Cerebral Malaria and Toxoplasmosis: Could their Concomitant Presentation Worsen Psychotic Condition?

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Abstract

Malaria and toxoplasmosis are two important parasitic diseases with significant public health concerns in the Sub-Saharan African countries. Some aspects of pathogenesis of the two parasitic diseases involve the central nervous system manifesting neuropsychiatric disorders. Studies have implicated the single infection by Plasmodium spp. and Toxoplasma gondii in development of psychosis. Although concomitant infection of the two parasites suggests an aggravated psychotic condition, there is currently no reported study. This article reviewed some studies which implicated malaria and toxoplasmosis in psychosis. It further explored the likely role of concurrent infection by the parasites on psychosis, the dynamics of their pathology and possible effects of certain psychosis-associated cytokines and other biomolecules on the central nervous system. We recommend evidence-based research efforts in this field for the effective management of these two parasitic diseases to abate the public health burden of psychosis.

Keywords: Malaria, toxoplasmosis, central nervous system, comorbidity, psychosis
1.0 Introduction

Malaria is a mosquito borne parasitic disease with high prevalence in several tropical and subtropical countries of the world. It is the most rated parasitic disease in term of associated burdens and public health importance recording 300-500 million cases and more than 1 million mortalities annually (World Health Organization (WHO), 2018). Malaria parasites invade the hepatocytes and the erythrocytes resulting in acute febrile disease with associated symptoms like periodic fever, anaemia, vomiting and jaundice (Mueller et al., 2015). Toxoplasmosis, like malaria, is caused by an apicomplexan parasite but unlike malaria, it has a worldwide distribution. *Toxoplasma gondii* infects a wide range of vertebrates and about a third of human population globally has been documented to harbour *T. gondii* infection (Robert-Gangneux and Dardé, 2012). The infection can spread to several organs and could lead to death in immunocompromised individuals (Lee et al., 2019).

Despite the possibility of co-infection of protozoan parasites, there are limited information on studies addressing their concomitant infections. Several studies have implicated cerebral malaria (Sowunmi, 1993; Vanni et al., 1998; Ekram et al., 2016; Singh et al., 2016; Jenkins et al., 2019) and toxoplasmosis (James et al., 2013; Yolken et al., 2017; Lindgren et al., 2018; Wokem and Onosakponome, 2018) in psychosis. Malaria parasites and *T. gondii* share similarities in their pathology, energy metabolism and immune modulation (Onkoba et al., 2015). The concomitant occurrence of the two pathogens in a human host may imply a competitive interaction that may modulate the clinical outcomes associated with the two diseases. A study has implicated co-infection of *Plasmodium falciparum* and *T. gondii* in pregnant women as a risk factor for increased birth defects like low birth weight, anaemia, still birth and hypertension compared with maternal infection with *T. gondii* only (Blay et al., 2015). The severity of morbidities was, however, higher in a single infection of *P. falciparum* compared with the co-infection or single infection with *T. gondii* (Blay et al., 2015). Although co-infection of the two apicomplexans has been associated with pregnancy-related complications owing to their close interaction with the placenta, little is known about their ability to induce psychotic disorders. This is important as both pathogens are known to be capable of crossing the blood-brain barrier (BBB) (Nishanth and Schlüter, 2019). Indeed, with increasing evidence of psychosis and related mental disorders in malaria and toxoplasmosis single infections (Kampondeni et al., 2013; Yolken et al., 2017), it becomes important to assess the effect of the duo in the course of their co-occurrence in the brain.

This review examined available studies on co-infection of malaria parasites and *T. gondii* with a view to understanding the pathogenesis of psychosis in concurrent infections. This will be useful for appropriate clinical management of the two parasitic infections and as well as identify future research directions in the field.

2.0 Epidemiology of psychosis

Psychosis is a global issue associated with significant morbidity and premature death (Hayes et al., 2017; Hjorthøj et al., 2017). This mental disorder was globally ranked top 15 amongst leading causes of disability in 2016 (Global Burden of Disease (GBD), 2017). The global incidence of all psychotic disorders was 26.6 per 100 000 persons (Jongsma et al., 2019). Despite its low prevalent level, it exerts a significant estimated economic burden ranging from 0.02% to 1.65% gross domestic product (Chong et al., 2016). Geographical locations at higher latitudes and urban centres have been reported to show higher incidences of psychotic disorder (Saha et al., 2006; Vassos et al., 2012).

The risk factors of psychosis can be divided into biological or organic (Sowunmi, 1993; Vanni et al., 1998; Ekram et al., 2016; Singh et al., 2016; James et al., 2013; Yolken et al., 2017; Lindgren et al., 2018; Wokem and Onosakponome, 2018; Jenkins et al., 2019), social, and psychological factors. Systematic review of cross-sectional and longitudinal studies has identified social and psychological risk factors for psychosis at different levels of evidence. For instance, there is robust evidence that social factors such as being a minority group in a fairly homogeneous society, being an immigrant, and living in urban slums are all strong social risk factors for psychosis while childhood adversity (multiple negative life events) and socially withdrawn trait in childhood are strong psychological risk factors (Radua et al., 2018).

At least one study conducted in Africa has established some of these risk factors among Africans with psychosis (Jenkins et al., 2010). However, these risk factors for psychosis often do not occur in isolation.

Keshavan and Kaneko (2013) have highlighted the biological or organic risk factors of psychosis to include physical trauma, congenital brain disorders, psychoactive substance, cerebrovascular disorders, metabolic and endocrine diseases, nutritional disorders, auto-immune diseases and infectious diseases. These organic risk factors-associated psychoses are common in Africa, especially among children and adolescents. Some infectious agents implicated as risk factors of psychosis include *Chlamydia pneumoniae* (Xavier et al., 2005), urinary tract infection (Carson et al., 2017), Zika virus (Corrêa-Oliveira et al., 2017) amongst others have been reported to increase the risk of psychosis. Maternal bacterial infection during pregnancy was also reported to increase the risk of neonatal psychotic disorders (Lee et al., 2019). In Nigeria, high rate of psychosis was reported among tuberculosis patients (Lasebikan and Ige, 2015). Psychosis therefore is likely a multifactorial condition of environmental, psychosocial or infectious agents' origin.

There is a wide variation in the prevalence of psychosis across the world and also within countries, with countries in Sub-Saharan Africa recording higher rate compared to the developed countries (Umukoro, 2016). This may not be surprising owing to the poor health management system in many African countries, and high rate of insecurity and social injustice which may negatively impact on the mental health of the people. The occurrence of psychosis is generally low in the general population but the risk of occurrence becomes higher in specific population like the men and young people, mental
disorder patients, refugees, migrants, homeless persons and those that use substances (Table 1).

In three villages in Bangladesh, the prevalence of psychotic disorder was 1.17%. Of the nine individuals reported to be suffering from psychosis, four are schizophrenic. Education and marital status were not associated with neuropsychiatric disorders in the population. However, economic burden measured by the size of the family was identified as major risk factor of psychosis and other mental disorders in the study (Hosain et al., 2007). Binbay et al. (2012) reported no correlation between psychosis and urban residence in Turkey. Conversely in Bangladesh, the occurrence of neuropsychiatric disorders was more common in urban centres than in the rural areas (Islam et al., 2003). The probable reason attributed to this disparity was that poor people living in rural areas are unlikely to give priority to the treatment or management of emotional and mental problem (Binbay et al., 2012). Thus, the number of reported cases in rural areas are significantly lower. This also accounts for dearth of information on psychosis and other neuropsychiatric disorders in many rural communities in Sub-Saharan Africa. As a matter of fact, the information provided in Table 1 on Sub-Saharan African countries were sourced from the urban centres, hence, the high prevalence of psychosis in the region. This is not to say psychosis is not of public health importance in rural areas of the region. On the other hand, poor health management facilities, lack of qualified health personnel and poor awareness on mental health could make it a less prioritised health issue in such areas. In the developed world such as Netherlands, psychotic related disorders become a public health concern among ethnic minority population with prevalence ranging between (33.0-49.0%) (Adriaanse et al., 2015). The prevalence of psychosis could be as much as 20 times lower in developed countries compared to values recorded in developing countries like Bangladesh and Nigeria in the general population. The wide gap between the public health system and priority placed on mental health in the regions could be responsible for the discrepancy.

3.0 Toxoplasmosis and neuropsychiatric disorders

Toxoplasma gondii is an intracellular coccidian protozoan parasite of the family, Sarcocystidae that causes the transmissible disease called toxoplasmosis. It is a tissue cyst-forming coccidia whose lifecycle alternates between a sexual stage in a definitive host (felines) and an asexual stage in a range of intermediate hosts such as ruminants, mammals, carnivores and birds (Robert-Gangeux and Dardé, 2012). However, transmission is also possible between definite hosts as well as between intermediate hosts (Robert-Gangeux and Dardé, 2012; Esch and Petersen, 2013). The felines, domesticated and wild cats, acquire infection after eating intermediate hosts, especially rodents and birds harboring the infective tissue cysts. Acutely infected cats shed the oocysts in their faeces in large numbers for 2 weeks and rarely longer (Robert-Gangeux and Dardé, 2012; Esch and Petersen, 2013; Watts et al., 2015). The shed oocysts become infective after sporulation occurs in 1 to 5 days depending on the environmental temperature and aeration. The ingestion of sporulated oocysts by the intermediate hosts results in tissue cyst development. Toxoplasma gondii in these intermediate hosts is present in form of tachyzoites or bradyzoites. The tachyzoites are the rapidly dividing trophozoite form of T. gondii responsible for the spread of the infection and are destructive to tissues. The bradyzoites are the encysted form of T. gondii in muscle tissues or central nervous system (Esch and Petersen, 2013).

