followed participants as outpatients and Natama et al. [26] followed malaria exposed neonates by passive case detection.

In some district hospitals, GPs reported to treat neonates born from mothers who had malaria for bacterial infection risk. At birth, they would request initial septic work up and start antibiotics. Our literature search did not find any report where neonates exposed to malaria during pregnancy or during labour were routinely treated for neonatal bacterial infection risk. In the study by Lesi et al., only sick neonates exposed to malaria were tested for neonatal sepsis; malaria would be considered if sepsis is ruled out [25]. It is important that neonates born from mothers with malaria during pregnancy or during labor be reviewed by a knowledgeable health professional. This has been also suggested by Gülaşı in their case report [50].

Recognition of clinical features of neonatal malaria

Malaria in the first month of life manifests like sepsis or other congenital infections such as TORCH infections [13]. Our results indicate that participant GPs expressed the knowledge that malaria can be a differential diagnosis in any neonate with fever in this endemic region. The clinical features of neonatal malaria reported are fever, respiratory distress, anemia, pallor, hepatomegaly, diarrhea, jaundice, bloody stools, lethargy, irritability, asphyxia, splenomegaly, hypothermia, vomiting, seizure (myoclonic jerks), apnea, cyanosis, abdominal distension, hypoglycemia, and jitteriness [51]. These symptoms are also reported by Mohan et al. in the review article [57]. However, Lesi et al. found that fever was not common in neonates with malaria and most of the infants in their study were presenting with jaundice [25]. Our participating GPs reported to know most of these features. Some features like hepatomegaly, splenomegaly, bloody stool, asphyxia, hypothermia, hypoglycemia, jitteriness and loose stool were not reported by our respondents.

The onset of clinical features of infants presenting with congenital malaria in high transmission malaria areas appears between 10 to 30 days. This timing is thought to be the half-life of maternal anti-malaria IgG in the neonate [13]. Ibhanesebhor and Lesi et al. reported that the

mean time for congenital malaria clinical presentation is three days [25,51] Some participants reported that the clinical features can be present from the first day of life.

Our results suggest that congenital malaria features are not specific and are the same as those of neonatal sepsis. This was also reported in the journal of Mohan et al. and that neonatal malaria may look like toxoplasmosis, other, rubella, cytomegalovirus, and herpes (TORCH) infections and bronchopneumonia [57]. Untreated malaria is life threatening, its symptoms are not specific and it is recommended that neonatology wards in malaria endemic area should avail guidance for diagnosing malaria in any sick neonate [13].

Investigations of a neonate with the potential for congenital malaria - Diagnosis of neonatal malaria:

In this study, participants reported to use a blood smear to investigate for malaria in neonate infants born from mothers who had malaria during pregnancy. Some GPs suggested sending the placental sample to a referral hospital for parasitological examination.

The National guidelines for the Treatment of Malaria in Rwanda recommend blood smear as the standard test for parasitological diagnosis of malaria at the level of health centers, district hospitals and referral hospitals. Rapid diagnostic tests (RDTs) are suggested to be used at the community level or at health facilities for emergency cases [52,53]. These guidelines may be applied to neonates despite not being specific to them. Some researchers recommend doing a blood smear as part of routine investigations for every newborn who present with fever. Lack of clinical suspicion index many increase the hospital stay and contribute to the morbidity and mortality [13].

Adjunct tests: Some authors on congenital malaria suggest that a test for plasmodium species be included in the TORCH screening panel in non-endemic areas [58]. Screening every infant with a suspected infection for malaria would prevent delays in its diagnosis. It is important to follow up on neonate infants born from mothers who had malaria during pregnancy. This follow up should ideally be done by a neonatologist or a pediatrician [50].

Investigations for complications of malaria: Participants revealed their opinions on the complications of malaria and will investigate for them. Neonatal infection is considered as a differential diagnosis of malaria. In this regard, a full blood count (FBC) and reactive protein (CRP) tests will be done to investigate for malaria and to check for anemia and thrombocytopenia. Liver and renal function tests are administered to check for acute liver failure and acute kidney injury, respectively.

