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Prevalence, Risk Factors and Treatment Outcomes of Congenital Malaria among Neonates Hospitalized in Hospitals of Douala, Cameroon

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Abstract The relevance of transplacental acquired malaria is still not clear in many malaria endemic areas. This study was designed to evaluate the prevalence, risk factors and antimalarial treatment outcomes of laboratory-confirmed congenital malaria cases in Douala. **Methodology.** This was a hospitalized-based cross-sectional study undertaken among under seven days neonates hospitalized between January 2018 and May 2018 in the neonatalogy units of three Douala-based hospitals in Cameroon. For each eligible neonate, maternal and perinatal data were collected. The newborn was immediately examined for physical and clinical symptoms by a pediatrician or a neonanatologist, peripheral blood was screened in laboratory for detection of malaria parasites using microscopy and the "One Step Malaria HRP-II (P.f) and pLDH (Pan) Antigen Rapid Test" malaria rapid diagnostic test. Each laboratory-confirmed malaria case was treated accordingly as severe malaria. Data were analyzed as univariate with Pearson Khi^2 and Fisher Exact Tests considering a *P-value*< 0.05 as statistically significant. **Results.** A total of 139 hospitalized neonates aged less than 7 days were included in the study. The sex ratio was 1.17. The prevalence of laboratory-confirmed congenital malaria was 3.6% by both microscopy and RDT. Only *Plasmodium falciparum* asexual stage was detected. *Plasmodium* loads were low (range: 192-320 asexual stages/µl of blood). Hyperthermia and jaundice were most predictive clinical signs of *Plasmodium* congenital malaria. Young mother age (p=0.002) and malaria episode during pregnancy (p=0.01) were associated with congenital malaria. *P. falciparum* confirmed congenital malaria cases were successfully managed with antimalarial monotherapies namely artemether, artesunate or quinine. Mortality among *Plasmodium* carrying neonates who received antimalarial treatment was 0%. **Conclusion.** *Plasmodium falciparum* congenital malaria was an etiology of neonatal infection among neonates hospitalized in Douala. Laboratory-confirmed congenital malaria cases were treated successfully as severe malaria. Congenital malaria should therefore be included in the list of differential diagnosis of neonatal infection at least in neonate with fever or jaundice, and those born to young mothers or mothers with pregnancy malaria.

Keywords: *congenital malaria, newborn, microscopy, rapid diagnostic test, prevalence, risk factors, outcomes, Douala, Cameroon*

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1. Introduction/Background

Malaria is a life-threatening parasitic infection which in 2020 affected an estimated 241 million persons in 85 malaria endemic countries with pregnant women and children aged less than five years being the most vulnerable groups, the World Health Organization (WHO) African Region accounting for about 95%of cases and a malaria case incidence at 59‰ [1,2]. Due to negative health impact of malaria, the WHO together with public health ministries of malaria endemic countries have implemented highly promising specific control strategies to overcome this disease as a public health problem most at risk groups including intermittent preventive therapy (IPT) in pregnant women, sleeping under an insecticide-treated nets (ITNs), and case management of malaria illness and anemia [1,2,3]. Although these control strategies have significantly decreased the incidence as well as malaria-related mortality, malaria remained a killer disease causing an estimated 627 000 deaths in 2020

owing a mortality rate of 6.2‰, children aged under five years representing 77% of total malaria deaths [1]. Also, malaria has remained a major concern in pregnancy due to its consequences on the pregnant mother, the fetus, the newborn and the pregnancy outcomes including abortion, still birth, intra-uterine growth retardation, low birthweight, premature delivery, fetal anemia, and maternal deaths [1,4,5,6].

Congenital malaria, which is presence of live *Plasmodium* in blood of newborn baby is another consequence of pregnancy malaria as it is a result of transplacental transmission of malaria parasites from the *Plasmodium* carrying mother to her fetus [7,8]. Unlike malaria acquired after birth through mosquitoe bites, the health relevance of congenital malaria has been usually underestimated due to scarcity of reports on its prevalence. However, reports found through multiple years reviews have usually shown congenital malaria as rare in endemic areas of Africa and outside Africa [9,10,11,12]. There are however increasing data recorded through case reports and cross-sectional studies which are indicating high frequency and low to moderate prevalence of laboratory-confirmed congenital malaria among newborns hospitalized for neonatal infections (sepsis) as well as asymptomatic newborns in malaria endemic areas in Africa [13,14,15,16,17] and outside Africa [18,19,20]. The public health importance of congenital malaria is therefore being increasingly highlighted since *Plasmodium* sp infection among newborns is actually known as a life-threatening condition with specific high lethality if not early treated and severe complications among *P. falciparum* confirmed clinical congenital malaria cases in African countries [9,15,21] and Indonesia [18]. Such severe outcomes of congenital malaria indicated that early detection and management of *Plasmodium* infection should be considered as a differential diagnostic in the early days of life among less than seven days newborns with any symptom of neonatal infection. A systematic integration of early diagnosis of congenital malaria will therefore highlight the public importance of malaria among newborns and enable strengthening implementation of prevention strategies in pregnant mothers in malaria endemic areas. Integrating malaria detection as differential diagnostic of neonatal infection in the early days of newborn has been encouraged by data in previous reports which indicated high efficacy of some antimalarial monotherapies for management of laboratory-confirmed congenital malaria cases due to *P. falciparum* as well as *P. vivax* in Africa [22,23,24,25,26] and Asia [10,19,20,27].

