Dear Sir

Malaria with estimated annual global mortality from 700,000 to 2.7 million, caused by *Plasmodium falciparum*, the most deadly *Plasmodium* species prevails mainly in Africa (1,2). The pleomorphic clinical outcomes display a remarkable range of disease from acute primary stages to complicated clinical presentations, depending on the transmission intensity, age, immunity and genetic background of the affected individuals (3). Cerebral malaria (CM) is one of the manifestations of severe malaria with enormous morbidity and mortality worldwide. It affects approximately more than 500 million people annually, primarily in sub-Saharan Africa (WHO 2011). CM with the high case fatality rate remains one of the major causes of acquired disability throughout much of the tropical and subtropical world plagued by malaria (4,5). It imposes a substantial economic and palliative care and cost burden to households, which impedes economic development in countries with low national gross products.

**PRESENTATION OF THE HYPOTHESIS**

CM is characterised by a generalised systemic process with high overall level of cytokines related to predominant Th1 response. The shift of immune balance towards Th1 arm is simultaneous with under presentation of the Th2/T (reg) immune regulatory (5). Overproduction of Th1-related proinflammatory cytokines, mainly as interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), interleukin-1b (IL-1b) and IL-6 combined with underproduction of Th2-related anti-inflammatory cytokines, mainly as IL-10, IL-4 and transforming growth factor-β (TGF-β) is seen in CM (6,7). Raised levels of proinflammatory cytokines have been consistently observed in the cases affected with CM followed by schizont rupture (8). Th1-related proinflammatory cytokines modulate production of eicosanoides (prostaglandines and leukotrienes), thromboxane B2, 5-LOX, phospholipase A2, COX1 and COX2 in peripheral circulation (9). The balance between induced immune suppressive versus immune stimulating state by prostaglandins and leukotrienes, respectively, is critical for development of CM (9). Finally, these excreted inflammatory mediators lead to the upregulation of intercellular adhesion molecule-1 (ICAM-1), nitric oxide (NO) production and immune proliferation within spleen (10,11). The pathological scenario evolved from these molecular events is enhanced vessel leakage following pronounced cytoadherence of parasitised erythrocytes and activated mononuclear cells to vascular endothelial cells (6). Preliminary animal and human investigations showed that prior infection with parasites such as *Schistosoma hematonium*, *Ascaris lumbricoides* and hookworms has been associated with reduced malaria severity in an age and dose-dependent manner (6,12). Pre-existing helmintic infection has been shown to exert 64% protection against murine CM (6). The suppression of both cellular and humoral immune responses essential for establishment and maintenance of coinfecting parasites has been speculated as the main mechanism (13). This competitive
parasitic milieu is owned by the influential effects of excessive production of IL-4 and IL-10 by stimulated Th2 lymphocytes and decreased Th1 responses (6). Decreased TNF-α production and IL-6 secretion could simply reflect amplified Th2 responses through non specific B lymphocyte presentation (13). This pattern of cytokine expression is also observed consistently in non CM (6). The induced CD23/NO pathway, increased immunoglobulin E concentrations, decreased ICAM-1 expression and cytoadherence of parasitised red blood cells exert additive effects in this context (12). Therefore, it is translated clinically that factors which alter the polarisation of naïve T helper cells towards the Th2 phenotype can potentially improve disease profile. Several factors rather than pathogens can influence the host immune network particularly those causing chronic inflammation. Chronic non healing wounds, associated with arose chronic inflammatory state, alter the sum of Th1 versus Th2/T (reg) cytokines with promoted differentiation of precursor Th cells into the Th1 subset (14). Mutually, wounds might get chronic non healing state by standing in deteriorating Th1-dominant immune milieu. Complex inflammatory cascade in chronic non healing wounds is extensively characterised by suppression of IL-10, a prowound healing cytokine (14). Thus coexistence of persistent wounds might play a role in changing the clinical course of CM through elicited pathogenic Th1-type immune response. Lack of IL-10 predominance in chronic non healing wounds is such event seen in episodes of CM (6). The observed microcirculatory dysfunction and angiogenic failure in chronic non healing wounds is a favoured milieu for induction of CM’s pathogenesis (15,16). Hence, non healing wounds would synergistically enhance load on immune system in CM. The possible influence of chronic wounds on the acquisition of immunity against CM would likely result in a higher rate of CM. This combination might confer lethality and exacerbation of symptoms.

TESTING THE HYPOTHESIS
It needs to be determined at the population level whether patients with underlying chronic non healing wounds require a higher sequestered parasite biomass to develop CM or not. Each stage of wound carriage might play an important role in shaping the immunity against malaria and CM and this shared exposure should not be neglected simply. Both of these multifactorial diseases are largely seen in association with poor nutrition and socioeconomic status. The possible influence of chronic wounds on the immune response to malaria, parasite development and cytoadherence phenomena needs to be determined. Chronic non healing wounds continue to be a pandemic health problem (17). Animal studies would be of paramount value in this regard.

IMPLICATIONS OF THE HYPOTHESIS
Chronic wounds are major public-health problem in developing countries prone to CM: coendemic. The possibility that chronic non healing wounds could markedly affect the CM disease burden in malaria endemic area and their relevance to clinical disease deserves further investigations. Comparison between rate of CM resistance or tolerance between population widely devastated by chronic wounds and wound-free areas will illuminate the possible wound–CM interaction. Comparison of wound distribution among sites with peak occurrence of CM and variable malaria transmission intensities also seems helpful. This implies that treating one burden (wounds) could potentially relieve the other (CM), but it is not yet clinically proved. This would offer affordable means to roll back CM and its consequent complications and costs. If deleterious effects of concomitant non healing wounds on CM are confirmed, vigorous therapeutic measures for chronic wounds might become a priority in malaria endemic area before the progress towards CM. Perhaps, little paid attentions to the pre-existing non healing wounds merely before the onset of rainy seasons with the peak malaria transmissions would be of paramount impact on CM elimination. This seasonal attention to wounds or even every factor able to aggravate much of the hyperimmune responsiveness associated with CM expected to be economically more cost effective. The data regarding favoured season could be derived from district statistics and informed to resident clinicians. Considering the high prevalence of chronic non healing wounds in malaria endemic area
as sub-Saharan Africa and the fatality rate of CM in this area, the fundamental practical implication of dewounding on the outcome of CM will be perceived easier. It is also convincible to address this hypothesis that wounds will get non healing fate in the cases experienced fatal CM.

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REFERENCES