Although studies on toxoplasmosis abound in Africa (Kistiah et al., 2012; Rouabhi et al., 2019; Oyeyemi et al., 2020), very few associated the parasitic disease with psychosis or any of psychosis-related variables (James et al., 2013; Wokem and Onosakhonm, 2018). Most case control studies on association between seroprevalence of T. gondii and psychotic disorders were conducted in the Middle Eastern countries of the world (Table 2). Data from different parts of the world have consistently showed an increase in the burden of chronic toxoplasmosis measured by anti-Toxoplasma gondii IgG antibodies in patients with neuropsychiatric disorders (Table 2). Unfortunately, despite the high burden of toxoplasmosis and psychosis in the Sub-Saharan African countries, very few case control studies on impact of toxoplasmosis on psychosis are available in the region.

A meta-analysis of case-control studies showed that acute psychosis was significantly associated with higher level of T. gondii IgM antibodies in comparison to the control group (Monroe et al., 2015). In another study, increased occurrence of antibodies against T. gondii was also observed in patients with first episode of schizophrenia (Torrey et al., 2007). Additional evidence on post-mortem brain tissue also confirmed the same (Arias et al., 2012). The seroprevalence of chronic T. gondii infection in the Middle East ranges from 31-78%. This increase may not be unconnected to the unrest in the region. The frequent unrest in the Middle East (Iran and Iraq) may trigger both psychological distress and poor socio-economic conditions of many people in the region which have been strongly linked to increase in the incidence of toxoplasmosis (Carellas et al., 2014). War and unrest could render a number of the people homeless and increase their exposure to T. gondii oocysts. In Sub-Saharan African countries, similar conditions are expected as poor socio-economic conditions have been strongly associated to psychiatric conditions (Ardinton and Case, 2010). However, there are no sufficient data to validate the seroprevalence of toxoplasmosis in psychiatric patients in the region. In South America, psychotic disorder is higher among racial minority such as immigrants, African American/Black, and Latino American/Hispanic. A large proportion of these groups are prone to economic hardship that can induce psychotic condition and increase exposure to T. gondii.

4.0 Falciparum malaria: life cycle and clinical epidemiology of cerebral malaria

Malaria parasite has a complex life cycle comprising a female Anopheles mosquito (the definitive host) and a human host (intermediate host). Plasmodium infective stage called the sporozoites are conveyed into the liver following an infected female Anopheles mosquito bite. The infective form invades the liver cells and multiplies repeatedly to produce a schizont comprising several merozoites which are released into the bloodstream. These merozoites invade the red
blood cells and multiply asexually to form schizonts which rupture to release several other merozoites which invade new red blood cells. Some of these blood stage merozoites become differentiation into male and female gametocytes which are taken up by mosquitoes during blood meal and undergo series of morphological and biochemical changes in order to be ready to infect another human host. There are three major clinical manifestations of severe malaria caused by *P. falciparum* viz; cerebral malaria (CM), severe malarial anaemia and respiratory distress (Kotlyar et al., 2014). Among these forms of severe malaria, CM is considered to be the most life threatening form and responsible for most malaria death accounting for approximately 15% and 20% mortalities among children and adults, respectively (Wang et al., 2015). It was also previously reported that CM is responsible for at least 2.3 million deaths annually with 0.5 million African children contributing to this number (Boivin, 2002).

Clinically, the main symptoms of the disease are headache, mild neck stiffness, impaired consciousness, muscle pain, seizures, convulsion and neurological abnormalities along with coma (Luzola and Ngoyi, 2019). Indeed, in African children, these neurological abnormalities manifest as three primary deficits: differences in cognitive and behavioural aspect, motor abnormalities, and even epilepsy (Luzola and Ngoyi, 2019). The latter might serve as the causal link between the CM and psychosis. Hence, understanding the complex interrelationship and partnership between these two deadly partners will require a thorough overview of the studies that attempt to interconnect the two or, at least, their related parameters. This will especially be more appealing when the entire African continent, the hotspot of the CM, is considered.

Starting from West Africa, five studies were reported mainly from Ghana and Gambia (Table 3). Among them, the oldest study was from Accra, Ghana, involving 31 pediatric patients where 20 (64.5%) were confirmed to have CM based on a consistent clinical course, parasitaemia and diagnostic histopathology (Wolf-Gould et al., 1992). For these patients, the mean initial Glasgow coma score was 10.4 which suggest that they would withdraw from painful stimuli without localization or would require painful stimuli before opening their eyes in addition to confusion and incoherence during verbalisations. These clearly indicate a wide range of changes in mental status in the CM patients (Wolf-Gould et al., 1992). Subsequently, Armah et al. (2007) used a post-mortem data from the Ghanaian children, with 64.2% CM as the mortality cause, to demonstrate that the parasite induces a local cerebral dysregulation in the production of IP-10, IL-8, MIP-1β, PDGFβb, IL-1ra, Fas-L, sTNF-R1, and sTNF-R2 and that, these modulatory effects may be involved in CM neuropathology. With these observations, both inflammatory and apoptotic mechanisms may be elicited locally in the human brain during CM that could have led to the damage of the constituent cells of the BBB (Armah et al., 2007). Although the authors did not monitor the direct link of their findings to psychosis but such a breakdown of the BBB demonstrated in the study might be associated with occurrence of psychotic event. Other studies have also confirmed that the disruption of BBB is a mechanism that facilitates the transmission of apicomplexes like *T. gondii* and *P. falciparum* into the brain (Wohlfert et al., 2017; Nishanth and Schlüter, 2019), and the occurrence of the two in the brain has been strongly linked to psychosis (Wokem and Onosakponome, 2018; Jenkins et al., 2019). Conversely, in a study from the same site in Accra, Ghana, 45% of severe malaria patients had CM which was significantly associated with retinal whitening, a sign of retinal ischaemia (Essuman et al., 2010). Such a high prevalence of retinopathy in these CM patients is an indication that the retina and the brain may be suffering from ischaemia (Essuman et al., 2010). In addition to the above-mentioned CM-induced effects, post recovery neurological sequelae such as convulsions, behavioural problems as well as visual and hearing defects have been reported in West African CM patients. Specifically, 23.3% survivors of CM in the Gambia had neurological sequelae on discharge from the hospital which was decreased to 8.6 and 4.4% at 1 and 6 months, respectively (van Hensbroek et al., 1997). However, these numbers were reduced to 3.3% and 5.3% when the patients were treated with artemether and quinine respectively after five months of discharge (Table 3).

CM is associated with short- to long-term cognitive impairments as a result of brain injury in many of its child survivors (Bangirana et al., 2006). Hence, the frequency of these cognitive deficits such as working memory, attention and learning among Ugandan CM children were investigated (Boivin et al., 2007). Initially, 23.5% of the study population had CM and 6 months after discharge, 21.4% of the children with CM had some form of cognitive impairment including working memory (11.9%) and attention (16.7%) in addition to increased seizure frequency and prolonged coma duration (Boivin et al., 2007). However, in a 2 year follow up study, these children with CM had cognitive deficits primarily in the area of attention (18.4%) with a 3.67 fold increased risk for a cognitive deficit compared to normal children in the community suggesting a long term cognitive impairment in 1 of 4 child survivors (John et al., 2008). Furthermore, hyporeflexia on admission and neurologic deficits were recorded in the patients during the 2 year follow up. Meanwhile, in a retrospective study where 31.2% of the study population had CM, a prevalence of epilepsy was recorded (9%) in addition to deficits in cognition, behaviour and other neurological deficits (Carter et al. 2005). Unfortunately, these are the few studies available from the East Africa to provide insights into the epidemiology of the disease, especially in relation to some neuropsychological manifestation of CM. Meanwhile, the data clearly demonstrated high prevalence of CM in addition to its profound effects on cognitive developments (Table 3).

Retinopathy has been identified as an important clinical sign in the diagnosis and prognosis of CM. This informed the decision of most authors with interest in CM from the Southern Africa to focus more attention to the retinal pathology in paediatric CM (Table 3). In a prospective study of 326 patients with complicated malaria, 278 (85.3%) patients were reported to have CM and among them, 170 (61.15%) had some degree of retinopathy which was strongly associated with subsequent death in the CM patients (Beare et al., 2004). However, other studies showed that 79.7% (Postels et al., 2014) and 54.6% of the Malawian CM patients had retinopathy (White et al., 2009). Moreover, another prospective cohort study of the retinopathy-positive CM patients identified 31.8% to have neurological sequelae such as epilepsy and behavioural disorders (Kampondeni et al., 2013) and surprisingly, some adverse neurological
outcomes were also observed in retinopathy-negative CM patients (Postels et al., 2014). Meanwhile, the retinopathy-positive and retinopathy-negative CM in Malawian children could be distinguished by the level of plasma concentrations of the parasite histidine rich protein 2 (pHRP2) which is a known predictor of intracerebral parasite sequestration (Seydel et al., 2012). Although most of the CM-based studies from the Southern Africa originate from Malawi and highly focused to retinopathy, it is clear that there is a high prevalence of the CM in the region with long term consequences on the productivity of the country while it is difficult to extrapolate or associate the data to psychosis, at least, in the present form (Table 3).

