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Review

Establishing a conceptual framework of the impact of placental malaria on infant neurodevelopment

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ABSTRACT

A novel conceptual framework to describe the relationship between placental malaria and adverse infant neurodevelopmental outcomes is proposed. This conceptual framework includes three distinct stages: (1) maternal and environmental risk factors for the development of placental malaria; (2) placental pathology and inflammation associated with placental malaria infection; and (3) postnatal impacts of placental malaria. The direct, indirect, and bidirectional effects of these risk factors on infant neurodevelopment across the three stages were critically examined. These factors ultimately culminate in an infant phenotype that not only leads to adverse birth outcomes, but also to increased risks of neurological, cognitive, and behavioural deficits that may impact the quality of life in this high-risk population. Multiple risk factors were identified in this conceptual framework; nonetheless, based on current evidence, a key knowledge gap is the uncertainty regarding which are the most important and how exactly they interact.

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Introduction

Malaria remains a global public health concern. Despite continuing efforts and substantial funding, cases of malaria are rising. Between 2015 and 2017, the global number of malaria cases increased from 211 million to 219 million, with a concomitant increase in deaths (WHO, 2018). Approximately 97% of malaria cases occur in Sub-Saharan Africa (SSA) and Southeast Asia (WHO, 2018), regions that are burdened by poor sustainable child development indices (Black et al., 2017).

Nearly 85.3 million pregnancies occurred in areas of *Plasmodium falciparum* transmission in 2007 (Dellicour et al., 2010). A unique risk when infected with *P. falciparum* during pregnancy is placental malaria (PM), which is prevalent in approximately 32.3% of pregnant women in SSA (Guyatt and Snow, 2004). Parasitized erythrocytes sequester in the placenta via the expression of variant surface antigen 2-chondroitin sulfate A, allowing binding to placental chondroitin sulfate A in the placental intervillous space. This causes a maternal immune-inflammatory response, placental pathological changes, and poor birth outcomes. PM is a significant risk factor for gestational hypertension and preeclampsia (Adam et al., 2011; Sartelet et al., 1996), both of which are well-known predeterminants of adverse birth outcomes. It is likely that the combination of these factors may negatively impact infant neurodevelopment and long-term outcomes.

Neurodevelopment, a complex interplay of genes, the intra- and extra-uterine environment, family socio-economic status, and the developing brain, is essential for optimal motor, socio-emotional, neurosensory, and cognitive functioning. Low socio-economic status, infection, inflammation, and aberrant placental function are well-established independent predictors of adverse short- and long-term neurodevelopmental outcomes. These risk factors are prevalent in malaria-endemic low- and middle-income countries (LMICs), creating circumstances where they may combine to increase the risk of neurodevelopmental adversities. Approximately 250 million children worldwide, the majority residing in SSA and Southeast Asia, are not reaching their developmental potential (Black et al., 2017). PM may be an important contributor to pathways of causation of impaired neurodevelopment and future developmental disorders.

Converging evidence from animal and human studies has demonstrated that PM can adversely impact foetal and infant neurodevelopment. In animal models, the offspring born to malaria-infected pregnant mice displayed impaired non-spatial learning and memory, and depressive-like behaviour in infancy that persisted through to adulthood (McDonald et al., 2015a). In human studies, the cingulate sulcus developed faster in the foetuses of malaria-infected women compared to uninfected controls, although no statistically significant difference between head circumference and brain volumes or overall rate of sulci development was seen (Rijken et al., 2012). While this evidence is contradictory, it does indicate that exposure to PM has some degree of impact on brain development. Finally, in a recent case report of placental malaria-discordant dizygotic twins, lower motor, cognitive, and language scores were seen in the PM-exposed twin relative to the PM-unexposed twin, at both 1 and 2 years chronological age (Conroy et al., 2019), indicating poorer neurodevelopmental outcomes as a result of exposure to PM. Given this evidence, more research is required to define the incidence of various types and degrees of neurodevelopmental impairment in infants affected by PM.

A comprehensive synthesis of the existing literature was conducted and a conceptual framework developed to propose potential pathways by which PM leads to adverse neurodevelopment. As shown in Figure 1 (and supported by evidence presented in Table 1), this conceptual framework is presented in three stages: (1) maternal and environmental risk factors for the development of PM; (2) placental pathology and dysfunction associated with PM infection; and (3) postnatal impacts of PM. These have direct, indirect, and bidirectional effects on infant neurodevelopment and

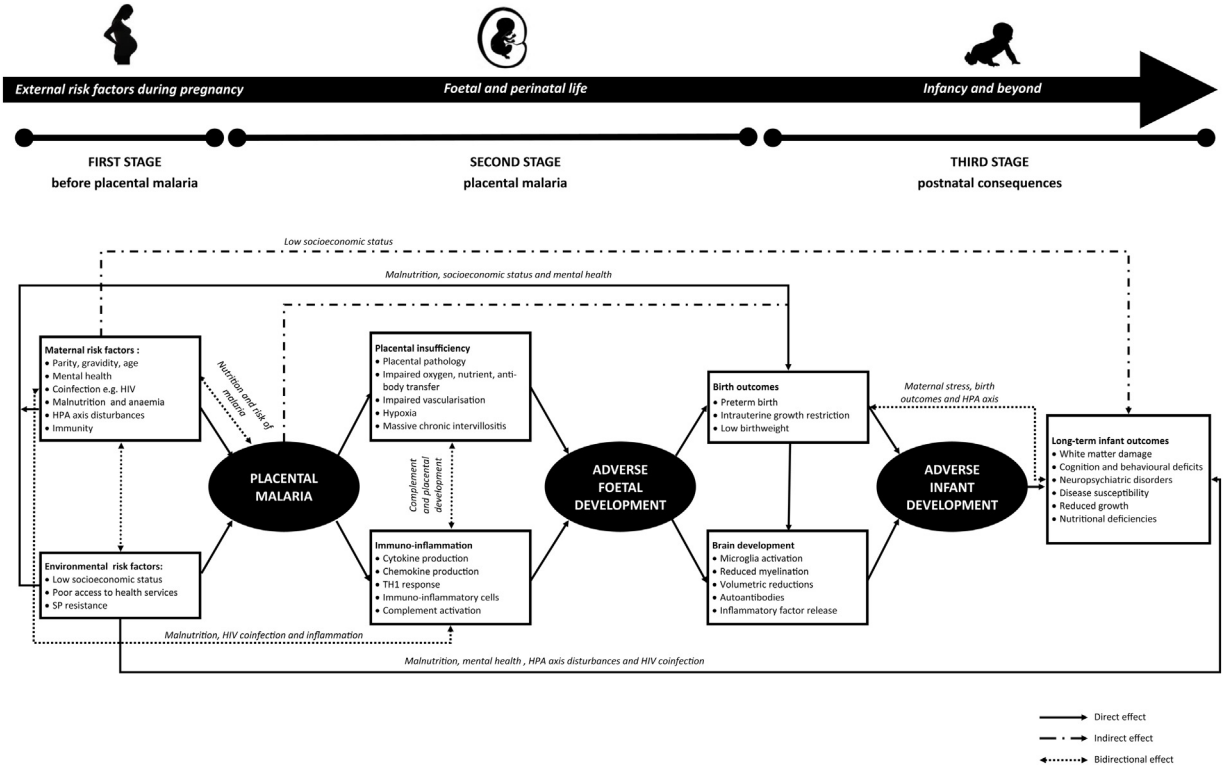

Figure 1. Conceptual framework to describe the progression from placental malaria to adverse infant neurodevelopment.

