

## IMPACT OF *PLASMODIUM FALCIPARUM* MALARIA ON PERFORMANCE AND LEARNING: REVIEW OF THE EVIDENCE

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**Abstract.** Despite the growing recognition that *Plasmodium falciparum* malaria constitutes a major threat to child survival, the indirect consequences of disease and infection on general human development have been less well described. This review suggests that malaria in childhood is likely to have effects on general cognitive and behavioral development, which range from subtle to profound. Nevertheless, our understanding of the numbers of affected children, and the persistence of and recovery from impairment remains ill defined. Only through large long-term studies will we be able to establish the wider consequences of malaria on communities in areas of the world where malaria is endemic.

### INTRODUCTION

Population scientists tend to focus on defining the direct fatal and morbid consequences of *Plasmodium falciparum* infection, whereas the indirect, consequential effects of malaria infection and disease remain poorly defined. In this article, we review the evidence and speculate on the potential influences of malaria on cognitive development, performance, and behavior, with an emphasis on malaria's effects on brain function.

The significance of the brain is undisputed in terms of overall human function, from supporting life to sensory functions and cognition to determining mood and social functioning. Cognition is a broad term that encompasses the acquisition of knowledge and the skills required to think and reason. The measurement of cognitive development involves the observation of performance on tasks from which the ability to apply internal mental processes can be inferred. Although the anatomy of the brain at birth appears complete, its functional development, which is dependent on the formation of intercellular connections, is concentrated after birth. This development occurs through a combination of physiological maturity and experience. Insult to the brain, or depletion in nutrients to supply brain tissue, can result in either complete or partial loss of function.

In general, the potential effects of malaria on cognitive development, performance, and motivation can be crudely divided into 2 groups: the debilitating effects resulting from brain insult due to an acute episode of severe and complicated malaria; and the potential impact on performance mediated through the effects of chronic infection, repeated illness, anemia, and undernutrition.

**The effects of brain insult on neurological, learning, and behavioral performance.** *The effects of age at insult on long-term neuropsychological impairment.* In assessing what might impact the persistence of or recovery from neuropsychological impairment, age emerges as a potentially important variable. There have been many debates about whether the young brain is more or less vulnerable to insult. Long-term impairments of cognition often follow early disease and injury, with new learning apparently more vulnerable to insult than already-learned procedures and skills. Impairments that develop early are not necessarily generalized, and not all children with apparently the same brain insult

have the same outcome. The immature brain does appear to have greater resilience to hypoxia, infarction, and local inflammation, all potentially important pathophysiological mechanisms involved in severe malaria.<sup>1</sup> Dramatic recovery of function can be observed and is often more rapid in younger children, possibly due to greater neuronal plasticity.<sup>2,3</sup> However, compensatory growth may not always be beneficial, and later development may be suboptimal because the earlier stages were not completed optimally.<sup>4,5</sup> Thus, deleterious effects may not emerge until several years later, and in addition, as children mature and the tasks required of them become more complex and demanding, the impact of even minor deficits is likely to be more profound.<sup>6,7</sup> There is thus a complex interaction between age of onset and recovery of function, such that the potential effects of early onset can best be explained by recognizing elements of both vulnerability and plasticity.<sup>1,3,8</sup>

The majority of patients with severe malaria with neurological involvement occur after the period of maximum cellular growth in the brain (< 12 months of age), during a period characterized by the rapid maturation in all brain regions but before the accelerated development of the frontal lobes (> 7.5 years of age).<sup>9</sup> The localization of many functions, such as language, may thus have already been established, but higher order functions (planning, decision-making, self-awareness, and social sensitivity) will have yet to be learned. Consequently, specific impairments—say, of language or memory—are likely to be directly attributable to damage to specific locations. Impairment in higher order (executive) functions, however, may be a consequence of suboptimal development during earlier stages of brain maturation, rather than direct damage per se.

*Gross neurological impairment after cerebral malaria.* Cerebral malaria is defined in clinical terms as the presence of coma due to malaria; however, its pathology stems from a series of complex mechanisms that may operate independently but that all result in a brain insult (Marsh K, unpublished data). Several factors may increase the risk of neurological sequelae after cerebral malaria, including hypoglycemia, multiple seizures, reduced cerebral perfusion pressure associated with raised intracranial pressure, hypoxia associated with microvascular obstruction, and tissue damage after induction of cytokine cascades (Marsh K, unpublished data).