Biologically, almost all previous reports indicated in clinical congenital malaria a predominance of low parasite loads and low prevalence of infection in high malaria endemic areas in Central Africa [13,15], East Africa [9,22] as well as low malaria transmission settings in West Africa like Burkina-Faso [21]. Main *Plasmodium* species identified in congenital malaria cases were *P. falciparum* as the only causative in African countries [9,13,15,16,17,21], predominantly *P. vivax* in association with *P. falciparum* and *P. malariae* in Asia and America [10,12,18,19,20,27].

Light microscopy of peripheral blood smears sometimes associated to malaria rapid diagnostic tests was the most laboratory techniques used for confirmation of congenital malaria cases in Cameroon [13,14], other African countries [11,17,28,29,30] and outside Africa [18,19]. Polymerase chain reaction technique was shown highly sensitive detection in submicroscopic congenital malaria in Africa [30] and America [12].

Clinically, congenital malaria was reported both among asymptomatic and symptomatic newborns. Asymptomatic congenital malaria was the most frequent feature at birth and the early days of life in malaria endemic countries, then clinical manifestations appear within days after birth thereby delaying clinical diagnosis [14,25,31]. In case of clinical congenital malaria, clear and early clinical diagnosis is difficult as its symptoms vary significantly between cases and often mimic neonatal bacterial and viral infections irrespective to the causative *Plasmodium* specie [10,13,14,16,20,21,24,26,27,29]. Hyperthermia has however been the most predictive manifestation of both *P. falciparum* and *P. vivax* congenital malaria [10,13,22,24]. Fever could be associated to one or more of the following symptoms namely anemia, splenomegaly, jaundice, paleness, diarrhea, vomiting, convulsion, coma, low birth weight, absence of sucking reflex, general weakness [10,13,22,24]. Delayed appearance of malaria-like symptoms render many congenital malaria cases undiagnosed or misdiagnosed, necessitating repeated microscopy diagnostic tests for an accurate diagnosis and urges the need to implement sensitive diagnostic tools for early detection of this infection closer to birth [14].

Main recurrent risk factors of suspicion of congenital malaria included newborn with hyperthermia, obstetrical factors including history of malaria during pregnancy in *P. falciparum*, maternal age, gravidity, attendance to antenatal visits, gravidity, malaria prevention during pregnancy in malaria endemic countries of Africa and outside Africa [13,14,15,18]. Due to the life-threatening consequences of congenital malaria and difficulties to diagnose this disease based on clinical signs, an active surveillance might be necessary for neonates born to mothers with and without any history of malaria.

As in many African countries, few reports are available on congenital malaria in Cameroon concerning both prevalence, differential diagnostic as well as treatment outcomes. The Ministry of Public Health of Cameroon adopted two main strategies to prevent malaria in pregnant woman including distribution of insecticide treated bednet to prevent mosquitoe bites since 2004, and disease prevention through chemoprevention using chemoprevention with sulfadoxine/pyrimethamine also known as intermittent preventive treatment (IPT-SP) at antenatal visits since 2011 [32]. Since the launch of these malaria control tools in pregnant woman, few data on prevalence of congenital malaria in Cameroon are available. This prospective cross-sectional study was designed 14 years after launching of bednet distribution and 7 years after implementation of systematic IPT-SP with the aim to assess the prevalence and identify factors associated to laboratory-confirmed congenital malaria as well as treatment outcomes among less than 7 days old neonates hospitalized in the neonatalogy units of three hospitals in Douala town (Cameroon) namely the Douala General Hospital, the Gynaeco-Obstetric and Pediatric Hospital of Douala and Bonassama District Hospital.

2. Methodology

2.1. Study Type, Period and Place

This was a hospitalized- based cross-sectional and analytical study undergone from January 2018 to May 2018 in the neonatology units of three Douala-based healthcare facilities in Cameroon for recruitment of patients, and the Faculty of Medicine and Pharmaceutical Sciences of the University of Douala. The health facilities included two tertiary health facilities namely the General Hospital of Douala and the Gynaecology-Obstetric and Pediatric hospital of Douala, and a secondary health facility namely the Bonassama District Hospital. These are high standing hospitals with physicians specialized in neonatalogy as well as pediatric, and trained laboratory technicians. Douala itself is the economic capital of Cameroon, located in a stable malaria transmission area with four seasons during the year namely two rainy seasons and two dry seasons. Douala is situated in the Equatorial zone with annual mean temperature about 26°C, heavy rainfall in the rainy seasons. Relative damp is usually 99% in rainy season and 80% in the dry season.