Investigations not suggested by GPS: No GPs reported the use of a cord blood to test for congenital malaria. Malaria parasites can be more detectable in cord blood than on peripheral blood from a newborn [28]. In cases of suspected congenital malaria, RDTs can be used to

support clinical assessment and blood smear results in settings where the test is available. In cases where RDT is negative, it does not rule out congenital malaria [52]. The National Guidelines for the Treatment of malaria in Rwanda states that RDTs are simple and sensitive tool to detect low parasitemia when its user is well trained [53]. The same guideline recommends using RDT in any emergency situation or when no microscopist is available to do a blood smear. RDTs were not reported by our participants to be used in diagnosing congenital malaria at the district hospital level in Kigali. Ignoring the use of RDTs in diagnosing congenital or acquired neonatal malaria may hinder rapid intervention in cases of neonates suffering from malaria where microscopy may not be easily accessible.

Classification of neonatal malaria

Most participants reported that a neonate with a positive blood smear plus one of the following symptoms will be considered as having simple malaria: fever, refusal of breastfeeding, and inconsolable cry. Participants reported that severe neonatal malaria is when the neonate presents with one or more of the following symptoms: convulsions, anemia, renal failure, respiratory distress, and hypoglycemia. One participant said that different levels of hemoglobin in neonate should be considered to confirm severe malarial anemia. Other participants suggested that every case of neonatal malaria should be considered as severe malaria giving the reasoning that it is more likely to cause anemia and jaundice. Several participants reported that they don't know how they would classify neonatal malaria as simple or severe.

Our literature search did not reveal any information on the classification of neonatal malaria. Most of the same features that are used in the World Health Organization (WHO) guidelines for malaria treatment are used in the national guidelines for the treatment of malaria in Rwanda as signs of severity. According to these WHO and national guidelines, severe falciparum malaria is defined as one or more of the following, occurring in the absence of an identified alternative cause and in the presence of *P. falciparum* asexual parasitemia: Impaired consciousness, Prostration, multiple convulsions, acidosis, hypoglycemia, severe malarial anemia, renal impairment, jaundice, pulmonary edema, shock, hyperparasitemia (Table 3) [3,53].

Practically, it would be difficult to apply many of the above mentioned measurements like bilirubin and hemoglobin to the neonate population. Premature neonates who have malaria may also have respiratory distress which may be due to either prematurity or malaria or both. In this case it would be difficult to decide if it is severe malaria with pulmonary manifestation.

Clinicians working in neonatology or pediatric units should to be aware of possible malaria complications in neonates. Guidelines on how to identify and approach a neonate with complications should be available in all neonatology units in malaria endemic area.

Management of malaria in neonates

Our findings revealed that GPs working at district hospitals in Kigali would treat neonatal malaria with intravenous artesunate. Regarding the dose, some participants reported to follow the national guideline (2.4mg/kg), while others would adopt the WHO guideline (3mg/kg in children weighing less than 20kg). There was variation in the reported duration for the neonatal malaria treatment. One participant reported that it is possible to use artemether-lumefantrine (Coartem) to treat neonates with malaria. Most of our participants reported to have no enough information on how they should treat preterm neonates who have malaria. In this situation, they would ask for information from their colleagues who might be more experienced.

The current 2015 WHO guidelines provide no specific information regarding the diagnosis and management of malaria in the subgroup of neonates (including premature and very low birth weight) [3]. It is possible that this age group of neonates belongs in the category of those who weigh less than 5 kg. According to the WHO, children weighing <20kg who have severe malaria are treated with higher parental dose of artesunate (3mg/kg/dose). Infants weighing <5kg with uncomplicated malaria are treated with artemisinin-based combination therapy (ACT) at the same dose as in children weighing >5kg (5-24mg/kg body weight of artemether and 29-144mg/kg body weight lumefantrine) (strong WHO recommendation) [3]. There is lack of sufficient evidence for confidence in current treatment recommendation in infants weighing <5kg because in most clinical studies, this subgroup was not considered different from older children.