5.0 Concomitant occurrence of malaria and toxoplasmosis: the known to the unknown

The co-existence of malaria and toxoplasmosis within a single host is influenced by the ability of mosquito vectors of *Plasmodium* spp. and sporulated oocyst of *T. gondii to thrive in similar environmental conditions (Oyeyemi et al., 2020; Okunola and Oyeyemi, 2020). In sub-Saharan Africa, malaria and toxoplasmosis are highly prevalent thus increasing the chances of co-infection.

While studies abound on epidemiology of single infection by *P. falciparum and T. gondii*, very few reports are available on co-infection of the two parasites. Meanwhile, several reports have associated malaria and toxoplasmosis with infections like hepatitis virus, HIV and helminths (Simpore et al., 2006; Ouermi et al., 2009; Cuadros et al., 2011; Morenikeji et al., 2016a,b; Jegele et al., 2017; Helegebe et al., 2018; Anabire et al., 2019). Only three countries in Sub-Saharan Africa had epidemiological data on co-infection of malaria and toxoplasmosis (Table 3). These studies were mostly conducted among pregnant women and children aged (0-6 years). This is expected as these population strata suffer the greatest morbidities associated with these parasitic infections. Prevalence of co-infection of the two parasites was as high as 17.7% in pregnant women in Ghana and 20.0% among Cameroonian children. This is of serious public health importance owing to reported disease sequelae such as low birth weight, anaemia, still birth and hypertension common to the two infections (Blay et al., 2015). There is paucity of data on the co-infection of these pathogens, therefore, robust evidence-based epidemiological data are needed to ascertain the true dynamics of clinical pictures associated with the co-occurrence of malaria and toxoplasmosis.

Several single infection studies involving *Plasmodium* spp. and *T. gondii* have established similarities in their cellular processes and biochemical pathways. This suggests that during co-infections, competitive interactions between the parasites may influence the dynamics of the pathogenicity of the parasites, pregnancy outcomes (Hill and Dubey, 2002), severity of anaemia and mortality (Desai et al., 2007; Marchioro et al., 2015), and the extent of neurological and cerebral pathology (Torrey and Volkens, 2003; Renia et al., 2012). The damage of placental disc resulting from sequestration of the two parasites in the placental can also influence foetal and pregnancy outcomes (Onditi et al., 2015). Despite the possibilities of increase in morbidities due to co-infection of the two protozoan parasites, information on epidemiology, immunology and interactions of their concomitant infections are strikingly limited.

The history of implication of malaria in neuropsychiatric disorders dates back to the aftermath of World War I (WWI) in 1916–1918 (Forrester, 1920). As early as this period, several reports had consistently linked baffling set of several neuropsychiatric disorders including psychosis to malaria (Pope, 1914; Carlill and Korsakow, 1917; Paiseau, 1919; Papastratigakis, 1922). The same are recently reported in different populations (Yorasan et al., 2015; Ekram et al., 2016; Idro et al., 2016; Singh et al., 2016; Okere, 2018; Jenkins et al., 2019). While malaria-induced psychosis is caused by *Plasmodium vivax* found predominantly in Asia and Latin America, in Sub-Saharan Africa, cerebral malaria caused by *P. falciparum* has also been associated with mental health disorders especially in children (Sowunmi, 1993; Murphy and Breman, 2001; Idro et al., 2016). Several mechanisms have been linked to CM pathogenesis. These include microvasculature obstruction due to cytoadherence of *P. falciparum* (using PIEMP-1 and ICAM-1) with erythrocytes, excessive production of TNF-α, activation of endothelial cell, dysfunction of BBB, and intracranial hypertension (Idro et al., 2010; Smith, 2014). These processes are inter-related during induction of brain injury. Impaired BBB may result in intracranial hypertension which in turn causes hypoxia, reduction in nutrient delivery and cerebral perfusion pressure. The outcomes of these pathological interactions could result in ischemic injury, cerebral herniation, brainstem compromise and death (Walker et al., 1994; Newton et al., 1997). Some of these processes at one stage or the other can result in a psychotic disorder (Duggal, 2005; Jellinge, 2012). It is important to also note, however, that some of the treatment for malaria can also induce psychosis independently. For instance, there are reports of a possible meloquine-induced psychotic disorder preceded by a prodromal phase of dizziness, sleeplessness, and generalised anxiety (Tran et al., 2006). Other antimalarial drugs, especially other 4-aminopyrimidines (e.g. chloroquine) and 8-aminoquinolines (e.g. primaquine and pamaquine), have also been implicated in acute onset of psychotic states in patients (Nevin and Croft, 2016).

**Toxoplasma gondii** invades the central nervous system (CNS) to establish a chronic infection in the host. Similar to severe *P. falciparum* infection, *T. gondii* is able to compromise the integrity of the BBB in order to establish infection in the brain (Schütler and Barragan, 2019). *T. gondii* has strong affinity for almost all nucleated cells within and around the CNS. The parasite’s cysts persistence in the CNS during chronic infection even after clearance from peripheral organs and the primary manifestation of congenital infection in the CNS make *T. gondii* infection neurotropic. The transmission and persistence of *T. gondii* is closely related to resulting immune responses which minimize parasite-inflicted damage, and promote spread and induction of *T. gondii*-associated immunopathology (Schütler and Barragan, 2019). A correlation between *T. gondii* infection in mice and increased level of dopamine, the main neurotransmitter implicated in psychosis, in the brain has been reported (Huber et al., 2005). Changes in the dopaminergic neuromodulatory system have also been reported among patients with latent *Toxoplasma* infection (Skalova et al., 2006; Krishnan et al., 2009). There are presently no study on concomitant morbid effects of malaria parasites and *T. gondii* on psychosis.
Evidence from single infection by each parasite, however, suggests a grievous consequence should infection of the two parasites occur concurrently.

Organic psychosis and the underlying immunological and inflammatory processes can shed more light on pathophysiology of the more common non-organic psychotic disorders such as schizophrenia (Keshavan and Keneko, 2013). Anisman and Hayley (2012) reviewed the relationship between pro-inflammatory immune response, many non-communicable diseases and mental disorders but studies that have evaluated this three-way relationship in malaria and toxoplasmosis are very few. A recent study, however, has implicated some malaria-associated inflammatory mediators in the pathogenesis of psychotic disorders (Jenkins et al., 2019) while some relatively larger studies have implicated cerebral toxoplasmosis in the pathogenesis of psychosis (Khalil and Rashwan, 1996; Meira et al., 2014).

Tumour necrosis factor alpha (TNF-α) has been suggested as the pro-inflammatory cytokine that underlies the mechanism of depression. Up-regulation of TNF-α through activation of serotonin transporters (SERT), hypothalamo-pituitary-adrenocortical axis (HPA axis), and indoleamine 2,3-dioxygenase 1 enzyme (IDO 1) results in tryptophan depletion (Krishnasad et al., 2012). The cellular mediated immune responses in malaria parasite and T. gondii infections are similar with TNF-α playing a central role. High level of TNF-α was reported to be associated with severe malaria (including cerebral malaria) and cerebral toxoplasmosis (Meira et al., 2014; Nasr et al., 2014). In a recent study conducted in Kenya among patients with malaria, association was found between the presence of psychotic symptoms and increased levels of IL-6, IL-8, and IL-10, and lower levels of IL-1β among patients with malaria (Jenkins et al., 2019). In the same study, a statistically significant association was found between increased serum levels of TNF-α and psychotic symptoms in malaria. Pro-inflammatory cytokines such as IFN-γ, IL-1, IL-4 and IL-10 which are differentially expressed by neurons, specialized glial cells, microglial cells, CD4+ and CD8+ T cells have been reported to worsen mental disorders (Miller et al., 2011). These immune mediators have also been strongly linked to malaria and toxoplasmosis pathogenesis (Roberts et al., 1996; Meira et al., 2014; Jenkins et al., 2019). They play important role through modulation of neurotransmission with co-infection of malaria and toxoplasmosis potentiating the latent ability to exacerbate neuropsychiatric disorders such as psychosis.

6.0 Management of cerebral malaria and toxoplasmosis in relation to psychotic conditions

Prompt and effective treatment of malaria helps to prevent development into a severe disease. Parenteral artesunate is generally adopted as the recommended standard treatment option for severe malaria in children and adult following two clinical trials that established its superiority over quinine (Dondorp et al., 2005; 2010). Data have shown that intravenous and intramuscular administration of artesunate are equally potent in causing a significant reduction in P. falciparum burden in cases of severe malaria in children (Kremsner et al., 2016). Despite the improved chemotherapy potency of artesunate, the case fatality rates of cerebral malaria remain high (Dondorp et al., 2005). To confer therapeutic advantage of reducing morbidity due to severe malaria, an adjunctive therapy in addition to artemisinin-derivatives was proposed. However, none of the suggested adjunctive therapy has been successful in reducing death and neurological disorders associated with severe malaria (Varo et al., 2018). It is important to state that nearly all other antimalarial drugs have presented neuropsychiatric adverse effects including psychosis except artesunate or its combined therapies (Aneja et al., 2019). This therefore makes artemisinin-based antimalarials the therapies of choice due to improved efficacy and minimal drug-induced psychotic disorders.