2.2. Ethics

The study protocol was approved by the institutional ethic committee of the University of Douala and the regional delegation of public health in Douala. An authorization to undergo the study was also secured from the ethic committee of each of the three hospitals. A written informed consent was obtained from each mother's child before his inclusion in the study.

2.3. Study Criteria

Neonates aged less than 7 days hospitalized for suspicion of neonatal infection in any of the neonatalogy unit of the study hospitals whose legal parent gave their written inform consent for their participation into the study were included in the study. The newborn should not have taken any antimalarial treatment since birth.

2.4. Data Collection

For each neonate who filled the study criteria, the protocol was read and explained to the legal parent or guardian, a copy of the participant study sheet was given to the later then he was asked to sign the study inform consent if he (or she) authorized his soon to participate in the study. Data related to neonates and respective mother were collected from the patient's file. Data related to the mother were age, parity, bednet use, number of antenatal visits undergone, number of IPT-SP swallowed during the pregnancy, malaria in pregnancy (before or at delivery). Data related to the newborn included birth weight, gestational age, delivery term and reanimation at hospitalization and during hospitalization.

Then a thin and a thick blood smears and also a malaria rapid diagnostic test (RDT) were made using the peripheral blood drops of the newborn collected after heel prick. The kits of malaria rapid diagnostic test used were the « One Step Malaria HRP-II (P.f) and the pLDH (Pan) Antigen Rapid Test» made by Standard Diagnostic (SD). This RDT detects specifically *P. falciparum* infection and non specifically infections due to other *Plasmodium* species. RDT kits were procured at the National Center for Essential Drug Control of the country Ministry of Public Health. Thin and thick blood smears were stained with a 5% Giemsa stain solution and examined at high magnification under light microscope according to specific guidelines [33,34,35]. Results of the RDT were read at spot according to the manufacturer's guidelines. Giemsa-stained blood smears were blinded examined by two trained microscopists, and discrepant readings cross-checked by the study investigator. Microscopy results were expressed as number of each *Plasmodium* stage per µl of blood after examining fields in the thick film for 500 white blood cells (WBC) considering the results from its full blood counts as reported in the patient's file. A thick blood film was considered negative after review of 300 high-magnification microscopic fields. *Plasmodium* load was classified as low (less than 1000 asexual or sexual stage/µl of blood), moderate (1001 to 2000 asexual or sexual stage/µl of blood) and high (greater than 2000 asexual or sexual stage/µl of blood). Prevalence of laboratory-confirmed congenital malaria were also classified as low (less than 10%), moderate (between 10% and less than 20%) and high (greater than 20%).

2.5. Management of Laboratory-confirmed Congenital Malaria Cases

Laboratory-confirmed congenital malaria newborn babies were treated immediately according to national regulations with monotherapies using either intramuscular injection of quinine or an artemisinine derivative relayed by an oral treatment with an artemisinine-based combination therapy (ACT) adapted from the national malaria control programme guide on severe malaria management [36]. Treatment with artemisinine derivatives as monotherapies were administered according to the following regimen: 1/intramuscular injection of artemether on five consecutive days as follow: 3.6mg/kg the first day and 1.6mg/kg/day from the second day to fifth day; 2/ three intramuscular injections of artesunate as follow: 3mg /kg at inclusion, 12 hours and 24 hours after inclusion. The outcomes of the antimalarial treatment were also recorded as recovery, dead and time spent in hospitalization.

2.6. Data Analysis

Data analysis was processed using SPSS.20 software. Association of congenital malaria with risk factors was undergone using univariate analysis through Pearson Khi^2 and Fisher Exact Tests considering a *P-value* < 0.05 as statistically significant.

3. Results

3.1. Prevalence of Congenital Malaria, Plasmodium Species Identified and Parasite Loads

A total of 139 hospitalized newborns babies aged less than 7 days were included in the study. Newborns aged less than 5 days were predominant (85.6%). Male

newborns represented 54% of the study sample and the sex ratio of 1.17.

Prevalence of *Plasmodium* infection confirmed congenital malaria was 3.6% by both light microscopy and malaria rapid diagnostic test. All the positive malaria RDT newborns showed malaria parasites in blood smears. *Plasmodium falciparum* was the only specie diagnosed by both tests. *Plasmodium* loads were low (range: 192 asexual stage/µl of blood, 320 asexual stages/µl of blood).

3.2. Predictive Factors of Congenital Related to the Newborns

As indicated in Table 1, factors investigated with relationship to newborn were gestational age, birthweight, reanimation and clinical signs during hospitalization.