Table 1
Summary table of studies included in the literature review and conceptual framework.

Reference	Stage in conceptual framework	Risk factor	Findings
Achan et al. (2012)	First stage	Maternal co-infection	In this study, lopinavir–ritonavir-based antiretroviral therapy, as compared with non-nucleoside reverse-transcriptase inhibitor-based antiretroviral therapy, was seen to reduce the incidence and recurrence of malaria.
Adam et al. (2011)	First stage & Second stage	Maternal gravidity & Placental pathology	In this study, placental malaria was significantly associated with preeclampsia. On univariate analysis, primigravidae were associated with preeclampsia.
Adamo and Oteiza (2010)	First stage	Maternal nutrition	This review found that zinc deficiency during gestation may increase the risk of behavioural and neurological disorders in infancy, adolescence and adulthood.
Agostoni et al. (2010)	First stage & Third stage	Maternal malnutrition & Nutritional deficiencies	This expert panel presented guidelines on the nutrition of preterm infants. This commentary discusses the conflicting data surrounding iron supplementation, and highlights studies that have found adversities associated with excessive iron supplementation.
Agudelo et al. (2014)	Second stage	Hypoxia	The authors found that the hypoxia markers, COX-1 and COX-2, were significantly higher in women with PM, when compared to uninfected controls.
Altshuler (1993)	Second stage	Hypoxia & Impaired vascularization	A thorough review of studies associating neurodevelopmental disorders with placental pathology.
Aucott et al. (2008)	First stage & Third stage	HPA axis disturbances & Low birth weight	This study aimed to evaluate the relationship between cortisol concentrations and short-term outcomes in low birth weight infants. The authors found that infants with high cortisol concentrations had significantly higher odds of severe intraventricular haemorrhage.
Basilious et al. (2015)	Second stage & Third stage	Placental insufficiency & White matter damage	A systematic review summarizing the neurological outcomes of placental insufficiency in animal models, including reduced hippocampal and corpus callosum size, hypomyelination and neuronal apoptosis.
Basu et al. (2017)	First stage	Maternal nutrition	This study found that maternal iron deficiency anaemia was associated with lower foetal hippocampal volumes and brain-derived neurotrophic factor, and that the degree to which the infant was affected was proportional to the severity of maternal anaemia.
Bergman et al. (2007)	First stage	Maternal mental health	In this study, maternal stress during pregnancy was negatively correlated with mental development and positively associated with fearfulness in infants.
Black et al. (2017)	Third stage	Cognition and behavioural deficits	This review used proxy measures of stunting and poverty and found that approximately 250 million children in LMICs are at risk of not reaching their developmental potential. The majority of these infants reside in SSA (94.8 million) and South Asia (88.8 million).
Black et al. (2008)	Third stage	Nutritional deficiencies	A comprehensive review of the health consequences of maternal and child undernutrition. In particular, a 1.73-point decrease in IQ was seen for every 10 g/l decrease in haemoglobin in children.
Blencowe et al. (2013)	Third stage	Birth outcomes & Cognition and behavioural deficits	This study found that approximately 2.7% and 4.4% of preterm infants who survived beyond the first month had moderate/severe and mild neurodevelopmental impairment, respectively.
Boeuf et al. (2013)	Third stage	Birth outcomes	This study found alterations of amino acid transportation in PM cases, particularly in cases with local inflammation. The authors conclude that, as opposed to PM, inflammation is more likely to blame for compromised amino acid transport and subsequent IUGR.
Boeuf et al. (2008)	Second stage	Hypoxia	This study found significantly higher levels of the hypoxia marker, hypoxia inducible factor-1α, in PM cases. However, the authors conclude that there is little evidence to suggest PM itself causes hypoxia.
Boivin et al. (2007)	Third stage	Disease susceptibility & Cognition and behavioural deficits	In a Ugandan cohort, 21.4% of children who had cerebral malaria had cognitive deficits after discharge.
Bouyou-Akotet et al. (2005)	First stage	Maternal mental health	This study found significantly higher cortisol concentrations among *P. falciparum*-infected women, relative to uninfected women. Furthermore, cortisol levels were significantly higher among *P. falciparum*-infected primigravidae relative to uninfected primigravidae.
Brabin (1983)	Second stage	Impaired oxygen, nutrient, antibody transfer	It was seen that the maximum parasite rate of pregnant women recruited at ANC visits in Western Kenya occurred at 13–16 weeks of gestation. It is likely that the presence of parasites at this time can disrupt vasculogenesis and impair placental transfer.
Brabin (1991)	First stage & Third stage	Maternal gravidity & Birth outcomes	This study found that the risk of LBW is increased among primigravidae in malaria-endemic areas, significantly correlating with parasite rate at delivery.
Buehler (2011)	Second stage & Third stage	Cytokine production & Neuropsychiatric disorders	This paper details a model describing the impact of proinflammatory cytokines on foetal brain development, and the relationship of cytokines to neuropsychiatric disorders, including autism and schizophrenia.
Chawanpaiboon et al. (2019)	Third stage	Birth outcomes	A systematic review of global, regional and national levels of preterm birth in 2014. There was an estimated 14.84 million live preterm births.
Conroy et al. (2019)	Third stage	Cognition and behavioural deficits	A case report of the neurodevelopmental outcomes in placental malaria-discordant dizygotic twins. The PM-exposed twin showed consistent delays across cognitive, motor and language domains, relative to the unexposed twin.
Conroy et al. (2013)	Second stage	Complement activation	This study investigated the role of complement. Complement was seen to be elevated in PM cases and, interestingly, blocking C5a in a murine model improved foeto-placental vessel development and foetal growth and survival and reduced placental vascular resistance.
Cusick et al. (2014)	First stage	Maternal nutrition	Vitamin D insufficiency is associated with severe malaria in children; the authors suggest a potential role for vitamin D deficiency in the aetiology of severe malaria.
Darling et al. (2017)	First stage & Third stage	Maternal nutrition & Cognition and behavioural difficulties	In this study, the offspring of women who were vitamin D insufficient during gestation had adversities in motor and social development, relative to offspring of women who were vitamin D sufficient. Maternal 25(OH)D deficiency was associated with mental and motor deficits in infants 16–18 months of age, poorer gross and fine motor development at 30 months, and lower social development at 42 months. However, associations were not seen at older ages.
Dellicour et al. (2010)	First stage	Maternal parity, gravidity, age	Using global estimates, it was concluded that 85.3 million pregnancies occurred in areas with *P. falciparum* transmission in 2007.
Djontu et al. (2016)	Second stage	Cytokine production	This study investigated the expression of cytokines in mothers and infants exposed to PM. Placental and peripheral malaria infection correlated positively with peripheral plasma levels of IL-6.
	Third stage	Reduced growth	

Table 1 (*Continued*)