There are limited therapeutic options for toxoplasmosis. The administration of haloperidol (an antipsychotic medication) and valproic acid (used to stabilize mood) in T. gondii infected individuals can help to prevent abnormal behaviours (Webster et al., 2006). In mouse model, behavioural responses during latent toxoplasmosis can be modified by dopamine uptake inhibitor GBR12909 (Skalova et al., 2006). Other effective drugs work to circumvent the folate pathway by inhibiting dihydrofolate reductase (DHF) and dihydropteroate synthetase (DHPS) enzymes (Konstantinovic et al., 2019). Pyrimethamine and trimethoprim are DHFR inhibitors used to manage acute toxoplasmosis. The potency of the two drugs is improved when used in combination with sulfonamides which are DHPS inhibitor. Treatment needs may vary in pregnant women at different gestational age. The minimal adverse effects of spiramycin a macrolide antibiotic makes it a drug of choice in pregnant women to prevent maternal-fetal transmission of T. gondii. However, the drug suffers from its ability to cure congenital infection once established as it lacks the ability to cross the placental wall (Robert-Gangneux et al., 2011). Pyrimethamine-sulfonamides based chemotherapy (especially Pyrimethamine-sulfadiazine combination) is recommended for congenital toxoplasmosis infection in pregnant women from 16th gestational week onwards (Dunay et al., 2018). A study reported 72% lower odds of intracranial lesions in neonates of mothers treated with pyrimethamine-sulfonamides based chemotherapy within 4 weeks after seroconversion (Gras et al., 2005). This may denote decreased risk of psychosis in infants of treated mothers as intracranial lesions has been associated with late onset of psychosis (Galasko et al., 1988). The 1994 Chicago Collaborative Treatment Trial (CCTT) has recommended a continuous entire first year treatment with pyrimethamine-sulfadiazine combination therapy in congenitally infected child (Maldonado et al., 2017).
# Table 1: Prevalence of psychosis and psychotic related disorders in selected countries

| Countries      | Location                                                                 | Sample size | Methods of confirming diagnosis | Type of population          | Prevalence (%) | References                  |
|----------------|---------------------------------------------------------------------------|-------------|---------------------------------|------------------------------|----------------|-----------------------------|
| Bangladesh     | Savar-Nabinagar area                                                      | 766         | Clinical                        | General population           | 1.17           | Hosain et al. (2007)        |
| Chile          | Six different cities and 5 regions of the country                         | 1008        | CIDI                            | Prisoners                   | 0.8 – 5.7      | Mundt et al. (2013)         |
| Ethiopia       | Addis Ababa                                                               | 217         | SCAN                            | Homeless                     | 41.0           | Fekadu et al. (2014)        |
| Kenya          | Kisumu, Meru, Murang, Nairobi, Nakuru, Mombasa, and Port Reitz             | 2963        | CIDI                            | University students          | 23.0           | Ndetel et al. (2012)        |
| Kenya          | Northern district of Nairobi                                              | 169         | MINI Plus                       | Mental health outpatients    | 56.3           | Aillon et al. (2014)        |
| Netherland     | Dutch provinces of North Holland, South Holland, Utrecht, Gelderland, North Brabant and Limburg | 1545       | K-SADS                          | Ethnic minority youth        | 33.0-49.0%     | Adriaanse et al. (2015)     |
| Nigeria        | Southwester and North-central Nigeria                                     | 4985        | CIDI                            | General population           | 21.06          | Gureje et al. (2010)        |
| Nigeria        | Ibadan                                                                    | 115         | SCID                            | TB patients                  | 81.7           | Lasebikan and Ige (2015)    |
| Norway         | Sogn and Fjordane                                                         | 1080        | CIDI                            | General population           | 0.4            | Kringleen et al. (2006)     |
| Somalia        | Minnesota                                                                 | 600         | SCID                            | Somalia refuge mental health patient | 80.0         | Kroll et al. (2011)         |
| South Africa   | Cape Town                                                                 | 100         | SCID                            | Methamphetamine dependence   | 13.0           | Akindipe et al. (2014)      |
| Turkey         | Izmir metropolitan area                                                   | 4011        | CIDI                            | General population           | 0.74           | Binbay et al. (2012)        |
| Turkey         | Urban area of Izmir                                                       | 1268        | CIDI                            | General population           | 3.6            | Alptekin et al. (2009)      |
| Uganda         | Jinja and Iganga in Busoga region                                          | 387         | SCID                            | Mental health patients consulting traditional healers | 29.7     | Abbo et al. (2009)          |

SCID: Structure Clinical Interview for DSM-IV, CIDI: Composite International Diagnostic Interview
SCAN: Schedules for Clinical Assessment in Neuropsychiatry, K-SADS: Kiddie Schedule for Affective Disorders and Schizophrenia, MINI Plus: Mini Plus International Neuropsychiatric Interview five
Table 2: Seroprevalence of toxoplasmosis among schizophrenic patients from case control studies

| Countries     | Region      | Sample size (n)     | Prevalence (cases vs control) | References                  |
|---------------|-------------|---------------------|--------------------------------|------------------------------|
| Iran          | Middle East | 100 cases 99 control| IgG; 59.0% vs 39.3%            | Khodashenas et al. (2019)    |
| Iran          | Middle East | 80 cases 99 control | IgG; 35.0% vs 25.3%            | Ahmad et al. (2010)          |
| Iran          | Middle East | 100 cases 200 control| IgG; 78.0% vs 53.3%            | Khademvatan et al. (2014)    |
| Iraq          | Middle East | 96 cases 96 control | IgG; 53.0% vs 23.0%            | Mahmoud and Hasan (2017)      |
| Saudi Arabia  | Middle East | 63 cases 55 control | IgG; 31.57% vs 14.55%          | Al-Hussainy et al. (2015)     |
| Brazil        | South America| 48 cases 40 control  | IgG; 56.41% vs 56.25% IgM; 7.5% vs 4.17% | Campos-Carli et al. (2017) |
| United States | North America| 1481 cases 571 control | IgG; 9.6% vs 6.1%          | Yolken et al. (2017)         |
| United States | North America| 219 cases 618 control | IgG; 41.4% vs 35.2%          | Xiao et al. (2009)          |
| China         | Asia        | 94 cases 87 control  | IgG; 25.53% vs 10.34%         | Sun et al. (2005)           |
| Malaysia      | Asia        | 101 cases 55 control | IgG; 51.5% vs 18.2% IgM; 4.0% vs 0% | Omar et al. (2015)          |
| Malaysia      | Asia        | 144 cases 144 control| IgG; 37.5% vs 34.0%           | Emelia et al. (2012)        |
| Nigeria       | Wes Africa  | 140 cases 140 control| IgG; 30.7% vs 17.85% IgM; 7.14% vs 8.57% | James et al. (2013)         |
| Egypt         | North Africa| 60 cases 20 control  | IgG; 56.7% vs 40.0%           | El-Sayed et al. (2012)       |
| Tunisia       | North Africa| 236 cases 117 control| IgG; 74.8% vs 53.8%           | Eshili et al. (2016)         |
Table 3: Epidemiology of cerebral malaria among children in Sub-Saharan African countries