According to gestational age, babies born in the normal term were predominant (74.1%). There was not any association between gestational age and occurrence of congenital malaria among the newborns (p=0.6). However, 80% of babies infected by *P. falciparum* were born within normal term, and the fifth case was of a preterm delivery.

Considering birthweight, babies with normal birthweight were predominant (66.9%) and those with very low birthweight were least represented (5.8%). There was no association between birth-weight and having congenital malaria (p=0.6). Newborns infected by *Plasmodium* were however found predominantly among normal birthweight (80%). The remaining case of Plasmodium infected newborn was a low birthweight.

Of the included newborn babies, 20.9% were reanimated. Having reanimation was not associated with occurrence of congenital malaria in this study (p=0.8). In fact, all the laboratory-confirmed congenital malaria cases were recorded were among newborn who did not experienced reanimation.

As indicated in Table 1, newborns included in this study had at least a sign of neonatal infection namely breathing distress (28.1%), jaundice (22.3%), hypotonia (15.8%), cyanosis(13.7%), hyperthermia (12.2%), hypothermia (2.2%), convulsion(3.6%), pallor(2.2%). *P. falciparum* infected newborns were recorded among those who had hyperthermia, jaundice or breathing distress. However, hyperthermia and jaundice were more predictive of congenital malaria among newborns as the prevalence of laboratory-confirmed congenital malaria was highest among those who had hyperthermia (26.3%) followed by babies who had jaundice (12.9%), and newborns who respiratory distress had the least prevalence (2.6%). Among the five congenital malaria confirmed cases, C-reactive protein (CRP) was negative; urine culture and blood culture were also sterile.

3.3. Influence of Factors Related to Mothers on Occurrence of Congenital Malaria

As indicated in Table 2, malaria parasites were detected mostly among young mothers, primigravidae (60%), mothers who underwent less than four antenatal visits (60%), mothers who swallowed less than three doses of IPT-SP (100%) and mothers who had malaria during their pregnancy (80%). Higher frequencies of *Plasmodium* infection were also recorded among mothers who used mosquitoe bednets (80%) and among newborns with normal birthweight newborn babies (80%).

As indicated in Table 2, mothers of newborn babies were aged between 18 years and 41 years with a mean age of 29± 2.7 years. Mothers aged above 30 years were most represented (49.7%) whereas those under 20 years old were the least represented (4.3%). Young mother age was associated with risk of congenital malaria in newborns (p=0.002). Of the infected newborns, 80% were born from mothers aged less than 30 years. Prevalence of *P. falciparum* congenital malaria was highest among newborns of mothers aged less than 20 years (33.3%) followed by those aged between 20 years and 29 years (3.1%).

As indicated in Table 2, primigravidae and multigravidae were least represented in the study sample (27.3% and 29.5% respectively) whereas paucigravidae were predominant (43.2%). The prevalence of *P. falciparum* parasites carriage was highest among primigravidae mothers (7.89%) and lowest among paucigravidae (1.67%). There was however no association between laboratory-confirmed *Plasmodium* congenital malaria and gravidity (P=0.4).

Table 1. Perinatal characteristics and clinical presentations of the newborns associated to prevalence of congenital malaria

Factor		Sample size	Malaria positive	Prevalence (%)	*P*
Gestational age	<37 weeks	35(25.2%)	1	2.9	0.6
	37-40 weeks	103(74.1%)	4	3.9	
	>41SA	1(0.7%)	0	0	
Birthweight	<1500 g	8(5.8%)	0	0	0.6
	1500-2499 g	38(27.3%)	1	2.6	
	≥2500 g	93(66.9%)	4	4.3	
Reanimation	No	110(79.1%)	5	4.5	0.8
	Yes	29(20.9%)	0	0	
Clinical signs, symptoms and *Plasmodium* infection prevalence among neonates					
Breathing distress		39(28.1%)	1	2.6	
Jaundice		31(22.3%)	4	12.9	
Hypotonia		22(15.8%)	0	0	
Cyanosis		19(13.7%)	0	0	
Fever (hyperthermia)		17(12.2%)	5	26.3	
Normal temperature		122(87.8%)	0	0	
Convulsion		5(3.6%)	0	0	
Pallor		3(2.2%)	0	0	

Table 2. Maternal factors and occurrence of congenital malaria

Maternal factor		Sample size (%)	Malaria positive		*P*
			n	**Prevalence**	
Maternal age (years)	< 20	6(4.3%)	2	33 .3	0.002
	20-29	64(46.04%)	2	3.1	
	≥30	69(49.64%)	1	1.5	
Gravidity	Multigravidae	41(29.5%)	1	2.4	0.43
	Paucigravidae	60(43.2%)	1	1.7	
	Primigravidae	38(27.3%)	3	7.9	
Antenatal visits	≤ 3	90(64.7%)	3	3.3	0.52
	> 3	49(35.3%)	2	4.1	
Bednet use	No	37(26.6%)	1	2.7	0.83
	Yes	102(73.4%)	4	3.9	
IPT-SP	<3	109(78.4%)	5	4.6	0.8
	≥3	30(21.6%)	0	0	
Malaria in pregnancy	No	120(86.3%)	1	0.8	0.01
	Yes	19(13.7%)	4	21.1	