Reference	Stage in conceptual framework	Risk factor	Findings
Dombrowski et al. (2017)			This study from Brazil found that *P. falciparum* infection during pregnancy significantly increased the odds of the occurrence of small head and microcephaly in exposed infants, relative to unexposed infants.
Duthie and Reynolds (2013)	First stage	HPA axis disturbances	A comprehensive review of changes to the HPA axis during pregnancy, and the impact on foetal outcomes. With relation to this framework, the HPA axis is dysregulated by maternal stress, increasing the transfer of glucocorticoids from mother to foetus, which are associated with LBW and adverse infant neurodevelopmental outcomes.
Fitri et al. (2015)	Second stage & Third stage	Cytokine production & Low birth weight	This study investigated the influence of concentrations of IL-17 and IL-10 in malaria-infected placentas on foetal weight. The authors concluded that sequestration of parasites directly causes LBW in PM cases, while cytokines act indirectly.
Fox et al. (2012)	Third stage	Autoantibodies & Cognition and behavioural deficits	This review discusses the possible association between maternal autoantibody production during gestation and infant neurodevelopmental consequences.
Fried et al. (1998)	Second stage	TH1 response	In this study, cytokine concentrations were measured in PM-positive and negative placentas. Significantly higher TNF-α and TGF-β concentrations and significantly lower IL-10 concentrations were seen in PM-positive placentas, leading the authors to conclude that maternal malaria increases the concentration of type 1 cytokines.
Gelaye et al. (2016)	First stage	Maternal mental health	This systematic review summarized the prevalence of perinatal depression and its association with infant/child outcomes in LMICs.
Gibson et al. (1991)	Third stage	Disease susceptibility & Nutritional deficiencies	This cross-sectional study investigated zinc status in children in a sub-district of Papua New Guinea. The authors believed that the suboptimal zinc status seen may have been due to the high prevalence of malaria.
Gibson and Huddle (1998)	First stage	Maternal nutrition	This study assessed zinc status and infection among rural Malawian women. Hair zinc concentrations was significantly associated with malaria infection ($p = 0.01$).
Girardi et al. (2006)	Second stage	Immuno-inflammatory cells & Complement activation	Using a mouse model of spontaneous miscarriage and IUGR, the authors demonstrated that complement activation is a necessary intermediary in placental and foetal injury.
Giurgescu (2009)	First stage	Maternal mental health & HPA axis disturbances	This review highlights the association between maternal cortisol levels and preterm birth.
Guyatt and Snow (2004)	First stage	Maternal parity, gravidity, age	A comprehensive review on the pathological effects of malaria in pregnancy; data from 15 studies indicate an overall prevalence of malaria of 32.3% among pregnant women.
Harrington et al. (2009)	First stage	SP resistance	A prospective delivery cohort examining the IPTp on the level of parasitemia and inflammation in the placenta. The use of IPTp was associated with an increase in resistant parasites, increased parasitemia and more intense placental inflammation.
Imamura et al. (2002)	Second stage	Placental pathology	This study investigated tissue factor expression and fibrin deposition in *P. falciparum*-infected placentas. The tissue occupancy ratio of fibrin was found to be 5-fold higher in infected relative to uninfected placentas. The authors conclude that perivillous fibrin clot formations narrow and plug the intervillous space, interrupting the placental blood supply.
Kauye et al. (2014)	First stage	Maternal mental health	This study found that common mental disorders at outpatient services in Malawi were commonly misdiagnosed as malaria.
Keelan et al. (1999)	Second stage & Third stage	Cytokine production & Preterm birth	This study investigated inflammation in the gestational tissue of women with preterm labour. Significantly higher cytokine concentrations were seen in amniotic and chorionic-decidual tissues from women with preterm deliveries.
Keim et al. (2014)	First stage & Third stage	Maternal malnutrition & Cognition and behavioural deficits	This study investigated the impact of maternal and cord blood 25(OH)D concentrations on child development and behaviour. IQ at 7 years was associated with both maternal and cord blood 25 (OH)D concentrations.
Kuban et al. (2009)	Third stage	Reduced growth	An investigation into developmental correlates of congenital microcephaly and at 2 years in extremely preterm infants. In this cohort, the authors found that congenital microcephaly is only a risk factor for cognitive impairment if microcephaly persists to 2 years.
Lang et al. (2005)	Second stage	Autoantibodies	In a cohort of Kenyan children, levels of antibodies to the voltage-gated calcium channels increased with the severity of malaria.
Lang et al. (2003)	Second stage	Autoantibodies	A review discussing the associations between autoantibodies and CNS disorders.
Le Hesran et al. (1997)	Third stage	Disease susceptibility	This study conducted in Cameroon found that offspring exposed to PM were more likely to develop a malaria infection between 4 and 6 months of age and to have higher parasite prevalence rates at 5 to 8 months of age.
Lee et al. (2017)	Third stage	Birth outcomes	This review found that, in 2012, approximately 23.3 million infants in LMICs were born small for gestational age.
Liew et al. (2015)	Second stage	Autoantibodies	This study investigated the autoantibody profile of patients infected with *P. knowlesi* relative to uninfected patients.
Loureiro et al. (2017)	First stage & Third stage	Maternal nutrition, White matter damage & Cognition and behavioural deficits	In this study, infants with severe anaemia at birth displayed white matter injuries, which were related to global developmental delay, behavioural and learning problems.
Martinez et al. (1998)	Second stage & Third stage	Cytokine production & White matter damage	In this study, amniotic fluid IL-6 was an independent risk factor for periventricular leukomalacia and intraventricular haemorrhage.
McDonald et al. (2015a,b)	Third stage	Cognition and behavioural deficits	In a murine model of malaria, offspring born to malaria-infected pregnant mice displayed impaired non-spatial learning, memory and depressive-like behaviour in infancy that persisted through to adulthood.
McDonald et al. (2013)	Second stage & Third stage	Complement activation, Impaired vascularization & Cognition and behavioural deficits	A review discussing the role of the complement system in placental malaria, placental insufficiency and adverse neurodevelopmental outcomes.
McDonald et al. (2015a,b)	Second stage & Third stage		A review of the role of complement in pregnancy, and the possible consequences on infant neurodevelopmental outcomes.

Table 1 (*Continued*)