| Countries | Region          | Sample size (n) | Prevalence of cerebral malaria and associated morbidities                                                                 | References                        |
|-----------|-----------------|-----------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Ghana     | West Africa     | 19              | Mortality case was 64.2%                                                                                                      | Armah et al. (2007)               |
| Ghana     | West Africa     | 58              | • 45% had CM • 45% had severe anaemia • 10% had respiratory distress                                                        | Essuman et al. (2010)             |
| Ghana     | West Africa     | 31              | • 64.5% had CM                                                                                                                | Wolf-Gould et al. (1992)          |
| Gambia    | West Africa     | 576             | • 20.5% death mortality (in artemether group) against 21.5% in quinine group                                                  | van Hensbroek et al. (1996)       |
| Gambia    | West Africa     | 624             | • 23.3% of survivors had neurologic sequelae on discharge                                                                   | van Hensbroek et al. (1997)       |
| Uganda    | East Africa     | 65              | 12–14% of children with a history of CM may develop long-term cognitive impairments.                                           | Bangirana et al. (2004)           |
| Uganda    | East Africa     | 165             | At 2-year follow-up testing, 26.3% of children had CM and 18.4% with uncomplicated malaria had cognitive deficits in ≥1 area, as compared with 7.6% of community children. | John et al. (2008)                |
| Uganda    | East Africa     | 186             | • 23.5% had CM 6 months after discharge, 21.4% of children with CM had cognitive deficits, compared with 5.8% of community children. | Boivin et al. (2007)              |
| Kenya     | East Africa     | 487             | • 31.2% had CM and 9% were reported to have epilepsy, • 32% had malaria with complicated seizures and were reported to have epilepsy  • The epilepsy was ‘active’ in 5% survivors of CM and 6% for malaria with complicated seizures | Carter et al. (2005)              |
| Malawi    | Southern Africa | 326             | 85.3% had CM and of these 61.15% had some degree of retinopathy                                                               | Beare et al. (2004)               |
| Malawi    | Southern Africa | 2464            | • 17% mortality (between 1996-2010) • Mortality is higher in cerebral malaria coinfection with HIV (23%) than HIV-uninfected children (17%) | Hochman et al. (2015)             |
| Malawi    | Southern Africa | 38              | Neurological deficits indicative of cerebral malaria; • behavioural disorders (31.8%), • developmental delay/gross neurologic deficits (60.5%), • | Kampondeni et al. (2013)          |
| Malawi    | Southern Africa | 34              | 64.7% had CM associated with retinopathy                                                                                       | Lochhead et al. (2003)            |
| Malawi    | Southern Africa | 173             | • Mortality rate was 9.2% • 22.2% had preexisting neuroradiologic abnormality                                                   | Postels et al. (2014)             |
| Malawi    | Southern Africa | 152             | • 79.7% had CM associated with retinopathy • 50% had moderate-to-severe increased cerebral volume • 10% had cerebellar herniation • 66.4% had CM associated with retinopathy | Potchen et al. (2012)             |
| Malawi    | Southern Africa | 101             | • 50% had moderate-to-severe increased cerebral volume • 10% had cerebellar herniation • 66.4% had CM associated with retinopathy | Seydel et al. (2012)              |
| Malawi    | Southern Africa | 168             | • 15% died • 84% had severe brain swelling • 27% of the survivors had severe brain swelling                              | Seydel et al. (2015)              |
| Malawi    | Southern Africa | 64              | • 54.6% had CM • 45.3% had comas from other illness                                                                            | White et al. (2009)               |
| Zambia    | Southern Africa | 83              | • 17% death mortality (in deferoxamine group) against 22% in placebo group • 50.6% recovery rate (in deferoxamine group) against 49.4% in placebo group • 80% survival in quinine group against 79% in artemotil group | Gordeuk et al. (1992)             |
| Zambia    | Southern Africa | 95              |                                                                                                                             | Thuma et al. (2000)               |
Table 4: Epidemiology of co-occurrence of malaria and toxoplasmosis in some Sub-Saharan Africa countries

| Countries  | Location   | Sample size (n) | Population        | Prevalence of coinfection (%) | Year | References                                      |
|-----------|------------|----------------|-------------------|-------------------------------|------|------------------------------------------------|
| Cameroon  | Nkolbisson | 315            | Febrile children  | 5.6                           | 2014 | Achonduh-Atijegbe et al. (2016)                 |
| Cameroon  | Nkolbisson | 315            | Febrile children  | 20.0                          | 2015 | Cumber et al. (2016)                            |
| Ghana     | Accra      | 79             | Pregnant women    | 17.7                          | 2015 | Blay et al. (2015)                              |
| Ghana     | Kumasi     | 183            | Pregnant women    | 2.1                           | 2014 | Arthur-Mensah et al. (2018)                     |
| Sudan     | Gadaref    | 28 (malaria positive cases) | Blood donors | 7.0                           | 2013 | Salih et al. (2014)                             |

7.0 Conclusion

Malaria and toxoplasmosis remain a major global health challenge in Sub-Saharan Africa. Studies abound on the epidemiology of their single infections and their related morbidities but their concomitant infections are rarely studied. Although psychosis has been widely linked to social and psychosocial factors, evidence from this review had further suggested that the two parasites may contribute to symptoms of psychosis. However, it is impossible to adequately appreciate the exclusive dual contribution of malaria and toxoplasmosis to psychosis-related symptoms as there are no existing data that examine this. Efforts therefore should be channeled in this direction. The complex interactions between these parasites in the brain and their roles in upsetting psychosis-related neurotransmitting factors should be especially examined. The impact of treatment of the two diseases on improvement or exacerbation of psychiatric conditions should be evaluated. Evidence-based studies on the impact of malaria and toxoplasmosis concurrent infection on psychotic condition is recommended.

Conflict of interest

The authors declare that there are no potential conflicts of interest

Author’s contribution

Conception: MAI, OA, AM, EJA, IAO, AM, CUC, OTO.

Design: OTO

Review co-ordination: MAI, EJA, IAO, OTO

Writing of manuscript: MAI, OA, AM, EJA, IAO, AM, CUC, KNU, OTO

References

Abbo, C., Ekblad, S., Waako, P., Okello, E., Musisi, S., 2009, The prevalence and severity of mental illnesses handled by traditional healers in two districts in Uganda. African Health Sciences, 9(S2):16-22.

Achonduh-Atijegbe, O.A., Mfuh, K.O., Mhange, A.H.E., Chedjou, J.P., Taylor, D.W., Neurukar, V.R., 2016, Prevalence of malaria, typhoid, toxoplasmosis and rubella among febrile children in Cameroon. BMC Infectious Diseases, 16:658.

Adriaanse, M., van Domburgh, L., Hoek, H.W., Susser, E., Doreleijers, T.A.H., Velting, W., 2015, Prevalence, impact and cultural context of psychotic experiences among ethnic minority youth. Psychological Medicine, 45:637–646.

Ahmad, D., Mehdi, S., Sayed, H.H., Sayed, A.K., Shirzad, G., 2010, Serological survey of Toxoplasma gondii in schizophrenia patients referred to Psychiatric Hospital, Sari City, Iran. Tropical Biomedicine, 27(3):476–482.

Aillon, J., Ndetei, D.M., Khasakhala, L., Ngi, W.N., Achola, H.O., Akinyi, S., Ribero, S., 2014, Prevalence, types and comorbidity of mental disorders in a Kenyan primary health centre. Social Psychiatry and Psychiatric Epidemiology, 49:1257–1268

Al-Hussainy, N.H., Al-saedi, A.M., Al-lehaibi, J.H., Al-lehaibi, Y.A., Al Sehli, Y.M., Afifi, M.A., 2015, Serological evidences link toxoplasmosis with schizophrenia and major depression disorder. Journal of Microscopy and Ultrastructure, 3:148–153.

Alptekin, K., Ulas, H., Akdeke, B.B., Tüümüldü, M., Akvardar, Y., 2009, Prevalence and risk factors of psychotic symptoms: in the city of İzmir, Turkey. Social Psychiatry and Psychiatric Epidemiology, 44(11):905-910.

Akindipe, T., Wilson, D., Stein, D.J., 2014, Psychiatric disorders in individuals with methamphetamine dependence: prevalence and risk factors. Metabolic Brain Disease, 29:351–357.

Anahire, N.G., Aryee, P.A., Abdul-Karim, A., Quaye, O., Awandare, G.A., Helegbe, G.K., 2019, Impact of malaria and hepatitis B co-infection on clinical and cytokine profiles among pregnant women. PloS One 14(4): e0215550.

Aneja, J., Goya, D., Choudhary, B., 2019, Psychosis consequent to antimalarial drug use in a young child. Journal of Family Medicine and Primary Care, 8(5):1781–1783.

Anisman, H., Hayley, S., 2012, Illness comorbidity as a biomarker? Journal of Psychiatry & Neuroscience, 37(4):221–223.

Ardington, C. and Case, A. (2010). Interactions between mental health and socioeconomic status in the South African national income
dynamics study. Journal for Studies in Economics and Econometrics, 34(3):69-85.

Arias, I., Sorlozano, A., Villegas, E., de Dios Luna, J., Mckenney, K., Cervilla, J., Gutierrez, B., Gutierrez, J., 2012, Infectious agents associated with schizophrenia: a meta-analysis. Schizophrenia Research, 136(1-3):128-136.

Armah, H.B., Wilson, N.O., Sarfo, B.Y., Powell, M.D., Bond, V.C., Anderson, W., Adjei, A.A., Gyasi, R.K., Tettey, Y., Wiredu, E.K., Tongren, J.E., 2007, Cerebrospinal fluid and serum biomarkers of cerebral malaria mortality in Ghanaian children. Malaria Journal, 6(1):147.

Arthur-Mensah Jr, R., Blay, E.A., Ayi, L., Larbi, J., Suzuki, T., Ohta, N., 2016, Effectiveness of SP- IPTp for malaria and evidence for the need of T. gondii infection preventive policy during pregnancy in Ghana. Journal of Infectious Diseases and Epidemiology, 2018.

Bangirana, P., Idro, R., John, C.C., Boivin, M.J., 2006, Rehabilitation for cognitive impairments after cerebral malaria in African children: strategies and limitations. Tropical Medicine & International Health, 11(9):1341-1349.

Beare, N.A., Southern, C., Chalira, C., Taylor, T.E., Molyneux, M.E., Harding, S.P., 2004, Prognostic significance and course of retinopathy in children with severe malaria. Archives of Ophthalmology, 122(8):1141-1147.

Binbay, T., Alptekin, K., Elbi, H., Zagli, N., Drukker, M., Aksu Tanik, F., Ozkunay, F., Onay, H., Os, J.V., 2012, Lifetime prevalence and correlates of schizophrenia and disorders with psychiatric symptoms in the general population of Izmir, Turkey. Turkish Journal of Psychiatry, 23:149–160.

Blay, E.A., Ghansah, A., Otchere, J., Koku, R., Kwofie, K.D., Bimi, L., Takashi, S., Ohta, N., Ayi, L., 2015, Congenital toxoplasmosis and pregnancy malaria detection post-partum: Effective diagnosis and its implication for efficient management of congenital infection. Parasitology International, 64(6):603–608.