Cerebral malaria has a high case-fatality rate when man-

aged under routine hospital conditions in developing countries (~30–40%). One assumes that in the absence of clinical intervention, survival is unlikely. The cerebral insult in patients who survive intervention potentially serves as a precursor of neuropsychological impairment. Observed impairments include hemiplegia or hemiparesis (weakness in one or both limbs on one side of the body), speech disorders, behavioral disorders, blindness, hearing impairment, epilepsy, and cerebral palsy. Children with cerebral palsy have a generalized increase in muscle tone and are severely disabled, requiring constant attention from a caregiver. The limited number of studies that has been undertaken in Africa suggests that gross neurological sequelae among hospital admissions who survive is 5–20%. The wide difference in methodology and in definitions of cerebral malaria underpin this variation in reported incidence.

We have therefore concentrated on 6 more recent studies that have used comparable diagnostic criteria (Peshu N and others, unpublished data from Kilifi, Kenya).<sup>10–14</sup> These studies report on a total of 1,854 children with cerebral malaria, of whom 302 (16.3%) died and 248 (16% of survivors) were reported to have neurological sequelae at discharge. Even with standardized criteria for the definition of cerebral malaria, the reported incidence varied between 9% ( $n = 118$ ) and 23% ( $n = 122$ ). Most of this variation probably stems from differences in what is taken to constitute a significant deficit on discharge, and many children examined within a few days of an encephalopathic illness will have residual problems such as ataxia that resolve rapidly over the next few weeks or months. More significant are those neurological sequelae that are persistent. The 6 studies differed in follow-up schedules and completeness of follow-up. Four of the studies covering 1,258 children had follow-up periods of at least 6 months; among this series, the overall rate for persisting neurological sequelae was 5.6% (Peshu N and others, unpublished data).

The prevalence of sensory and physical handicaps is far greater in children who also have mental handicaps compared the general population.<sup>15</sup> This does not mean that the neurological impairments described above will necessarily be accompanied by widespread impairment of cognitive function, but the association exists, and some overlap between the two is to be expected. Neurological sequelae will also have a direct impact on a child's development and functioning, with the impact of the impairment possibly changing over time and potentially being felt as much by other members of the family as the affected children themselves. For example, children with hemiparesis may be restricted socially through limitations on the games they can play with others. They may only be able to attend school if it is within easy walking distance, and they may be able to make only a limited contribution to domestic physical work (plowing, planting, washing, etc.). The contribution that they can make within the family may therefore become more limited as time progresses. Those more severely disabled place an added burden on caretakers as they grow: lifting and bathing a fully grown adult requires much greater physical strength than that required to care for a young child.

The impact of physical handicaps is also to a large extent dependent on the availability of aids and specialized equipment (e.g., hearing aids and wheelchairs). To many families

in areas in which malaria is endemic, this equipment is unavailable, too expensive to purchase, or unsuitable for the environment (e.g., wheelchairs have limited value on sandy terrain with no paved surfaces). Specialist educational provision is likewise limited. The consequence of a lack of appropriate resources is a restriction in the opportunities for learning and training and thus in the independence of the affected child. The burden of physical impairments after cerebral malaria, although showing a dramatic reduction in the numbers affected over time, is likely to have a greater impact with time on those children left with residual impairments and their families.

*Cognitive sequelae after brain insults during malaria.* There have been 2 published studies that have looked at the cognitive and neuropsychological sequelae of cerebral malaria in children, one in The Gambia and the other in Kenya.<sup>16,17</sup> The Gambia study included 36 children who were assessed only in terms of nonverbal functioning and motor development by use of translations of tests standardized for Western populations. The study excluded children who had a Blantyre Coma Score of  $> 2$  or who had gross neurological sequelae on discharge.<sup>10</sup> This study reported that among the 36 patients, the only residual effects after 41 months, when compared with matched controls, were on a test of balance, implying some impaired motor development. The results were interpreted as evidence of an absence of cognitive impairment in the absence of neurological impairment at discharge. This suggests that where impairment is observed, it will be generalized in nature, directly attributable to brain insult, and confined to ~5% of survivors.