The number of antenatal visits undergone by the newborn's mothers ranged between 0 to 9 antenatal visits. Mothers who underwent more than three antenatal visits during their pregnancy were predominant (64.7%). There was however no association between number of antenatal visits and occurrence of congenital malaria though the prevalence of *Plasmodium*-confirmed congenital malaria was lower among those who underwent not more than three antenatal visits (p=0.52).

Considering malaria chemoprevention with IPT-SP during pregnancy and occurrence of congenital malaria, having swallowed less than three IPT-SP was not associated with malaria infection in the newborns (p=0.8). In fact, mothers who swallowed less than three IPT-SP during the pregnancy were most represented (78.4%). All *Plasmodium* infected newborns were born to mothers who swallowed less than three IPT-SP during the corresponding pregnancy.

Regarding bednet use, newborn babies born to mothers who used mosquitoe bednets during pregnancy were most represented (73.4%). Using a bednet by pregnant mothers seemed not protective against congenital *Plasmodium* infection in this study. As indicated in Table 2, babies born to mothers who used mosquitoe net during pregnancy had the highest prevalence of *Plasmodium* infection as four of the five infected neonates born to mothers who used ITN during the pregnancy.

3.4. Malaria in Pregnancy and Association with Occurrence of Congenital Malaria

A total of 19 mothers of the sample study had a microscopy and malaria RDT confirmed malaria infection during their pregnancy. These mothers were treated according to national regulations using either quinine sulfate through parenteral route (43.8%), intramuscular injection of artesunate (37.5%) or artemether (12.5%). Of the five laboratory-confirmed congenital malaria cases recorded in this study, 80% were born of mother who had malaria during the corresponding pregnancy.

Plasmodium infection was found predominantly among newborns from mothers who experienced a malaria episode during pregnancy than those born from mothers without a malaria like episode (χ^2=19,3; p=0.01).

3.5. Antimalarial Treatment Outcomes of Congenital Malaria Confirmed Newborn

Inpatients neonates spent between 1 day and 21 days in the neonatalogy unit with a mean hospitalization spent time of 7.5±3.8 days. Mean hospitalization time was higher but not significant in the congenital malaria infected neonates (8.5±1.86 days) than *Plasmodium* free neonates (p=0.47).

A total of 12 neonates were treated with antimalarial medication including 7 neonates treated empirically and 5 *Plasmodium* infection confirmed neonates. Antimalarial treatments used included artesunate by intramuscular route, artemether by intra-rectal route and quinine by intravenous route. All five neonates with confirmed *P. falciparum* infection recovered well and were discharged after the specific antimalarial therapy.

Regarding congenital malaria associated mortality, no death was recorded among neonates with confirmed *P. falciparum* infection owing a specific mortality of 0% in this study. However, mortality among *Plasmodium* negative neonates was 10.44%.

4. Discussion

This study aimed to detect *Plasmodium* parasites among less than seven days old newborns as a differential diagnostic of neonatal infections by identifying *Plasmodium* species, prevalence and load among *Plasmodium* infected newborns, then evaluating association *Plasmodium* infection perinatal as well as mother related factors and at last assess antimalarial treatment response of *Plasmodium* infected neonates.

Results of this study indicated that *P. falciparum* as the only causative of congenital malaria among included newborns at low prevalence and low asexual stage loads. Identification of *P. falciparum* as the unique pathogen of confirmed congenital malaria was in accordance with previous reports in Cameroon and other Central African countries [13,14,23] as well as other African countries in East Africa [9,17] and Sahelian countries of West Africa [16,21,24,29]. Detection of only *P. falciparum* may be related to the fact that it is known as the most frequent specie found in African countries. Since *P. falciparum* is

also the deadly specie, its presence among under 7 years newborns need therefore special attention in the management of neonatal-like infections through systematic implementation of laboratory diagnostic of *Plasmodium* as a differential diagnostic at the early age of the newborn baby. This attention should be strengthen since there exist no specific clinical signs of congenital malaria as reported in previous studies, furthermore *Plasmodium* loads are reportedly low.