Boivin, M.J., 2002, Effects of early cerebral malaria on cognitive ability in Senegalese children. Journal of Developmental Behaviour & Paediatric, 23(5):353–364.

Boivin, M.J., Bangirana, P., Byarugaba, J., Opoka, R.O., Idro, R., Jurek, A.M., John, C.C., 2007, Cognitive impairment after cerebral malaria in children: a prospective study. Pediatrics, 119(2):e360-e366.

Carellos, E.V., de Andrade, G.M., Vasconcelos-Santos, D.V., Janário, J.N., Romanelli, R.M., Abreu, M.N., da Silva, F.M., Loures, I.R., de Andrade, J.Q., Caiaffa, W.T., UFMG Congenital Toxoplasmosis Brazilian Group, 2014, Adverse socioeconomic conditions and oocyst-related factors are associated with congenital toxoplasmosis in a population-based study in Minas Gerais, Brazil. PloS One, 9(2):e88588.

Campos-Carli, S.M., Vieira, E.L.M., Rocha, N.P., Oliveira, K., Guimarães, F.C., Barbosa, L.G., Barros, J.L.V.M., Okusaga, O., Martins-Filho, O.A., Salgado, J.V., Teixeira, A.L., 2017, Toxoplasma gondii infection and chronic schizophrenia: is there any association? Archives of Clinical Psychiatry (São Paulo), 44(6):145-148.

Carilli, H. (1917). Korsakow’s psychosis in association with malaria. Lancet, 189:648–650.

Carson, C.M., Phillip, N., Miller, B.J., 2017, Urinary tract infections in children and adolescents with psychosis. Schizophrenia Research, 183:36-40.

Carter, J.A., Ross, A.J., Neville, B.G., Obiero, E., Katana, K., Mung’ala-Odera, V., Lees, J.A., Newton, C.R., 2005, Developmental impairments following severe falciparum malaria in children. Tropical Medicine & International Health, 10(1):3-10.

Corrê-a-Oliveira, G.E., do Amara, J.L., da Fonseca, B.A.L., Del-Ben, C.M., 2017, Zika virus infection followed by a first episode of psychosis: another flavivirus leading to pure psychiatric symptomatology. Revista Brasileira de Psiquiatria, 39:381–382.

Cuadros, D.F., Branscum, A.J., Crowley, P.H., 2011, HIV–malaria co-infection: effects of malaria on the prevalence of HIV in East sub-Saharan Africa. International Journal of Epidemiology, 40(4):931–939.

Cumber, S.N., Yvonne-Estelle, K.N., Jalla, S., 2016, The effects of toxoplasmosis and malaria coinfection on malaria parasite density and hematological parameters in children (0-6 Years) in the Nkolbisson Health District, Cameroon. Journal of Family Medicine and Health Care, 2(4):81-88.

Desai, M., ter Kule, F.O., Nosten, F., Asamoah, K., Brabin, B., Newman, R.D., 2007, Epidemiology and burden of malaria in pregnancy. Lancet in Infectious Disease, 7:93–104.

Dondorp, A., Nosten, F., Stepniewska, K., Day, N., White, N., 2005, Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. Lancet, 366:717–725.

Dondorp, A.M., Fanello, C.I., Hendriksen, I.C., Gomes, E., Seni, A., Chhaganlal, K.D., et al. 2010, Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. Lancet, 376:1647–1657.

Duggal, H.S., 2005, Idiopathic intracranial hypertension presenting with psychiatric symptoms. J Neuropsychiatry Clinical Neuroscience, 17(3), 146-147.

Dunay, I.R., Gajurel, K., Dhakal, R., Lisenfeld, O., Montoya, J.G., 2018, Clinical Microbiology Reviews, 31(4):e00057-17.

Ekram, T., Afzal, K., Saxena, R., 2016, Pediatric psychosis in the emergency room: Could it be Plasmodium vivax malaria? Current Pediatric Research, 20(1&2): 83-84.

El-Sayed, N.M., Ismail, K.A., Ahmed, S.A., Ezz-El-Din, H.M., Azzam, H.M.E., 2012, Possible association between Toxoplasma gondii infection and schizophrenia: Egyptian study. Infectious Diseases in Clinical Practice, 20(6):394–399.

Emilia, O., Amal, R.N., Ruzanna, Z.Z., Shahida, H., Azzubair, Z., Tan, K.S., Aadila, S.N., Siti, N.A.M., Aisah, M.Y., 2012, Seroprevalence of anti-Toxoplasma gondii lgG antibody in patients with schizophrenia. Tropical Biomedicine, 29(1):151–159.

Esch, K.J., Petersen, C.A., 2013, Transmission and epidemiology of zoonotic protozoal diseases of companion animals. Clinical Microbiology Reviews, 26(1):58–85.

Esshili, A., Thabet, S., Jemli, A., Trifa, F., Mechri, A., Zaafrane, F., Gaha, L., Juckel, G., Babba, H., Bel Hadj Jrad, B., 2016, Toxoplasma gondii
infection in schizophrenia and associated clinical features. Psychiatry Research, 245:327–332.

Essuman, V.A, Ntim-Amponsah, C.T, Astrup, B.S, Adjei, G.O, Kurztchals, J.A., Ndamu, T.A, Goka, B, 2010. Retinopathy in severe malaria in Ghanian children - overlap between fundus changes in cerebral and non-cerebral malaria. Malaria Journal, 12(9):232.

Fekadu, A., Hanlon, C., Gebre-Eyesus, E., Agedew, M., Solomon, H., Teferra, S., Gebre-Eyesus, T., Baheretieb, Y., Medhin, G., Shibre, T., Workneh, A., Tegegn, T., Ketema, A., Timms, P., Thornicroft, G, Prince, M., 2014. Burden of mental disorders and unmet needs among street homeless people in Addis Ababa, Ethiopia. BMC Medicine, 12:138.

Forrester, A. (1920). Malaria and insanity. Lancet, 195:16–17.

Galasko, D., Kwo-On-Yuen, P.F, Thal, L., 1988. Intracranial mass lesions associated with late-onset psychosis and depression. Psychiatric Clinics of North America, 11(1):151–166.

Global Burden of Disease (GBD) 2017. Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 390:1211–1259.

Gordeuk, V., Thuma, P., Brittenham, G., McLaren, C., Parry, D., Backenstose, A., Biemba, G., Msika, R., Holmes, L., McKinley, E., 1992. Effect of iron chelation therapy on recovery from deep coma in children with cerebral malaria. New England Journal of Medicine, 327(21):1473–1477.

Gras, L., Wallon, M., Pollak, A., Cortina-borja, M., Evengard, B., Hayde, M., Petersen, K., Gilbert, R., 2005. Association between prenatal treatment and clinical manifestations of congenital toxoplasmosis in infancy: a cohort study in 13 European centres. Acta Paediatrica, 94(12):1721–1731.

Gureje, O., Okwosegun, O., Adebayo, K., Stein, D.J., 2010. The prevalence and profile of non-affective psychosis in the Nigerian Survey of Mental Health and Wellbeing. World Psychiatry: Official Journal of the World Psychiatric Association (WPA), 9(1):50–55.

Hayes, J.F., Marston, L., Walters, K., King, M.B., Osborn, D.P., 2017. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000–2014. British Journal of Psychiatry, 211:175–181.

Helegbe, G.K., Aryee, P.A., Mohammed, B.S, Wemakor, A., Kolbila, D., Abubakari, A-W., Askanda, S., Alhassan, R., Barnie, C., Aboagwewaa, Donkoh, A.A., Ofosu, E., 2018. Seroprevalence of malaria and hepatitis B coinfection among pregnant women in Tamale metropolis of Ghana: A cross-sectional study. Canadian Journal of Infectious Diseases and Medical Microbiology, Article ID 5610981, 12 pages.

Hill, D., Dubey, J.P., 2000. Toxoplasma gondii: transmission, diagnosis, and prevention. Clinical Microbiology and Infection, 8:634–640.

Hjorthøj, C., St確保, A.E., McGrath, J.J., Nordentoft, M., 2017. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. Lancet Psychiatry, 4:295–301.

Hochman, S.E., Madalone, T.F., Wassmer, S.C, Mbale, E., Choi, N., Seydel, K.B., Whitten, R.O, Varughese, J., Grau, G.E, Kaniza, S., Molyneux, M.E., Taylor, T.E., Lee, S., Milner, D.A, Jr, Kim, K, 2015. Fatal pediatric cerebral malaria is associated with intravascular monocytes and platelets that are increased with HIV coinfection. mBio, 6(5):e01390-15.

Hosain, G.M.M., Chatterjee, N., Ara, N., Islam, T., 2007. Prevalence, pattern and determinants of mental disorders in rural Bangladesh. Public Health, 121:18–24.

Huber, M., Kirchner, E., Karner, M. and Pycha, R. 2007. Delusional parasitosis and the dopamine transporter: A new insight of etiology? Medical Hypotheses, 68(6):1351–1358.

Idro, R., Mwaesige, A. K., Asea, B., Bambirana, P., Opoka, R.O., Lubowa, S.K, Cikleman, M. S., John, C.C, Nalugya, J. 2016. Cerebral malaria is associated with long-term mental health disorders: a cross sectional survey of a long-term cohort. Malaria Journal, 15:184.