Reference	Stage in conceptual framework	Risk factor	Findings
		Complement activation & Cognition and behavioural deficits	
Menendez et al. (2000)	Third stage	Birth outcomes	This study investigated the impact of malaria-associated placental changes on birth weight. The severe fibrin deposition was significantly associated with an increased risk of preterm LBW on univariate and multivariate analysis.
Moore et al. (2000)	First stage	Maternal co-infection	A study investigating cytokine production in HIV-positive/negative PM-infected/uninfected women. It was concluded that HIV-mediated cytokine dysregulation and impaired interferon-gamma responses increased the susceptibility of HIV-positive pregnant women to malaria.
Moormann et al. (1999)	Second stage & Third stage	Cytokine production & IUGR	In this study, cytokine expression was compared in malaria-infected and uninfected placentas. Significantly increased concentrations of IL-1β, IL-8, and TNF-α were seen in infected placentas, and increased TNF-α or IL-8 was associated with IUGR.
Mount et al. (2004)	First stage	Maternal co-infection	A comparison of serum concentrations of antibodies to placental type variant surface antigens among pregnant women. Concentrations of IgG to variant surface antigens were lower in HIV-infected women than in HIV-uninfected women.
Muehlenbachs et al. (2010)	Second stage	Massive chronic intervillositis	This study developed a histological grading scheme for PM, including the presence of massive chronic intervillositis. The literature suggests massive chronic intervillositis is reported in 1.7–6.9% of PM cases.
Muehlenbachs et al. (2006)	First stage & Second stage	Maternal parity, gravidity and age & Impaired oxygen, nutrient, antibody transfer	This cross-sectional study assessed levels of soluble vascular endothelial growth factor receptor 1 (also known as soluble Fms-like tyrosine kinase 1), a preeclampsia biomarker, in primigravidae with either PM, hypertension, or both. Levels were found to be significantly increased, suggesting soluble Fms-like tyrosine kinase 1 may be involved in the relationship between chronic PM and hypertension in primigravidae.
Mutabingwa et al. (2005)	Third stage	Disease susceptibility	This study found that infants who were born to mothers with PM were more likely to have malaria earlier than infants born to unexposed mothers. Offspring of multigravida mothers with PM were more likely to have malaria during infancy, while it appeared that offspring of primigravidae had reduced susceptibility to PM.
Naing et al. (2016)	First stage	Maternal co-infection	A meta-analysis on the co-infection of HIV and malaria. It was estimated that there is an estimated pooled prevalence of HIV and malaria co-infection of 12% among pregnant women.
Nosarti et al. (2010)	Third stage	Birth outcomes, White matter damage & Cognition and behavioural deficits	This book discussed the evidence associating adverse birth outcomes (preterm birth and low birth weight) with an increase in the prevalence of neurodevelopmental adversities.
Nzila et al. (2014)	First stage	Environmental risk factors	A review investigating the impact of folate supplementation during pregnancy on SP efficacy. The authors summarize evidence suggesting that the use of folate may negate SP efficacy.
Opsjln et al. (1993)	Second stage & Third stage	Cytokine production & Preterm birth	This study measured levels of TNF, IL-1 and IL-6 in human pregnancies; these cytokines were seen to increase at the onset of labour, suggesting they may play a role in the onset of normal labour. The authors suggest that higher levels of these cytokines in PM cases may be a risk factor for preterm labour.
Ordi et al. (1998)	Second stage & Third stage	Massive chronic intervillositis & Low birth weight	In this study, massive chronic intervillositis was associated with PM, predominantly among primigravidae. Further, massive chronic intervillositis was associated with low birth weight.
Paintlia et al. (2008)	Second stage & Third stage	Immuno-inflammatory cells, Reduced myelination & White matter damage	This study investigated neuroinflammation and white matter injury in a series of mouse models. The authors found evidence of hypomyelination and astrogliosis in the brain of offspring of murine neuroinflammation models. The authors conclude that cerebral white matter injury may be due to maternal immune activation, such as occurs in PM.
Postels et al. (2018)	Third stage	Disease susceptibility & Cognition and behavioural difficulties	This study investigated electroencephalogram findings in survivors of cerebral malaria from Uganda and Malawi. It was seen that 44% and 11.3% of infants from Uganda and Malawi, respectively, had neurological sequelae at discharge.
Rijken et al. (2012)	Second stage	Brain development	A Thailand-based longitudinal observational investigation into the effect of malaria in pregnancy on foetal cortical brain development. Foetuses of infected and uninfected women showed no difference in foetal cortical development or brain volumes during pregnancy. However, the cingulate sulcus matured significantly faster in foetuses of malaria-infected women, suggesting some neurodevelopmental involvement.
Rogerson and Boeuf (2007)	Second stage & Third stage	Placental insufficiency, Immuno-inflammation & Birth outcomes	A comprehensive review on the relationship between malaria in pregnancy and foetal growth restriction. Of note, this review describes the role of intervillous monocytes, placental hypoxia, and impaired placental transfer that has been reported in the literature.
Rogerson et al. (2018)	First stage & Third stage	Maternal malnutrition & Nutritional deficiencies	This review discusses, among other factors, the association between malaria in pregnancy and maternal and infant anaemia.
Saraf et al. (2016)	First stage & Third stage	Maternal malnutrition & Nutritional deficiencies	A systematic review on global maternal and newborn vitamin D status. It was found that vitamin D deficiency is present in 54% of pregnant women and 75% of newborns globally.
Sartelet et al. (1996)	Second stage	Placental insufficiency	This study from Senegal found that preeclampsia was significantly associated with malaria in pregnancy ($p < 0.03$).
Scherjon et al. (1998)	Third stage	Cognition and behavioural deficits	This study investigated neurodevelopmental outcomes in IUGR, preterm infants. Adverse neurodevelopmental outcomes at 3 years were significantly associated with low head circumference ($p = 0.01$).
Schwarz et al. (2008)	Third stage	Disease susceptibility	This study from Gabon investigated the effect of PM on the risk of malaria in the first 30 months of their offspring's life. Offspring of women with active PM at delivery were at significantly higher risk of clinical malaria in the first 30 months of life.
Shulman et al. (2001)	First stage & Third stage	Maternal malnutrition & Low birth weight	This study investigated the relationship between PM, anaemia and low birth weight. Overall, a significant interaction was seen between chronic or past malaria and severe anaemia, and their effects on birth weight.
Skinner-Adams et al. (2004)	First stage, Second stage & Third stage	Maternal co-infection, Placental insufficiency, Immuno-inflammation &	This study investigated the antimalarial activities of six commonly used antiretroviral agents. *P. falciparum* growth in vitro was inhibited by the HIV-1 protease inhibitors saquinavir, ritonavir, and indinavir. This information suggests a potentially protective interaction between HIV, PM and infant outcomes.

Table 1 (*Continued*)