The low prevalence recorded in this study was close to the overall prevalence of microscopy-confirmed congenital malaria reported earlier in sub-Saharan Africa as well as outside Africa namely the Americas and South-East Asia [10,11]. This prevalence was however higher than others reports in a Kenyan hospital located in a malaria highly endemic area [9] and among febrile hospitalized newborns in Nigeria [16]. Higher prevalence of microscopy-confirmed congenital malaria of 23.8% was reported in 2006 in neonatalogy units of healthcare facilities in Yaoundé [13] and 14.4% in the south region of Cameroon [15]. Data gathered in this study indicated a decrease of prevalence of congenital malaria among neonates compared to the only previous hospital-based data in urban area in Cameroon which was undertaken in 2006 just after launching of ITN to pregnant women and before systematic implementation of IPT-SP at antenatal visits [13]. High prevalence up to 14.4% reported in the most recent study on congenital malaria was done in health facilities of almost rural area in the south-west region of Cameroon and related to predominance of non use of malaria prevention tools during pregnancy [15]. Higher prevalence were also reported in other African countries namely Benin with 19% using both microcopy and malaria rapid diagnostic test [29], Burkina-Faso with 24.4% [21], 7.3% in Guinea [23], 26.5% among asymptomatic and 14.06% among symptomatic newborns in Niger [24], 14.7% among asymptomatic newborns in the University Teaching Hospital of Brazzaville in Congo [28], 32.3% among newborns in a Nigerian Teaching Hospital [37], 6.1% among hospitalized newborns in Uganda [20]. In Indonesia, prevalence up to 42.4% was reported among newborns including 20.6% among symptomatic and similar prevalence among asymptomatic [18]. However, a higher prevalence could be recorded in this study with molecular techniques as nPCR detected in Sudan 18.6% of congenital *Plasmodium* infection versus 0% with microscopy [38]. Also, nPCR showed highest sensitivity than light microscopy and histopathology in the detection of *P. falciparum* and *P. vivax* in placental blood, cord blood and peripheral blood of pregnant women in Colombia [39]. Also in Colombia,, qPCR showed higher sensitivity in laboratory diagnostic of congenital malaria in peripheral blood of newborns with submicroscopic detection in which qPCR detected a *Plasmofium* infection prevalence up to 2.2% including 1.3% due to *P. vivax* and 0.9% by *P. vivax* [12]. However, due to limited application of molecular diagnostic in field studies and health care laboratories in developing countries, light microscopy combined to malaria rapid diagnostic tests remain the gold standard recommended for diagnosis of congenital malaria early after birth.

Concerning parasite loads, predominant low load of *P. falciparum* asexual stages in microscopy-confirmed congenital malaria cases corroborated general trend reported in previous studies in health facilities in Cameroon through cross-sectional studies [13,15] as well as a case report [14]. These results were also similar to reports from other African countries including Kenya [9], Burkina-Faso [21], Benin [29], Niger [24] and Nigeria [16]. In almost all reports in sub-Saharan African countries, *P. falciparum* loads in hospitalized congenital malaria cases were below 200 asexual stages per µl of blood. Even among case reports studies, such predominance of low *P. falciparum* parasitaemia among laboratory-confirmed congenital malaria may result from a regulation by both maternal immunity which may confer protection to the fetus through transmission of immunoglobulin G antibodies (IgG) against malaria [40] and the presence of fetal haemoglobin (HbF) in the neonate [41]. However, high parasitaemia over 20 000 asexual of *P. falciparum* were reported in a Kenyan hospital [9]. Such low parasite loads may induce false negative malaria parasites diagnostic in the early days of the newborn baby as previously reported in a case report in Cameroon which required repeated thin and thick smears some days later for an accurate diagnostic of congenital malaria infection [14]. Following occurrence of laboratory-confirmed malaria cases among newborns hospitalized for sepsis in this study, we recommended strengthening implementation of malaria preventive tools in pregnant women and systematic laboratory screening of malaria infection among all neonates received in the hospital for neonatal-like infection.

Following analysis of perinatal factors as predictive of congenital malaria, no association was recorded concerning gestational age, low birthweight and reanimation after birth. However, newborn hyperthermia and/or jaundice were more likely carrier of *Plasmodium* in peripheral blood and should be considered at risk of congenital malaria. Absence of any significant association between gestational age and occurrence of congenital malaria was in accordance with previous reports in Cameroon [13] and Burkina-Faso [21]. Also, a case report on a microscopy confirmed *P. falciparum* congenital malaria described in an asymptomatic newborn from a mother with a clinically and parasitologically confirmed *P. falciparum* malaria was reported in a normal term born newborn in Sudan [25]. However, a report on congenital malaria indicated a significant association between preterm delivery and microscopy-confirmed congenital malaria among newborns received in hospitals in Indonesia [18]. We found no report concerning occurrence of congenital malaria and reanimation. This study however found congenital malaria cases only newborns who were reanimated after birth, indicating that this feature could be considered as predictive of congenital malaria in Cameroon.

Absence of any association of laboratory-confirmed congenital malaria with low birthweight did not corroborate with reports of a cross-sectional study in Indonesia which found low birthweight as predictive of clinical congenital malaria among newborns [18]. Findings in this study however with congenital malaria confirmed cases found mostly among normal weight newborns corroborated case reports of microscopy confirmed congenital malaria in Sudan where

Plasmodium-carrying newborns had normal birthweight and normal full blood count [25].