The available artemether-lumefantrine (Coartem) in current Rwandan settings is a tablet of 20mg artemether/120mg lumefantrine. With its recommended dose range, it may be understandable that a neonate weighing 2kg may receive a half or a whole tablet of Coartem. Clarifications are needed on whether and how neonates should be treated with oral ACT. It is also important to remember that, according to WHO, monotherapy use is not an appropriate and/or optimum approach to the treatment.

The Rwandan Pediatrics Clinical Treatment Guidelines of 2012 [2] and The Rwandan national guideline for the treatment of malaria of 2013 [53] recommend use of artesunate (2.4 mg/kg/dose) as a primary drug in the treatment of severe malaria; the treatment may be shifted to oral ACT after 24 hours if the patient is able to tolerate oral drugs. Intravenous quinine is the recommended second option when artesunate is not available. According to the same guidelines, artemether-lumefantrine is indicated in the treatment of simple malaria but it is contraindicated in children weighing <5kg suffering from simple malaria. They provide the option of using quinine 10mg/kg/dose 3 times daily for 7 days.

The Rwandan national guideline for the treatment of malaria (2013) is older than the current WHO guidelines for the treatment of malaria (2015), but some GPs prefer to follow the local guidelines. Therefore local guidelines should be amended to ensure adequate dose administration.

In the Rwandan neonatal guideline, we did not find specific information regarding the management of malaria in neonates. Some hospitals in Rwanda had updated their malaria treatment guidelines and they added recommendations regarding neonatal malaria investigations and management in their hospitals [59]. It is important that all health facilities have updated guidelines on malaria management in children and it would be beneficial if these guidelines contained information regarding the index of suspicion, diagnosing and management of neonatal malaria.

Family education

Our findings indicate that the participating GPs would educate families of neonates recovering from malaria on different item including undertaken management, malaria prevention, signs of danger in neonates, family planning, breastfeeding, and vaccination. These findings confirm that GPs working at district hospital in Kigali follow the national guidelines on the treatment of malaria which recommends to focus on most of these fore-mentioned items in order to strengthen the family information [53]. Lack of adequate vaccination and maternal non-use family planning were revealed by Gupta et al. to contribute to the childhood mortality in Rwanda [60]. Education on appropriate use of bed nets has also been shown to reduce occurrences and complication of malaria in under five years children in the study carried by Deribew et al. [61]. Appropriate family education at the time of discharge of newborns from the hospital is an important step in improving the survival of neonates, preventing malaria infection in mothers and their children and promoting familial healthy life in general.

Follow-up

Our participants mentioned the need to review neonates recovering from malaria in two to four weeks after discharge. Participants reported they would repeat some investigations like FBC, blood smear, liver and renal function test. Gülaş et al recommended that neonates recovering from malaria should be followed by pediatric specialist because of probable malaria complications [50]. The WHO recommends a follow up in patients who had hyperparasitemia and were treated with artesunate as they are at risk for hemolytic anemia [3].

Source of information on malaria in neonates

In this study, we found that GPs working in urban settings have different references where they can check for information regarding malaria in neonates. These include Rwanda National

Protocol on malaria treatment, pediatric protocol, the internet, Medscape, UpToDate, neonatology protocol, ETAT, and WHO guidelines on the diagnosis and management of malaria. Other participants reported that they would ask for information from their colleagues at work or consult pediatricians working at their respective district hospitals. Two participants reported having protocol containing information on congenital malaria at their hospital. Different writers on congenital malaria insist on the availability of evidence based guidelines on the management of neonatal malaria [13,62].