Reference	Stage in conceptual framework	Risk factor	Findings
		Long-term infant outcomes	
Soni et al. (1993)	Second stage	Autoantibodies	This South African study investigated the presence of anticardiolipin antibodies and *P. falciparum* infection. The authors concluded that there is a high prevalence of these antibodies in acute falciparum malaria cases.
Steketee et al. (1996a)	First stage & Third stage	Maternal co-infection & Disease susceptibility	This Malawian study investigated the association between HIV and *P. falciparum* infection in pregnant women. Parasitemia density and placental infection was significantly higher in HIV-infected women ($p < 0.001$), and newborns of HIV-infected women had higher rates of umbilical cord blood parasitemia.
Steketee et al. (1996b)	Third stage	Low birth weight	This study prospectively evaluated malaria prevention in pregnant women in rural Malawi between 1987 and 1990. In this population, it was found that clearing placenta and umbilical cord parasites resulted in a 3–5% reduction in infant mortality rate and reduced 35% of preventable LBW deliveries.
Suchdev et al. (2017)	First stage & Second stage	Maternal malnutrition & Immuno-inflammation	This review assessed the relationship between nutrition, inflammation and child neurodevelopment in low-resource settings. The authors hypothesize a bidirectional relationship between inflammation and nutrition, wherein nutrition can directly impact immune function and the inflammatory response.
Suguitan et al. (2003)	Second stage & Third stage	Cytokine production & Preterm birth	This study measured concentrations of IFN-γ, TNF-α, IL-4 and IL-10 in placental plasma of malaria-infected and uninfected Cameroonian women with premature and full-term deliveries. Elevated TNF-α and IL-10 were considered risk factors for malaria-associated preterm birth.
Sylvester et al. (2016)	Third stage	Disease susceptibility	This Tanzanian study found that, in the first 2 years of life, exposure to *P. falciparum*in utero both reduced the time from birth to first clinical malaria episode and increased their frequency.
ter Kuile et al. (2004)	First stage	Maternal co-infection	This review included 11 studies indicating higher peripheral and placental malaria in HIV-infected women. Malaria in pregnancy was associated with higher HIV-1 viral concentrations, although reports of mother-to-child-transmission were conflicting.
Umbers et al. (2011)	Second stage	Impaired oxygen, nutrient, antibody transfer	This study investigated concentrations of insulin growth factor 1 and 2, to determine whether PM and inflammation are associated with disturbances in the insulin-like growth factor axis, and thus play a role in foetal growth restriction. Insulin growth factor 1 was significantly reduced in PM cases ($p = 0.007$) and in their neonates ($p = 0.002$).
Umbers et al. (2013)	Second stage	Impaired vascularization	Trophoblast invasion, migration and viability were measured in pregnant women with malaria infection. Trophoblast invasion ($p = 0.06$) and migration ($p = 0.004$) was reduced in response to serum of malaria-infected pregnant women, relative to uninfected pregnant women.
Veerhuis et al. (2011)	Second stage	Complement activation	This review discusses the role of complement in CNS, and evidence of the production of neurotoxic substances in response to complement activation.
Walther et al. (2012)	Third stage	Reduced growth	This study investigated immune responses in the 12-month-old offspring of PM cases. Lower growth rates were seen in infants born to mothers with PM; infants had significantly lower weight ($p = 0.032$) and head circumference ($p = 0.041$) at 12 months. No differences were seen at birth, implying that reduced growth at 12 months was associated with PM.
WBG (2016)	First stage	Low socio-economic status	This report estimated global poverty. In 2013, approximately 389 million people survived on <USD $1.90/day.
Weobong et al. (2014)	First stage	Maternal mental health	This study investigated the adverse maternal and infant consequences of antenatal depression in Ghana. Interestingly, antenatal depression was associated with significant reductions in bed net use ($p = 0.005$).
WHO (2017)	First stage	Maternal malnutrition	The WHO estimates that approximately 10.9% of women of reproductive age in the African region are underweight (body mass index <18.5 kg/m2) and a median prevalence of 47.3% pregnant women are anaemic in the African region.
Yamada et al. (1989)	Second stage	Complement activation	This study assessed 20 placentas from PM cases in Malawi. It was seen that 15% of placentas stained strongly for the complement factor, C3.
Yoon et al. (1997)	Second stage & Third stage	Cytokine production & White matter damage	This study investigated cytokine expression in the amniotic fluid of women with complicated preterm gestations. Significant differences were seen in the concentrations of IL-1β and IL-6 between infants with and without white matter lesions, supporting the authors' hypothesis that inflammatory cytokines play a role in the genesis of brain white matter lesions.
Zimmerman et al. (2007)	Second stage	Autoantibodies	In this study, serum reactivity to prenatal, postnatal, and adult rat brain proteins was tested in mothers with autistic children and maternal and child controls. Reactivity to prenatal rat brain proteins was seen in autistic children and their mothers, and children with other neurodevelopmental disorders. These patterns of reactivity differed to controls and suggest a role of maternal antibodies in the development of autism and possibly other neurodevelopmental disorders, as well as evidence of transfer of autoantibodies across the placenta.

25(OH)D, 25-hydroxyvitamin D; ANC, antenatal clinic; CNS, central nervous system; HPA, hypothalamic-pituitary-adrenocortical; IFN-γ, interferon gamma; IL, interleukin; IPTp, intermittent preventative treatment of malaria in pregnancy; IUGR, intrauterine growth restriction; LBW, low birth weight; LMIC, low- and middle-income country; PM, placental malaria; SP, sulfadoxine–pyrimethamine; SSA, Sub-Saharan Africa; TGF-β, transforming growth factor beta; TH1/2, type-1/2 helper T-cell; TNF-α, tumour necrosis factor alpha; WBG, World Bank Group; WHO, World Health Organization.

ultimately culminate in an infant phenotype where, not only are there adverse birth outcomes commonly associated with PM, but also neurological, cognitive, and behavioural deficits that impact the quality of life from infancy and beyond in this high-risk population. Despite a comprehensive review of the literature, as summarized in Table 1, a key knowledge gap based on the current level of evidence is the uncertainty regarding which are the most important risk factors in this framework and how exactly they interact. Hence, this novel conceptual framework has been proposed to guide this critical line of research, as well as to potentially inform healthcare policy and clinical practice.

First stage: risk factors for placental malaria

While numerous factors are involved in the dynamics of malaria transmission, the proposed conceptual framework focuses on the maternal and environmental risk factors that increase the risk of PM, and thereby may increase the risk of neurodevelopmental adversities.

Maternal risk factors for placental malaria

It is well known that in malaria-endemic areas, infection is more common in younger compared to older pregnant women, and in primigravidae or secundigravidae compared to women who have been pregnant more than twice (Rogerson et al., 2018). Age, rather than gravidity, is considered a stronger predictor of malaria infection in pregnant women (Rogerson and Boeuf, 2007).

Maternal macro- and micro-nutrient malnutrition is closely associated with both the risk of malaria and, independently, adverse neurodevelopmental outcomes. One third of the global population is zinc deficient and, in developing countries, zinc deficiency is a significant risk factor for disease and illness. Zinc deficiencies are associated with malaria prevalence in pregnant women and children (Gibson et al., 1991; Gibson and Huddle, 1998), although this association is not consistent among children. Chronic haemolysis due to malaria increases the urinary excretion of zinc, resulting in maternal zinc deficiency, which when severe can cause foetal brain malformations, and which can impact cell signalling, neurotransmission, and neurological disorders in infancy and beyond (Adamo and Oteiza, 2010). Maternal and newborn 25-hydroxyvitamin D (25(OH)D) concentrations are highly correlated, with 54% of pregnant women and 75% of neonates diagnosed with a 25(OH)D deficiency (Saraf et al., 2016). Low levels of plasma 25(OH)D are associated with severe malaria in children (Cusick et al., 2014). Some studies, but not others, have found that maternal 25(OH)D deficiency is associated with mental and motor deficits and lower intelligence quotient (IQ) in infants (Darling et al., 2017; Keim et al., 2014).

The median prevalence of anaemia among pregnant women in Africa is 47.3% (WHO, 2017), and this is due to numerous risk factors, including malaria. Adequate maternal nutrition is vital for optimal transplacental exchange and foetal growth, and women with severe anaemia due to malaria have an increased risk of low birth weight (LBW) infants (Shulman et al., 2001). Malaria infection is associated with infant and maternal anaemia (Rogerson et al., 2018). Among the other causes of anaemia, maternal and infant iron deficiency anaemia are associated with poor infant neurodevelopmental outcomes: maternal iron deficiency anaemia is associated with lower foetal hippocampal volumes and brain-derived neurotrophic factor (Basu et al., 2017), while severe anaemia in neonates correlates with white matter injury, global developmental delay, and learning and behavioural difficulties (Loureiro et al., 2017). A meta-analysis estimated that every 10 g/l decrease in haemoglobin in children is associated with a 1.73-point decrease in IQ (Black et al., 2008), with significant improvements in IQ scores seen in children receiving iron supplementation.

However, iron deficiency is often associated with other nutritional deficiencies and co-morbidities. Furthermore, iron supplementation can have adverse effects leading to iron overload in patients with chronic haemolytic conditions (Agostoni et al., 2010), so while reducing the risk of iron deficiency is a well-established public health principle, the role of iron supplementation is uncertain in some populations. Nonetheless, it can be speculated that PM-induced maternal and infant anaemia could exacerbate anaemia due to nutritional deficiencies and contribute to infant neurodevelopmental adversities.