Clinical manifestations found in *Plasmodium* infected neonates included in this were consistent with previous reports in Cameroon which mentioned in almost congenital *Plasmodium* infected neonates at least one symptom of neonatal infection [13,14]. Finding hyperthermia as the leading clinical presentation in this study was in accordance with previous reports in Cameroon [13], Uganda [17,26], and Indonesia [18]. In most previous reports, fever was sometimes associated in some cases with one or more other clinical presentations namely jaundice, paleness, diarrhea, vomiting, irritability, failure to breastfeed and general weakness [3,10,14,16,21,24,26,29]. Such association of fever with another sign was also reported in a *P. vivax* congenital malaria case where the newborn showed in addition thrombocytopenia or hyperbilirubinemia [20,27].

Detection of malaria parasites only among neonates with clinical symptoms of neonatal infection was considered as a limitation of this study. Investigators of this study estimated that a higher prevalence of congenital malaria could be recorded if systematic laboratory screening of malaria parasites infection was undertaken among all neonates in these healthcare faculties including asymptomatic and symptomatic. In this regard, some reports have indicated that though occurrence of any symptom may predict malaria infection, microscopy-confirmed congenital malaria cases were recorded among asymptomatic neonates in the first days of life in health facilities in Niger [24], south Sudan [25] and Indonesia [18]. This symptomless status was reported to occur mainly in the early days of life of the newborn, then malaria-like symptoms appeared many days or weeks after birth, owing to difficult clinical diagnosis of congenital malaria in asymptomatic cases [14]. Such late appearance of malaria-like symptom likely causes misdiagnosed congenital malaria in many neonates and repeated diagnosis for an appropriate diagnosis [14,25]. This misdiagnosis of malaria in the early days of the newborn may also expose the later to complications as adequate health facilities are usually not close to households in most malaria transmission areas in Africa. Existence of asymptomatic congenital malaria therefore calls for systematic repeated screening of malaria in all malaria-like symptomless newborns up to many days after birth.

Unlike perinatal factors, two factors related to newborn's mothers namely young maternal age and malaria in pregnancy were significantly associated to congenital malaria in this study. Other mother related factors like primigravidity or paucigravidity, few antenatal visits, non use of bednet and swallowing less than three IPT-SP which are usually reported as predictive of congenital malaria had not significant association had no significant influence on occurrence of this disease.

This study found a significant association between young maternal age and occurrence of congenital malaria in newborns. This finding was in agreement with reports in Uganda [17], in Sudan [38] which reported microscopy-confirmed congenital malaria mostly among newborns of young mothers. Our finding was however not consistent with reports from among newborns received in hospitals in Indonesia where maternal age was not associated with occurrence of congenital malaria among low birthweight newborn babies selected for the study [18].

Considering gravidity, detection of highest prevalence of laboratory-confirmed malaria infection in newborns babies born to primigravidae than other mother groups was in accordance with previous reported in Cameroon which found primigravidae and paucigravidae as the most frequently malaria parasites infected neonate [13,15]. This same trend was reported other African countries namely Kenya [42], Congo [28], Nigeria [37], Uganda [17] and Sudan [38] where primigravidae and secundigravidae women with placental malaria were reported to be particularly at risk for congenital malaria infection. These reports indicated the necessity to implement a systematic laboratory screening of congenital malaria in the early days of life among newborns from primigravidae and even secundigravidae women. However, our data were not in accordance with data from a study in Burkina-Faso which reported higher risk of congenital malaria among newborn from women who had at least two pregnancies [21]. These data from Burkina-Faso may be due to the seasonal transmission type of malaria which does not confer an immunity which may regulate transmission of *Plasmodium* stages compared to in stable malaria transmission areas.

In this study, absence of any significant relationship between congenital malaria and less than three antenatal visits as well as less than three IPT-SP was unexpected since previous reports indicated that lack or having undergone less than 4 antenatal visits or IPT-SP as a risk factor for congenital *P. falciparum* malaria in health facilities in rural areas of South-West Cameroon [15] and elsewhere in Africa including Congo [28], Benin [29], Niger [24], Sudan [25] and Uganda [17,22]. WHO recommends at least three IPT-SP doses at each pregnancy to significantly influence occurrence of congenital malaria in the newborn [36]. In this regard, an previous report indicated that prevention of maternal malaria during pregnancy with intermittent preventive treatment in pregnancy (IPTp) using sulfadoxine–pyrimethamine showed a reduction of neonatal mortality by up to 61% [43]. Also, implementation of IPT-SP in pregnant women influence significantly placental malaria as demonstrated in Ghana where after six years of implementation of this strategy, placental malaria was reduced of up to 57% [44]. Since launching in Cameroon of morbidity control of malaria among in pregnant women using intermittent preventive treatment with sulfadoxine/pyrimethamine at each antenatal visit from the sixteenth week of amenorrhea, the national ministry of public health reported indicated an increasing compliance of pregnant women to this malaria control strategy between 2011 and 2014 [32]. Such increasing compliance may have reduced frequency of placental malaria and also downregulate transplacental transmission of malaria parasites.