Idro, R., Marsh, K., John, C.C, Newton, C.R.J., 2010. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. Pediatric Research, 68(4):267–274.

Islam, M.M., Ali, M., Ferroni, P., Underwood, P., Alam, M.F., 2003. Prevalence of psychiatric disorders in an urban community in Bangladesh. General Hospital Psychiatry, 25:353–357.

James, B.O., Agbonihe, I.O, Okolo, M., Lawani, A.O. and Omoaregba, J.O., 2013. Prevalence of Toxoplasma gondii infection among individuals with severe mental illness in Nigeria: a case control study. Pathogens and Global Health, 107(4):189–193.

Jegede, F.E., Oyeyi, T.L, Abdulrahman, S.A., Mbah, H.A., Badru, T., Agbakwuru, C., Adebokun, O., 2017. Effect of HIV and malaria parasites co-infection on immune-hematological profiles among patients attending anti-retroviral treatment (ART) clinic in Infectious Disease Hospital Kano, Nigeria. PloS One 12(3): e0174233.

Jellinger, K.A., 2012. Cerebral correlates of psychotic syndromes in neurodegenerative diseases. Journal of Cellular and Molecular Medicine, 16(5):995–1012.

Jenkins, R., Mbata, J., Singleton, N. and White, B, 2010. Prevalence of psychotic symptoms and their risk factors in urban Tanzania. International Journal of Environmental Research and Public Health, 7:2514-2525.

Jenkins, R., Ong’ech, M., Odongo, C., Ongeri, L., Sifuna, P., Omollo, R., Leonard, B., Ogutu, B., 2019. Malaria, mental disorders, immunity and their inter-relationships - A cross sectional study in a household population in a health and demographic surveillance site in Kenya. EBioMedicine, 39:369–376.

Jongsma, H.E., Turner, C, Kirkbride, J.B., Jones, P.B., 2019, International incidence of psychotic disorders, 2002–17: a systematic review and meta-analysis. Lancet Public Health, 4:e229–44.

John, C.C, Bangirana, P., Byarugaba, J., Opoka, R.O, Idro, R, Jurek, A.M., Wu, B, Boivin, M.J., 2008. Cerebral malaria in children is associated with long-term cognitive impairment. Pediatrics, 122(1):e92-e99.
Kistiah, K., Frean, J., Winiecka-Krusnell, J., Barragan, A., 2012, Unexpectedly low seroprevalence of toxoplasmosis in South Africa. Onderstepoort Journal of Veterinary Research 79(2), Art. #486, 1 page.

Lasebikan, V.O., Ige, O.M., 2015, Prevalence of toxoplasmosis in tuberculosis patients and their nontuberculosis family contacts in a multidrug treatment-resistant treatment center in Nigeria. General Hospital Psychiatry, 37(6), 542–547.

Lee, Y., Cherkerzian, S., Seidman, L.J., Papandonatos, G.D., Savitz, D.A., Tsuang, M.T., Goldstein, J.M., Buka, S.L., 2019, Bacterial infection during pregnancy associated with psychosis in offspring. American Journal of Psychiatry, 177(1):66-75.

Lindgren, M., Torniainen-Holm, M., Härkänen, T., Dickerson, F., Yolken, R.H., Surisraji, J., 2018, The association between Toxoplasma and the psychosis continuum in a general population setting. Schizophrenic Research, 193:329-335.

Lochhead, J., Movaffaghy, A., Falsini, B., Winstanley, P.A., Mberu, E.K., Riva, C.E., Molyneux, M.E., Taylor, T.E., Harding, S.P., 2003, The effect of quinine on the electroretinograms of children with pediatric cerebral malaria. The Journal of Infectious Diseases, 187:1342-1345.

Luzolo, A.L., Ngyoi, D.M., 2019, Cerebral malaria. Brain Research Bulletin, 145:53–58.

Khalil, S.S., Rashwan, E.A., 1996, Tumour Necrosis Factor-Alpha (TNF-alpha) in Human Toxoplasmosis. Journal of Egyptian Society of Parasitology, 26(1):53-61.

Kampondeni, S.D., Potchen, M.J., Beare, N.A., Seydel, K.B., Glover, S.J., Taylor, T.E., Birbeck, G.L., 2013, MRI findings in a cohort of brain injured survivors of pediatric cerebral malaria. The American Journal of Tropical Medicine and Hygiene, 88(3):542-546.

Keshavan, M.S., Kaneko, Y., 2013, Secondary psychoses: an update. World psychiatry: Official Journal of the World Psychiatric Association (WPA), 12(1), 4–15.

Khademvatan, S., Saki, J., Khajeddin, N., Izadi-Mazidi, M., Beladi, R., Shaﬁee, B., Salehi, Z., 2014, Toxoplasma gondii exposure and the risk of schizophrenia. Jundishapur Journal of Microbiology, 7(11):e12776.

Khodashenas, S., Foroughi-Parvar, F., Mosayebi, M., Ghasemi, M., Ghaeleha, A., Tapaket, L., 2019, A Case-Control Study of Seroprevalence of Toxoplasma gondii in Dementia Patients in Arak and Hamadan, West of Iran. Archive of Clinical Infectious Diseases, 14(5):e97116.

Konstantinovic, N., Guegan, H., Stijner, T., Belaz, S., Robert-Gangneux, F., 2019, Treatment of toxoplasmosis: current options and future perspectives. Food and Waterborne Parasitology, 12:e00036.

Kotlyar, S., Nteziyaremye, J., Olupot-Olupot, P., Akech, S.O., Moore, C.L., Maitland, K., 2014, Spleen volume and clinical disease manifestations of severe Plasmodium falciparum malaria in African children. Transactions of the Royal Society of Tropical Medicine and Hygiene, 108(5):283–289.

Kremser, P.G., Adegnika, A.A., Hounkpatin, A.B., Zinsou, J.F., Taylor, T.E., Chimalzeni, Y., et al, 2016, Intramuscular artesunate for severe malaria in African children: a multicenter randomized controlled trial. PLoS Medicine, 13:e1001938.

Kringlen, E., Torgersen, S., Cramer, V., 2006, Mental illness in a rural area: a Norwegian psychiatric epidemiological study. Social Psychiatry and Psychiatric Epidemiology, 41:713–719.

Krishnan, R.R., Keefe, R., Kraus, M., 2009, Schizophrenia is a disorder of higher order hierarchical processing. Medical Hypotheses, 72(6):740–744.

Kroll, J., Yusuf, A.L., Fujiwara, K., 2011, Psychoses, PTSD, and depression in Somali refugees in Minnesota. Social Psychiatry and Psychiatric Epidemiology, 46:481–493.

Mahmoud, S.S., Hasan, M.S., 2009, Seroprevalence of toxoplasmosis among Schizophrenic patients. Yemeni Journal for Medical Sciences, 3(1):1-7.

Maldonado, Y.A., Read, J., Committee on infectious diseases, 2017, Diagnosis, treatment, and prevention of congenital toxoplasmosis in the United States. Pediatrics, 139(2): e20163860.

Marchioro, A.A., Colli, C.M., Ferreira, E.C., Viol, B.M., Araújo, S.M., Falavigna Guilherme, A.L., 2015, Risk factors associated with toxoplasmosis and toxocariasis in populations of children from nine cities in southern Brazil. Journal of Helminthology, 89(4):428-432.

Meira, C.S., Pereira-Chioccola, V.L., Vidal, J.E., Brandão de Mattos, C.C., Motole, G., Costa-Silva, T.A., Gava, R., Frederico, F.B., de Mattos, L.C., 2014, Toxoplasma Groups. Cerebral and ocular toxoplasmosis related with IFN-γ, TNF-α, and IL-10 levels. Frontiers in Microbiology, 5:1-7.

Morenikeji, O.A., Eleng, I.E., Atanda, O.S., Oyeyemi, O.T., 2016a, Renal related disorders in concomitant Schistosoma haematobium-Plasmodium falciparum infection among children in a rural community of Nigeria. Journal of Infection and Public Health, 9(2):136–142.

Morenikeji, O.A., Adeleye, O., Omoruyi, E.C., Oyeyemi, O.T., 2016b, Anti-Schistosoma IgG responses in Schistosoma haematobium single and concomitant infection with malaria parasites. Pathogens and Global Health, 110(2):74-78.

Monroe, J.M., Buckley, P.F., Müller, B.J., 2015, Meta-analysis of anti-Toxoplasma gondii IgM antibodies in acute psychosis. Schizophrenia Bulletin, 41(4):989–998.

Montazemi, M., Mehrzadi, S., Sharif, M., Sarvi, S., Tanzifi, A., Aghayan, S.A., Daryani, A. 2018, Drug resistance in Toxoplasma gondii. Frontiers in Microbiology, 9:2587.

Muehler, L., Shahri, A.R., Chitnis, C.E., 2015, Development of vaccines for Plasmodium vivax malaria. Vaccine, 33:7489–7495.

Mundt, A.P., Alvarado, R., Fritsch, R., Poblete, C., Villagra, C., Kastner, S., Priewe, S., 2013, Prevalence rates of mental disorders in Chilean prisons. Plos One, 8(7):e69109.