Lastly, Suchdev et al. (2017) suggest a bidirectional interaction between nutrition and inflammation, wherein inflammation negatively impacts nutritional status and poor nutrition negatively impacts immune function (Suchdev et al., 2017). Potentially, reduced immune function due to malnutrition may increase the risk of PM.

In summary, nutritional deficiencies play a role in increasing the risk of malaria and poor birth outcomes and, independently, the risk of poor neurodevelopmental outcomes. This relationship appears to be better defined with regards to severe iron deficiency, but less clear for other nutrients including zinc and 25(OH)D. Further research into the role of nutritional deficits as a risk factor for PM and subsequent infant morbidity is recommended.

An estimated pooled prevalence of HIV and malaria co-infection of 12% has been reported among pregnant women (Naing et al., 2016). There are several important interactions between maternal HIV infection and PM. Maternal HIV infection increases the severity of malaria by impairing antibody development to variant surface antigens expressed by malaria-infected erythrocytes, dysregulating cytokine production and reducing protective interferon-gamma (IFN-γ) responses (Moore et al., 2000; Mount et al., 2004). Moreover, malaria increases HIV viral load in pregnant women and mother-to-child transmission, and it hastens the progression from HIV to AIDS (ter Kuile et al., 2004). HIV-infected women have higher rates of PM compared to uninfected women, and higher rates of umbilical cord parasitemia are reported in HIV-infected compared to uninfected newborns (Steketee et al., 1996a). Concurrently, there is an increased risk of antimalarial treatment failure in HIV-infected patients. However, antiretroviral treatment may mitigate malaria by inhibiting *P. falciparum* growth in vitro (Skinner-Adams et al., 2004). Malaria incidence was significantly reduced in Ugandan infants taking antiretroviral treatments (Achan et al., 2012). Therefore, while HIV infection may increase susceptibility to and the severity of PM, HIV treatment could play a protective role against malaria infection.

Poor maternal mental health may increase the likelihood of PM and directly contribute to poor birth and neurodevelopmental outcomes. Firstly, antenatal stress/mental health can increase vulnerability to malaria; indeed, antenatal depression is significantly associated with bed net non-use during pregnancy (Weobong et al., 2014). Secondly, prenatal depression is widespread in LMICs, with a recent meta-analysis finding a pooled prevalence estimate of antepartum depression of 25.3% (Gelaye et al., 2016). Thirdly, prenatal depression and stress are themselves well-known independent risk factors for poor infant cognitive and socio-emotional development (Bergman et al., 2007). This relationship between maternal mental health and PM requires further investigation; of note, common mental disorders have been misdiagnosed as malaria due to commonality of symptoms, including headache, fatigue, and joint pain (Kauye et al., 2014). Mental health problem is commonly under-recognized and undertreated in LMICs (Gelaye et al., 2016), and continued vigilance regarding the burden of both malaria and maternal mental health is required.

Environmental risk factors for placental malaria

Access to antimalarials and malaria prevention tools is essential for malaria elimination, and the lack of access to these services is a key risk factor for PM. In malaria-endemic areas, intermittent preventative treatment of malaria in pregnancy (IPTp) with the antifolate sulfadoxine–pyrimethamine (SP) is distributed at antenatal care visits alongside free long-lasting insecticidal-treated bed nets (LLINs). IPTp-SP is only administered in the second trimester due to concerns over its teratogenic effects; hence pregnant women rely mostly on LLINs for malaria prevention in their first trimester. Access to these interventions remains inadequate; in 2017, only 61% of pregnant women slept under an insecticide-treated bed net and 22% received the recommended three or more doses of IPTp in the African region (WHO, 2018). Clinical resistance to SP has been reported increasingly, with concerns regarding treatment efficacy in pregnancy (Harrington et al., 2009). The use of IPTp-SP in resistant areas may increase the proportion of resistant parasites, the level of placental parasitization, and placental inflammation

(Harrington et al., 2009). Folic acid supplementation is recommended in pregnancy to prevent foetal neural tube defects; however, the concomitant use of antifolate and folate may negate SP efficacy (reviewed by Nzila et al., 2014). Therefore, while benefitting the majority, IPTp-SP could paradoxically worsen PM and potentially worsen downstream infant neurodevelopment.

Globally, SSA accounts for 50% of the extreme poor, with approximately 389 million people surviving on less than USD $1.90/day in 2013 (WBG, 2016). Poor-quality housing that allows infected mosquitoes to enter and the inability to afford malaria prevention tools exacerbates the infection risk. One of the most frequently cited reasons for not owning a LLIN is lack of money. In addition to the increased risk of malaria, children born to socio-economically disadvantaged parents have higher odds of neurological abnormalities, suggesting there may be additive effects of low socio-economic status and malaria infection in impairing neurodevelopment.

Second stage: placental pathology and inflammation associated with placental malaria infection

Placental development

PM-induced placental pathological changes include infarction, decreased villous surface area, reduced capillaries per villus, and fibrin deposition. These can cause placental insufficiency (or placental dysfunction), a serious condition characterized by impaired placental transfer, as well as impaired metabolic, endocrine, and immune function.

Parasite sequestration causes the infiltration of maternal macrophages and monocytes and secretion of chemotactic β-chemokines by foetal villous and maternal mononuclear cells; β-chemokines attract more monocytes and inflammatory factors and initiate an inflammatory cascade (McDonald et al., 2015b). Macrophage migration inhibitory factor, a cytokine believed to retain and activate macrophages, is significantly higher in the placental intervillous space of PM cases (Rogerson and Boeuf, 2007). Macrophages are associated with fibrin deposition, and the tissue occupancy ratio of fibrin can be five-fold higher in PM (Imamura et al., 2002). Fibrin deposition can disrupt placental blood flow and impair gaseous exchange (Imamura et al., 2002), and perivillous fibrin deposition has been independently associated with an increased risk of preterm birth (Menendez et al., 2000).

Monocytes and fibrin in the intervillous space impair placental and foetal growth, likely due to the development of 'fibrin nets' around parasitized erythrocytes and macrophages that narrow and/or plug intervillous spaces, mechanically impairing blood flow and transplacental exchange (Imamura et al., 2002). Heightened inflammatory cells and mediators can dysregulate trophoblast invasion into the maternal uterine wall, which is essential for transformation of the spiral arteries and increased placental blood flow (Umbers et al., 2013). Inadequate trophoblast invasion (and consequent incomplete remodelling of the spiral arteries) is considered the main cause of placental ischaemia and hypoxic conditions, and may explain PM-associated foetal growth restriction and preeclampsia. In malaria-endemic areas, peak prevalence of infection occurs at 13–20 weeks of gestation, coinciding with the period in which increased uterine blood flow is required to meet foetal metabolic demands (Brabin, 1983). The presence of parasitemia during this period is believed to further disrupt vasculogenesis and impair placental blood circulation.

Massive chronic intervillositis (MCI), an idiopathic inflammatory lesion of the placenta, can show widespread fibrin deposition. MCI is associated with PM, particularly amongst primigravidae and in areas of ineffective malaria control and antimalarial resistance (Ordi et al., 1998). MCI is associated with adverse pregnancy outcomes, including intrauterine growth restriction (IUGR) (Ordi et al., 1998).