Strengths of this study

To our knowledge, this was the first qualitative study exploring the how GPs working at district levels take care of neonates who might be suffering from malaria. Despite unknown prevalence of neonatal malaria in Rwanda, addressing the gaps revealed by this work has the potential to reduce the mortality and morbidity due to malaria in Rwandan neonates.

In this study, we obtained rigor (formerly known as trustworthy) throughout its validity and reliability.

Validity (internal validity) : Validity is defined as the degree to which inferences made in a study are accurate and well-founded [63]. To obtain the internal validity for this study, enough time was taken to conduct interviews. The principal investigator (PI) conducted interviews by herself, every interview was transcribed, coded and analyzed before conducting the next interview and this helped to reach the sample size when the data were saturated. Our participants worked at four different district hospitals, thus our results were from different persons working in different hospitals. Different supervisors reviewed the codes and analyzed the results.

We understand that the PI had some knowledge and experience on the research topic, which can be the source of bias, but she tried to stay neutral during data collection, analysis and discussion and her knowledge helped her to understand the results and provide consistent analysis.

We are unsure if conducting this study in district hospitals that have more experienced pediatricians who work with GPs might have impacted our results. Similar studies involving hospitals in rural areas and areas that do not have pediatricians may provide further understanding on this topic.

Transferability/generalisability (external validity): Transferability consists of extending the research results, conclusions, or other accounts that are based on the study of particular individuals, setting, times or institutions; to other individuals, settings, times or institutions than those directly studied [63]. Malaria is endemic throughout the country for Rwanda and national

protocols on its diagnosis and management are really available to all district hospitals. Therefore, the results are likely to be appropriate for interpretation in district hospitals in Rwanda.

Limitations

Language: Some general practitioners feel more comfortable in French and/or Kinyarwanda. To overcome this limitation, these participants were able to give responses in French, English or Kinyarwanda depending on their comfort level and the translation was done after the transcription.

Study area: As our purpose was to have an idea of what general practitioners are experiencing while diagnosing and managing malaria in newborns, and not to generalize our data to all GPs, our study area was limited to Kigali in order to minimize the time and means spent on it. Therefore, this indicates that the opinions of non-urban GPs were not included.

Study type: Our findings are not generalized to the remaining of general practitioners working in our country. Rather, we found examples of behaviors and experiences of GPs regarding diagnosis and management of malaria in neonates [64].

Triangulation: Due to the limited time and means, triangulation of the thematic analysis with an alternative data source was not performed.

CHAPTER 5: CONCLUSION AND RECOMMENDATIONS

Conclusion

Findings of this study revealed that general practitioners working in the Kigali urban area are aware that neonates can acquire malaria from their mothers or from infected mosquito bite. GPs tend to understand that neonatal malaria has no specific features and may present similarly to other common illnesses like neonatal sepsis. They recognize that a blood smear is still the gold standard for malaria diagnosis but they lack information on the possibility of using cord blood and RDT for neonatal malaria investigations. GPs working in Kigali have different views on how to classify neonatal malaria and use intravenous artesunate to treat neonatal malaria. Neonates suffering from malaria are also treated with different doses of anti-malarial medication and different treatment duration. They provide family education on neonatal malaria and its prevention, danger signs for neonates, breastfeeding, vaccination and family planning. There is a strong need in the guidelines for management of neonatal malaria, especially at district hospitals.

Recommendation

To the university level:

- To conduct research on the prevalence of neonatal malaria in Rwanda.
- To gather experts' views on management plans for neonates born from mothers who have malaria during pregnancy or on labour.

To Rwanda Pediatric Association:

- To increase the awareness on existence and management of neonatal malaria during mentorship programs.
- To advocate for availability of sources of information for health care providers on neonatal malaria.

To the Ministry of Health:

- To avail the guidelines on index of suspicion, diagnosis and management of neonatal malaria.