Concerning prevention of malaria transmission to mother through use of bednet, data gathered in this study found all laboratory-confirmed congenital cases only among newborns of mothers who used bednets therefore indicating that using a bednet by some pregnant mothers did not prevent congenital *Plasmodium* infection. Our finding was not in accordance with previous reports in

Cameroon which found congenital malaria cases highest frequency among newborns from mothers who did not use ITN during the pregnancy [13,15]. Our data also contradicted reports in Senegal [45] and Niger [24] who reported congenital malaria cases only among neonates born to mothers who did not use ITN during their pregnancy. Observation in this study should therefore be considered with caution, since mosquitoe bednet is the foremost recommended barriers to prevent *Plasmodium* transmission. Therefore, mothers whose newborns had microscopy-confirmed congenital malaria may not used their mosquitoe bednet adequately. Also, mothers who did not use mosquitoe bednets may used other mosquitoe bites prevention tools like sprays, nets at the windows. Distribution of long lasting insecticide impregnated bednets to pregnant women started in Cameroon in 2004 and extended to mass distribution to all houses according to number of bedrooms in 2011 [32]. Persistent finding of congenital malaria cases in this study and other reports was so far in accordance with persisting low use of ITN by pregnant women which remained at 52.3% in 2016 [6].

Laboratory confirmed malaria in pregnancy was significantly associated with congenital malaria in this study. This finding corroborated previous reports which indicated that having history of malaria during pregnancy was predictive of congenital *falciparum* malaria in the south-West region of Cameroon [15], Uganda [17], Niger [24], Benin [29], Sudan [25,38]. Also, malaria during pregnancy was reported as predictive of *P. vivax* congenital malaria [19,20]. These findings were in accordance with reports which pointed history of fever (hyperthermia) in the third trimester of pregnancy and confirmed malaria in pregnancy as risk factors of congenital malaria in Benin, a seasonal malaria transmission country [29]. A study in Uganda indicated that appropriate treatment of confirmed malaria episode with quinine during pregnancy appeared to be protective of congenital malaria [17].

All laboratory-confirmed congenital malaria cases diagnosed in this study were successfully treated with antimalarial monotherapies with no death recorded among them. Successful antilamarial treatment with artesunate were reported previously among Chinese congenital malaria cases where these drugs showed high efficacy [10] and Uganda [22,26], Niger [24] and Guinea [23]. Another antimalarial monotherapy namely chloroquine which is less efficient for the management of uncomplicated malaria in endemic areas successfully treated *P. vivax* congenital malaria [20,27] and asymptomatic *P. falciparum* congenital malaria in South Sudan [25]. Successful treatment recorded in this study and previous reports emphasize the importance of systematic detection of malaria parasites and appropriate management of malaria during pregnancy and in the early days of newborns in endemic areas.

Absence of any death among antimalarial treated newborns with confirmed *P. falciparum* indicated that appropriate diagnostic and treatment of malaria in less than 7 days newborn babies should be recommended and strengthened in all healthcare facilities as specific mortality due to congenital malaria can be prevented. Previous reports among microscopy-confirmed *Plasmodium* infected hospitalized neonates with congenital malaria indicated mortality up to 6.9% in the south West region of Cameroon [15], 11.8% in Burkina-Faso [21] and 27% in a Kenyan hospital [9].

Despite absence of lethality among malaria infected newborns in this study, Congenital parasitic infections in early life must be considered an important public health problem which requires development of adequate control strategies, understanding of mechanisms and multiple factors involved in congenital transmission of parasites.

5. Conclusion

Congenital *Plasmodium falciparum* malaria was an etiology of neonatal infections among neonates hospitalized Douala though at low prevalence and low asexual stage loads. Parasitaemia. Hyperthermia and jaundice in neonates, young maternal age and malaria during pregnancy were risk factors of congenital malaria among less than seven days neonate babies. Antimalarial treatment with monotherapies of laboratory-confirmed *Plasmodium falciparum* congenital malaria was successful with no lethality.

6. Limitations

This study had several limitations. First, the study sample size was low. A higher sample simple could enable more accurate analysis. The second limitation saw the non use of molecular technique for diagnosis of malaria in newborns which could have detected a higher prevalence of congenital malaria among submicroscopic patients. The third limitation was the absence of parasitological results follow-up after antimalarial treatment of newborn's mothers which could have given some explanations on the efficacy of malaria treatment.

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Competing Interests

The authors declare that they have no competing interests concerning this research. There was no private financial support for this research.

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