With reference to the placental effects of PM on neurodevelopment, many associations are seen. Firstly, reduced hippocampal and corpus callosum size, hypomyelination, and neuronal apoptosis are seen in the offspring of animal models of placental insufficiency (Basilious et al., 2015). Secondly, placentas of infants with neurodevelopmental disorders demonstrate features of placental insufficiency and ischaemia (Altshuler, 1993). Lastly, both MCI and placental insufficiency are associated with poor birth outcomes, which are themselves related to adverse neurodevelopment. Indeed, placental insufficiency is one of the most common causes of foetal growth restriction, and given its association with PM, it is logical that this pathway contributes significantly to reduced foetal growth.

However, cases of MCI and PM are uncommon (reported in 1.7–6.9% of PM cases (Muehlenbachs et al., 2010)) and many environmental and maternal factors can cause placental insufficiency, irrespective of PM. Nonetheless, PM may be an important mediator for placental insufficiency and/or MCI in malarious areas. Indeed, it is recommended that malaria be considered in the differential diagnosis of MCI (Ordi et al., 1998). The neurodevelopmental outcome of infants exposed to MCI has not been studied, and represents an important gap in knowledge for which research is needed.

Inflammatory factors

PM-associated inflammation is known to impair glucose and amino acid transport (Boeuf et al., 2013; Umbers et al., 2011), suggesting a direct role of PM-induced placental inflammation in reduced foetal growth. There are varying reports as to the cytokines that are implicated in PM, although reports of inflammation are consistent. Markers of oxidative stress and hypoxia are seen in PM, and conditions suggestive of hypoxia are known to occur in PM cases (Agudelo et al., 2014; Boeuf et al., 2008); however, the role of placental hypoxia in the pathogenesis of PM is not always supported in the literature (Boeuf et al., 2008).

Placental hypoxia increases apoptosis in term human trophoblasts and increases the production of proinflammatory cytokines interleukin (IL)-1α, IL-1β, and tumour necrosis factor alpha (TNF-α) (Rogerson and Boeuf, 2007). In PM, there is evidence of a type 1 helper T-cell (TH1) cytokine/type 2 helper T-cell cytokine (TH2) immune response disequilibrium, characterized by increased TH1 cytokines in placental blood and tissue and lower TH2 cytokines (Fried et al., 1998).

Cytokines have been associated with perinatal brain injury, and the detrimental impact of maternal immune stimulation and cytokines on short- and long-term neurodevelopment has been discussed widely. Cytokines are known to stimulate astrocytes and microglia in the foetal brain to produce more proinflammatory cytokines, disrupting neuronal plasticity and brain growth (Buehler, 2011). Microglia activation in the foetal brain causes astrogliosis, an abnormal increase in astrocytes due to neuronal death, reducing oligodendrocytes and myelination in the postnatal brain and causing cerebral white matter injury (Paintlia et al., 2008). Animal models of prenatal immune activation show fewer oligodendrocytes, apoptosis in white matter, and deficits in neurogenesis, and elevated proinflammatory cytokines are seen in the plasma and cerebrospinal fluid of patients with neuropsychiatric disease, including schizophrenia and autism (Buehler, 2011).

There are inconsistencies regarding whether levels of IL-6, a TH2 cytokine with both pro- and anti-inflammatory properties,

increases or decreases in response to malaria. When compared to uninfected placentas, infected placentas have significantly decreased IL-6 (Moormann et al., 1999), although associations between increased levels of IL-6 and placental and peripheral *P. falciparum* parasitemia have been reported (Djontu et al., 2016). Importantly, elevated IL-6 levels in neonatal cord blood and amniotic fluid is an independent risk factor for intraventricular haemorrhage and periventricular leukomalacia in preterm infants; white matter lesions are seen in neonates born to mothers with elevated concentrations of TNF-α, IL-1β, and IL-6 in their amniotic fluid, while periventricular leukomalacia is seen in neonates with increased levels of IL-6 in cord blood plasma (Martinez et al., 1998; Yoon et al., 1997). Severe neurodevelopmental delays/deficits are common in children with intraventricular haemorrhage and periventricular leukomalacia.

Cytokines have been associated with poor birth outcomes. TNF-α, IL-1, and IL-6 can increase prostaglandin synthesis, hormones involved in cervical ripening and labour induction, causing preterm labour and preterm rupture of the membranes (Opsjln et al., 1993). High TNF-α is associated with IUGR (Moormann et al., 1999) and increased IL-6 is seen in preterm deliveries (Keelan et al., 1999). Specifically concerning malaria, elevated TNF-α and IL-10 are risk factors for malaria-associated preterm birth (Suguitan et al., 2003) and levels of IFN-γ are significantly higher in primigravidae with malaria and are associated with LBW (Fried et al., 1998). It has been hypothesized that cytokines act indirectly on birth outcomes in PM, by increasing immune responses that mechanically block nutrients and oxygen (Fitri et al., 2015), impairing foetal growth.

Overall, the evidence from the literature suggests both mediating and indirect roles of cytokines. Proinflammatory cytokines that cross the placenta are capable of damaging foetal white matter, while increased immune responses due to the presence of cytokines can mechanically impair transplacental exchange and foetal growth. Thus, in PM, TH1/TH2 imbalances and elevated cytokine levels may mediate foetal white matter damage and poor birth outcomes (and subsequently impact neurodevelopment), although the exact pathways remain unclear.

The complement system may also play a role. It comprises a series of plasma proteins that are crucial for innate immune responses to infection. Complement components are markedly increased in PM (Yamada et al., 1989). In the presence of malaria-infected erythrocytes, C5a causes monocyte release of the anti-angiogenic factor soluble Fms-like tyrosine kinase 1, which binds to vascular endothelial growth factor and placental growth factor, preventing signalling and preventing the promotion of angiogenesis (McDonald et al., 2013), thus impacting placental growth and function. High levels of soluble Fms-like tyrosine kinase 1 are seen in primigravidae with hypertension, PM, or both (Muehlenbachs et al., 2006). C5a in maternal and umbilical cord plasma is associated with spontaneous miscarriage and IUGR (Girardi et al., 2006); blocking C5a and its receptor in a mouse model of PM increased placental vascularization and offspring growth and survival (Conroy et al., 2013).

In the central nervous system (CNS), complement plays a critical role in synapse formation and development (Veerhuis et al., 2011). However, activation of the complement system in response to disease in the brain promotes inflammation and the production of proinflammatory cytokines and neurotoxic substances by glial cells (Veerhuis et al., 2011). Thus, maternal and foetal complement activation in response to PM may directly impair placental development and foetal growth, and lead to brain injury. Targeting complement as a therapeutic strategy to prevent poor birth outcomes in PM cases has been suggested (McDonald et al., 2015b) and continued research in this area should be encouraged.

Autoantibodies

Autoantibodies have the potential to cross the placenta and are increased in pregnant women (Fox et al., 2012) and in parasitic infections including malaria (Liew et al., 2015). Patients with severe malaria may have elevated levels of anticardiolipin antibodies (Soni et al., 1993), and autoantibodies against voltage-gated ion channels are seen in children with malaria (Lang et al., 2005). Autoantibodies are hypothesized to be involved in CNS disorders, although more research is required to define their role (Lang et al., 2003).

Maternal autoantibodies that recognize foetal brain antigens, and subsequent maternal autoantibody-induced brain injury, may underlie neurodevelopmental disorders including behavioural and cognitive deficits (Fox et al., 2012). Indeed, relative to serum from control mothers, serum from the mothers of children with autism, developmental delay, and attention-deficit/hyperactivity disorder is found to react with prenatal rat brain proteins. (Zimmerman et al., 2007). Investigation into brain-reactive autoantibodies in women with PM has not yet been conducted but should be considered in future research.