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APPENDICES:

Appendix 1: Consent form (French version available from the author if required)

Consent form for participation in a study on "A qualitative study of the knowledge, attitudes, and practices on malaria in neonates among general practitioners in district hospitals in Kigali City"

This study aims to deduct the knowledge, attitudes and practices of general practitioners (GP) regarding neonatal malaria. An interview will be performed using a preliminary set list of question. A recording of an interview will be done. Then the investigators will analyze the data.

I understand that I will not directly benefit from this study, but the information may be used by policy makers to improve the care for newborn infants. The results from this study may also be used for the purpose of medical teaching, or publication in medical textbooks or journal and electronic publications.

I understand that the results of this study may be read by members of general public, in addition to scientists and medical researchers that regularly use these publications in their professional education. Although my information will be used without identifying information such my name, I understand that it is possible that someone may recognize that I participated in such study.

By consenting to this study participation I understand that I will not receive payment from any party. I understand that participation is voluntary and refusal to consent to this study participation will in no way affect my career.

Participant name: _____ Date: _____

By signing the form above, I confirm that the consent form has been explained to me in terms that I understand.

If I have any questions or wish to withdraw this consent in the future, I will contact:

1. Dr Theodonata TUYISENGE: sengatheod@gmail.com, +250 788 828640 or
2. Dr Faustine AGABA: faustineagaba@yahoo.fr, +250 788 438 837

Names of participant: _____ Signature

Names of the investigator: _____ Signature:

Appendix 2: Questionnaire

Part I: DEMOGRAPHIC INFORMATION

Unique Participant Identifier	
Your initials	
Your year of birth	
Your gender:	male [ ] female [ ]
Year of qualification from medical school	
Months/Years of experience working at the district hospital	
Your primary place of work	
Your work status:	Full time [ ] part-time [ ] other [ ] ……..
In your clinical experience, how many times have you managed newborns with congenital or early neonatal malaria?	5-10 cases [ ] 3-5 cases [ ] 1-2 cases [ ] Never [ ]
How long did work in neonatology	

Part 2: INTERVIEW GUIDE (RQ – represents the Research Question in our Aims and Objectives and won't be read to the participants)

Question 1. How would you define a neonate? (Ice-breaker)

Question 2. How frequent did you treat a newborn with malaria?

Question 3. In your practice, where do you get information regarding diagnosing and treating malaria?

Question 4. In not yet mentioned in Q3, can you please tell us any malaria guideline you know?

Question 5. In your knowledge, how can a neonate acquire malaria?

We want you to imagine yourself in a clinical situation where you currently work. Imagine that you are caring for a neonate whose mother tested positive for malaria in labor or during pregnancy.

Question 6. In your opinion; how should this neonate be monitored after birth? (MONITORING)

Question 7. In your opinion; how should this neonate be investigated after birth? (INVESTIGATION)

Question 8. What would you consider as clinical features or indications to test a neonate for malaria? (CLINICAL FEATURES).

Question 9. If this neonate was found to have malaria (e.g. a positive blood smear), in your opinion, how would you classify "simple" and "severe" neonatal malaria? (CLASSIFICATION)

Question 10. If the neonate was term, malaria positive and stable, how would you treat this baby? (TREATMENT TERM)

If not specified already:

Question 11. What medication would you give? By what route would you give them? How long would you give it for?

Question 12. In preterm or low birth weight (LBW) neonates that tested malaria positive how would you treat the newborn?

If not specified already:

Question 13. What medication would you give? What route would you give it? How long would you give it for?

Question 14. What education would you give if a mother or neonate was found to be malaria positive? (EDUCATION)

Question 15. What is your discharge plan to the family of a neonate recovering from malaria? (FOLLOW-UP)

Question 16. Where do you check for information regarding the diagnosis and management of malaria in a newborn infant?