Murphy, S.C., Breman, J.G., 2001, Gaps in the childhood malaria burden in Africa: cerebral malaria, neurological sequelae, anemia, respiratory distress, hypoglycemia, and complications of pregnancy. In: Breman, J.G., Egan, A., Keusch, G.T. editors. The intolerable burden of malaria: a new look at the numbers: supplement to volume 64(1) of the American Journal of Tropical Medicine and Hygiene. Northbrook (IL): American
Paiseau, G., 1919, Malaria during the war. Lancet,

Ndeti, D.M., Muriungi, S.K., Owoso, A., Mutiso, V.N., Mbwayo, A.W., Khasakhala, L., Barch, D.M., Mamah, D., 2012, Prevalence and characteristics of psychotic-like experiences in Kenyan youth. Psychiatry Research, 196(2-3): 235–242.

Nevin, R.L., Croft, A.M., 2016, Psychiatric effects of malaria and antimalarial drugs: historical and modern perspectives. Malaria Journal, 15:332.

Newton, C.R., Crawley, J., Sowumni, A., Waruiru, C., Mwangi, L, English, M., Murphy, S., Winstanley, P.A., Marsh, K., Kirkham, F.J., 1997, Intracranial hypertension in Africans with cerebral malaria. Archives of Disease in Childhood, 76:219–226.

Nishanth, G., Schlüter, D., 2019, Blood-brain barrier in cerebral malaria: pathogenesis and therapeutic intervention. Trends in Parasitology, 35(7):516–528.

Okere, C.A. 2018, Psychiatric effects of malaria in Ibadan City, Nigeria. A Master of Public Health Thesis of the University of Roehampton, London, Pp 1-57.

Okunlola, O.A., Oyeyemi, O.T., 2019, Spatio-temporal analysis of association between incidence of malaria and environmental predictors of malaria transmission in Nigeria. Scientific Reports, 9:17500.

Omar, A., Bakar, O.C., Adam, N.F., Osman, H., Osman, A., Suleiman, A.H., Manaf, M.R., Selamat, M.L., 2015, Seropositivity and serointensity of Toxoplasma gondii antibodies and DNA among patients with schizophrenia. Korean Journal of Parasitology, 53(1):29-34.

Onditi, F.I., Nyamongo, O.W., Omwandho, C.O., Maina, N.W., Maloha, F., Farah, I.O., King, C.L., Moore, J.M., Ozwara, H.S., 2015, Parasite accumulation in placenta of non-immune baboons during Plasmodium knowlesi infection. Malaria Journal, 14:118.

Onkoba, N.W., Chimbari, M.J., Mukaratirwa, S., 2015, Malaria endemicity and co-infection with tissue-dwelling parasites in Sub-Saharan Africa: a review. Infectious Diseases of Poverty, 4:35.

Ouermi, D., Simpore, J., Belem, A.M.G., Sanou, D.S., Karou, D.S., Doumbia, N., Bisseye, C., Onadja, S.M., Pietra, V., Pignatelli, S., Gnoula, C., Nikiema, O., Ouermi, D., Simpore, J., Belem, A.M.G., Sanou, D.S., Karou, D.S., 2012, Genetic analysis of Toxoplasma gondii isolates collected from adult Toxoplasma gondii negative cerebral malaria. The American Journal of Tropical Medicine and Hygiene, 91(5):943-949.

Potchen, M.J., Kampondeni, S.D., Seydel, K.B., Birbeck, G.L., Hammond, C.A., Bradley, W.G., Demarco, J.K., Glover, S.J., Ugorji, J.O., Latourette, M.T., Siebert, J.E., Molyneux, M.E., Taylor T.E., 2012, Acute brain MRI findings in 120 Malawian children with cerebral malaria: new insights into an ancient disease. The American Journal of Neuroradiology, 33(9):1740–1746.

Rouabhi, M., Amairia, S., Amdouni, Y., Boussadoun, M.A., Ayadi, O., Al-Hosary, A., Rekik, M., Ben Abdallah, R., Aoun, K., Darghouth, M.A., Wieland, R., Gharbi, M., 2019, Toxoplasma gondii infection and toxoplasmosis in North Africa: a review. Infection par Toxoplasma gondii et toxoplasmosine en Afrique du Nord: synthèse. Parasite (Paris, France), 26:6.

Radua, J., Ramella-Cravaro, V., Ioannidis, J.P.A., Reichenberg, A., Phiphopthatsanee, N., Amir, T., Thoo, H.Y., Oliver, D., Davies, C., Morgan, C., McGuire, P., Murray, R.M., Fusar-Poli, P., 2018, What causes psychosis? An umbrella review of risk and protective factors. World Psychiatry, 17(1):49–66.

Renia, L., Howland, S.W., Claser, C., Gruner, A.C., Suwanarusk, R., Teo, T., Russell, B., Ng, L.F.P., 2012, Cerebral Malaria: Mysteries at the blood-brain barrier. Virulence, 3:193–201.

Robert-Gangneux, F., Dardé, M.L., 2012, Epidemiology of and diagnostic strategies for toxoplasmosis. Clinical Microbiology Reviews, 25(2):264–296.

Robert-Gangneux, F., Murat, J.-B., Fricker-Hidalgo, H., Brencher-Pinchart, M.-P., Gangneux, J.-P. and Pelloux, H. (2011). The placenta: a main role in congenital toxoplasmosis? Trends in Parasitology, 27(12):530–536.

Ruizendael, E., Tahita, M.C., Geskus, R.B., Versteege, I., Scott, S., d’Alessandro, U., Lombo, P., Derra, K., Trouwe-Coiluy, M., de Jong, M.D., Schallig, H.D.F.H., Tinto, H., Mens, P.F., 2017, Increase in the prevalence of mutations associated with sulfadoxine–pyrimethamine resistance in Plasmodium falciparum isolates collected from early to late pregnancy in Nanoro, Burkina Faso. Malaria Journal, 16:179.

Saha, S., Chant, D.C., Welham, J.L., Murgrath, J.J., 2006, The incidence and prevalence of schizophrenia varies with latitude. Acta Psychiatraca Scandinavica, 114:36–39.

Salih, A.S.A.A., 2014, Prevalence of malaria and toxoplasmosis in donated blood at the central blood bank, Gadarf State. A M.Sc. Thesis of the Department of Medical Laboratory Sciences – Parasitology and Medical Entomology – University of El-Neelain, Sudan, pp 35.

Schlüter, D., Barragan, A., 2019, Advances and challenges in understanding cerebral toxoplasmosis. Frontiers in Immunology, 10:242.
Seydel, K.B., Fox, L.L., Glover, S.J., Reeves, M.J., Penson, P., Muiruri, A., Mpakiza, A., Molyneux, M.E., Taylor, T.E. 2012. Plasma concentrations of parasite histidine-rich protein 2 distinguish between retinopathy-positive and retinopathy-negative cerebral malaria in Malawian children. The Journal of Infectious Diseases, 206(3):309-318.

Seydel, K.B., Kampondeni, S.D., Valim, C., Potchen, M.J., Milner, D.A., Muwalo, F.W., Birbeck, G.L., Bradley, W.G., Fox, L.L., Glover, S.J., Hammond, C.A., Heyderman, R.S., Chilingulo, C.A., Molyneux, M.E., Taylor, T.E., 2015, Brain swelling and death in children with cerebral malaria. New England Journal of Medicine, 372:1126-1137.

Simpore, J., Savadogo, A., Ilboudo, D., Ndambega, M.C., Esposito, M., Yara, J., Pignatelli, S., Pietra, V., Musumeci, S., 2006, Toxoplasma gondii, HCV, and HBV seroprevalence and co-infection among HIV-positive and -negative pregnant women in Burkina Faso. Journal of Medical Virology, 78(6):730-733.

Singh, V.B., Kumar, H., Meena, B.L., Chandra, S., Agrawal, J., Kanogiya, N., 2016, Neuropsychiatric Profile in HCV, and Yara, J., Pignatelli, S., Pietra, V., Musumeci, S., 2006, Toxoplasma gondii, HCV, and HBV seroprevalence and co-infection among HIV-positive and -negative pregnant women in Burkina Faso. Journal of Medical Virology, 78(6):730-733.
Wohlfert, E.A., Blader, I.J., Wilson, E.H., 2017, Brains and Brawn: Toxoplasma Infections of the Central Nervous System and Skeletal Muscle. Trends in Parasitology, 33(7):519-531.

Xavier, M., Correa, B., Canas, N., Guimarães, J., 2005, Sudden psychotic episode probably due to meningoencephalitis and Chlamydia pneumoniae acute infection. Clinical Practices and Epidemiology in Mental Health, 1:15.

Xiao, J., Buka, S.L., Cannon, T.D., Suzuki, Y., Viscidi, R.P., Torrey, E.F., Yolken, R.H. 2009, Serological pattern consistent with infection with type I Toxoplasma gondii in mothers and risk of psychosis among adult offspring. Microbes and Infection, 11(13): 1011–1018.

Yolken, R., Torrey, E.F., Dickerson, F., 2017, Evidence of increased exposure to Toxoplasma gondii in individuals with recent onset psychosis but not with established schizophrenia. PLoS Neglected Tropical Disease, 11(11): e0006040.