Third stage: birth and early life outcomes as a consequence of placental malaria that affect infant neurodevelopment

Malaria infection, preterm birth, foetal growth restriction, and low birth weight

PM is a risk factor for preterm birth, foetal growth restriction, and LBW. Annually, approximately 15 million infants are born preterm; the highest rates of preterm birth are in SSA and Asia, contributing to >60% of annual global preterm births (Chawanpaiboon et al., 2019). Similarly, in LMICs an estimated 23.3 million are born annually with foetal growth restriction or small for gestational age (Lee et al., 2017). The risk of LBW is increased among primigravidae in malaria-endemic areas, significantly correlating with parasite burden at delivery (Brabin, 1991). Clearing placenta and umbilical cord parasites resulted in a 3–5% reduction in infant mortality rate and reduced 35% of preventable LBW deliveries (Steketee et al., 1996b). It is well-recognized that preterm birth, foetal growth restriction, and LBW are associated with altered structural and functional brain maturation, adverse cognitive and behavioural deficits (Nosarti et al., 2010), and mild/moderate neurodevelopmental impairment (Blencowe et al., 2013).

Disease susceptibility

In addition to its effects on CNS development via effects on maternal immuno-inflammatory responses and placental function, PM increases malaria susceptibility among exposed infants. Offspring born to mothers with PM have a significantly increased risk of clinical malaria (Schwarz et al., 2008), higher parasite prevalence rates (Le Hesran et al., 1997), and a shorter time from birth to first clinical malaria episode (Sylvester et al., 2016) when compared to unexposed infants. Interestingly, interactions have been seen between gravidity and risk of malaria; two previous studies have found that infants born to multigravidae with PM have a higher risk of malaria compared to infants born to primigravidae, and in fact, infants born to primigravidae had a reduced risk of malaria compared to unexposed infants or infants born to PM-positive multigravidae (Mutabingwa et al., 2005; Schwarz et al., 2008). However, this interaction with gravidity is not consistent in the literature (Sylvester et al., 2016).

In malaria-endemic areas, infants <5 years of age are at increased risk of malaria and the development of severe disease.

Increased disease susceptibility is particularly concerning, as cerebral malaria is a critical risk factor for adverse neurodevelopment. In the year 2000, neurological deficits were seen in 4.4% of infants <5 years of age who had suffered from cerebral malaria in SSA, with recent reports finding neurological sequelae in 21.4–44.0% of cerebral malaria survivors in Uganda (Boivin et al., 2007; Postels et al., 2018). These findings highlight that firstly, mechanisms of immune responses in PM-exposed infants need to be further researched, especially given their potential impact on long-term neurodevelopmental outcomes, and secondly, women of all gravidities must be protected from malaria.

Reduced growth

Infants exposed to PM have alterations in growth patterns including significantly lower body mass index-for-age, weight-for-age, and weight-for-length at 3, 6, and 12 months, and lower weight and head circumference at 12 months compared to unexposed infants (Walther et al., 2012). Infants exposed to malaria in pregnancy have increased odds of a small head (head circumference <1 standard deviation below the median) and microcephaly (head circumference <2 standard deviation below the median), relative to controls (Dombrowski et al., 2017). Lower head circumference is associated with adverse neurodevelopmental outcomes at 3 years and major neurological abnormalities and lower IQ scores at 8 years (Scherjon et al., 1998). Interestingly, microcephaly that persists until 2 years of age only is associated with abnormal cognitive and motor outcomes, suggesting that microcephaly is a risk factor for cognitive impairment if there is no catch-up growth of head circumference (Kuban et al., 2009). This implies an indirect and long-term effect of PM on neurodevelopment via offspring growth; if PM impairs growth, particularly beyond infancy and into childhood, it is possible this will lead to persistent neurodevelopmental adversities.

Infant hypothalamic-pituitary-adrenocortical axis disturbances

The hypothalamic-pituitary-adrenocortical (HPA) axis is compromised in *P. falciparum* malaria: cortisol is significantly higher in women with malaria, particularly primigravidae, and a positive correlation between cortisol concentration and parasite load at delivery is evident (Bouyou-Akotet et al., 2005). The HPA axis is also dysregulated by maternal stress, as is the transfer of glucocorticoids from mother to foetus (Duthie and Reynolds, 2013). Increased foetal exposure to glucocorticoids is associated with LBW and is believed to lead to adverse infant neurodevelopmental outcomes (Duthie and Reynolds, 2013). High cortisol concentrations are positively associated with preterm birth (Giurgescu, 2009) and severe intraventricular haemorrhage in extremely LBW infants (Aucott et al., 2008). Speculatively, disruption of the maternal HPA axis due to PM and maternal stress could lead to HPA axis dysfunction in infants (primarily with regards to cortisol concentrations), which may contribute to poor infant birth and neurodevelopmental outcomes. Future research is required to clarify this relationship.

Conclusions

This article provides a comprehensive synthesis of the literature and a corresponding novel conceptual framework to identify the potential pathways that may explain adverse neurodevelopmental outcomes as a consequence of exposure to PM. The rationale for this proposal is based on three well-established findings: PM and associated maternal and environmental risk factors are common in LMICs, and can adversely impact neurodevelopment; PM leads to poor birth outcomes, including preterm birth, LBW, and IUGR, which are associated with short- and long-term adverse neurological outcomes; and finally, PM is associated with poor infant neurodevelopmental outcomes in animal and human studies.

Multiple risk factors are involved in this conceptual framework, and a key knowledge gap is the uncertainty as to which are the most important and most prevalent and how exactly they interact. While it is hypothesized that there are direct, indirect, and bidirectional roles at play, further research should investigate whether additive, augmentative, synergistic, or even protective relationships exist. Field studies are required to corroborate the true impact of PM on infants exposed in utero, with long-term follow-up to identify the contribution of PM to infant neurodevelopmental and health outcomes. Validating this relationship will increase awareness and advocate for interventions to prevent malaria in pregnancy that may ultimately help to improve infant neurological outcomes and prevent neurodevelopmental impairments later in life. Clinical practices and targeted early interventions need to be set in place to treat this high-risk population.

Finally, it is noteworthy that pregnant women remain mostly unprotected in their first trimester, coinciding with peak parasitemia prevalence, and are often excluded from population-targeted drug administration programmes. The development of methods of prophylaxis that are safe during the first trimester is urgently needed, as well as continued vigilance regarding increasing access and the use of LLINs throughout pregnancy.

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Author contributions

The corresponding author, Samudragupta Bora had full access to all of the study data and is primarily accountable for all aspects of the work, including the decision to submit for publication. Harriet L.S. Lawford: conceptualized and designed the review protocol, acquired data (literature search), interpreted the results, drafted and revised the initial manuscript, and approved the final manuscript as submitted. Anne CC Lee: Substantial contributions to the oversight of the conceptualization of the review, provided additional data (i.e., relevant references), interpreted the results, critically reviewed and revised the manuscript drafts, and approved the final manuscript as submitted. Sailesh Kumar: substantial contributions to the oversight of the conceptualization of the review, provided additional data (i.e., relevant references), interpreted the results, critically reviewed and revised the manuscript drafts, and approved the final manuscript as

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