Appendix 3: Approval Letter from College of Medicine and Health sciences/University of Rwanda

UNIVERSITY OF RWANDA

COLLEGE OF MEDICINE AND HEALTH SCIENCES

CMHS INSTITUTIONAL REVIEW BOARD (IRB)

Kigali, 26th /10/2018

Dr TUYISENGE Theodonata
School of Medicine and Pharmacy, CMHS, UR

Approval Notice: No 354/CMHS IRB/2018

Your Project Title ***"Knowledge, Attitudes and Practices of General Practitioners Vis-À-Vis Malaria In Newborns, Case Of District Hospitals In Kigali City – A Qualitative Study"*** has been evaluated by CMHS Institutional Review Board.

		Involved in the decision		
		Yes	No (Reason)	
Name of Members	**Institute**		**Absent**	**Withdrawn from the proceeding**
Prof Kato J. Njunwa	UR-CMHS	X		
Prof Jean Bosco Gahutu	UR-CMHS	X		
Dr Brenda Asiimwe-Kateera	UR-CMHS	X		
Prof Ntaganira Joseph	UR-CMHS	X		
Dr Tumusiime K. David	UR-CMHS	X		
Dr Kayonga N. Egide	UR-CMHS	X		
Mr Kanyoni Maurice	UR-CMHS	X		
Prof Munyanshongore Cyprien	UR-CMHS	X		
Mrs Ruzindana Landrine	Kicukiro district		X	
Dr Gishoma Darius	UR-CMHS	X		
Dr Donatilla Mukamana	UR-CMHS	X		
Prof Kyamanywa Patrick	UR-CMHS		X	
Prof Condo Umutesi Jeannine	UR-CMHS		X	
Dr Nyirazinyoye Laetitia	UR-CMHS	X		
Dr Nkeramihigo Emmanuel	UR-CMHS		X	
Sr Maliboli Marie Josee	CHUK	X		
Dr Mudenge Charles	Centre Psycho-Social	X		

After reviewing your protocol during the IRB meeting of where quorum was met and revisions made on the advice of the CMHS IRB submitted on 16th October 2018, **Approval has been granted to your study.**

Please note that approval of the protocol and consent form is valid for **12 months**.

EMAIL: researchcenter@ur.ac.rw P.O. Box: 3286, Kigali, Rwanda WEBSITE: http://cmhs.ur.ac.rw/ www.ur.ac.rw

Appendix 4: Approval letter from the Ministry of Health

REPUBLIC OF RWANDA

Kigali 03 DEC 2018
N °20/9714/ DGPHFIS/2018

MINISTRY OF HEALTH
P.O. BOX 84 KIGALI
www.moh.gov.rw

Dr Theodonata TUYISENGE
Resident in Pediatrics
School of Medicine and Health Sciences /University of Rwanda
Tel: +250788828640
Sengatheod@gmail.com
KIGALI

Dear Dr Theodonata,

Re: Authorization of Research

Reference is made to your letter dated November 2018 requesting for Authorization to conduct your research entitled **"Knowledge, Attitudes and Practices of general Practionners Vis a Vis Malaria in Newborns ,Case study of District Hospital in Kigali City ,A qualitative study "**

Based on Rwanda Health Sector Research policy approval from University of Rwanda National CMHIS Institution Review Board (RNEC) Ref No: 354/CMHS/2018 of October 22nd 2018 and National Health Research Committee Ref: NHRC/2018/PROT/045 of November 19th 2018.

I am pleased to inform you that the Ministry of Health has granted authorization to conduct this research and to collect data in Kibagabaga, Muhima,Masaka and Kacyiru District Hospitals of Kigali City according to the approved protocol and you are requested to share the results ,the final report and datasets with the Ministry of Health.

Sincerely,

MINISTERE DE LA SANTE

Dr. Diane GASHUMBA
Minister of Health

Cc:

- Hon. Minister of State in Charge of Primary Health Care
- Permanent Secretary/MOH
- Director General of Muhima District Hospital
- Director General of Kibagabaga District Hospital
- Director General of Masaka District Hospital
- Director General of Kacyiru District Hospital