A more complex picture was suggested by the Kenya study (Holding PA, unpublished data).<sup>17</sup> A total of 87 case patients were matched to controls and were assessed at ages 6–7 years, 3–4 years after discharge. Case patients were selected with a cutoff point of a Blantyre Coma Score of 4 or less (severe malaria with impaired consciousness). Children were only excluded if they were physically unable to manipulate the equipment at the time of assessment. The assessment battery applied had as its core information processing tasks, adapted from the Kaufman Assessment Battery for Children and included assessments of planning and attention, language development, achievement, visuomotor speed, and behavior problems.<sup>18</sup> Pairs were matched for age, sex, and socioeconomic and nutritional status.

Impairments of performance on the information-processing subtests, those most closely akin to the content of IQ tests, were concentrated in a minority “cognitively impaired” group. This group was defined as those whose performance fell at or below 2 standard deviations from the control group mean on 2 or more subtests. A total of 14% ( $n = 12$ ) of patients were so defined, compared with 5% of controls ( $n = 4$ ). The spectrum of impairment in this group ranged from severe (25% of the impaired group, requiring full-time care) to those with mild learning difficulties (50% of the impaired group, potentially requiring some specialist educational support in mainstream schools). The odds ratio associated with the development of cognitive impairment after severe malaria with impaired consciousness was found to be 4.5 (95% confidence interval, 1.2–16.5). Five (42%) members of the cognitively impaired group had shown no observable neurological impairment at discharge.

A more widespread continuum of deficits was found in other areas of functioning. A significantly depressed group performance was found in aspects of language, attention, and behavior, all with a quality of performance suggestive of an "immaturity" in the ability to initiate, plan, and carry out tasks, which comprise the executive functions. Impairment of these higher order functions is likely to be reflected in an increase in the difference between affected and unaffected children over time.

**Behavioral and psychiatric problems.** The relationship between severe malaria and behavioral problems has long been documented in adults, where severe malaria has been associated with psychotic and depressive disorders, memory impairments, irritability, and violence.<sup>19-22</sup> Several of these studies have suffered from methodological problems, not least of which is the problem in establishing a definitive diagnosis of malarial disease (studies were undertaken among discharged soldiers from the World War I, diagnosed as "neurasthenia," or retrospectively with traumatized veterans of the Vietnam war).<sup>19-22</sup> Nevertheless, there remains some evidence to suggest that cerebral malaria may result in major long-term neuropsychiatric symptoms.

Behavioral problems have also been recorded in children who had cerebral malaria in Nigeria.<sup>23,24</sup> In both studies, the problems that were documented in the children ranged from problems in self-care and independence, to the development of habitual routines and aggressive and abusive behavior, to hallucinations. No systematic study has yet been carried out in children that details the extent or persistence of these difficulties.

**Seizures as complications of clinical malaria: cognitive consequences.** Seizures are a common feature of malarial disease, regardless of its severity.<sup>25</sup> They occur in up to 85% of admissions with a diagnosis of cerebral malaria, with about half of these having an episode of status epilepticus.<sup>26</sup> The probable origin of seizures associated with malaria fall into 3 basic categories: those that are febrile; those that are associated with the excitotoxic process related to the presence of parasites; and those that are related to hypoxia (Crawley J, unpublished data).<sup>25,26</sup> Uncomplicated febrile seizures will have a good prognosis.<sup>27,28</sup> However, as > 50% of seizures begin with low or normal temperatures, malaria appears to be specifically epileptogenic.<sup>25</sup>

Of importance in determining outcome is the fact that even in children without other signs of neurological involvement, the majority of seizures appear to be prolonged, multiple, and complex. Without reference to malaria, all of these features have been associated with the development of subsequent unprovoked partial seizures and particularly with temporal lobe epilepsy.<sup>29</sup> A risk of 6% has been estimated for a single feature, up to 22% for a combination of features.<sup>30</sup> These children are also at a significantly increased risk of impairment in intellectual functions (~3 times more likely to score outside normal limits on IQ tests and to develop a range of social and educational difficulties).<sup>31-33</sup> The experience of one episode of status epilepticus has been shown to lead to cognitive sequelae (defined as IQ < 80) in ~30% of cases.<sup>34</sup> Temporal lobe epilepsy has been particularly associated with impairments of language and memory function and with behavioral disorders.<sup>35</sup>

Our own investigations have found that not all children

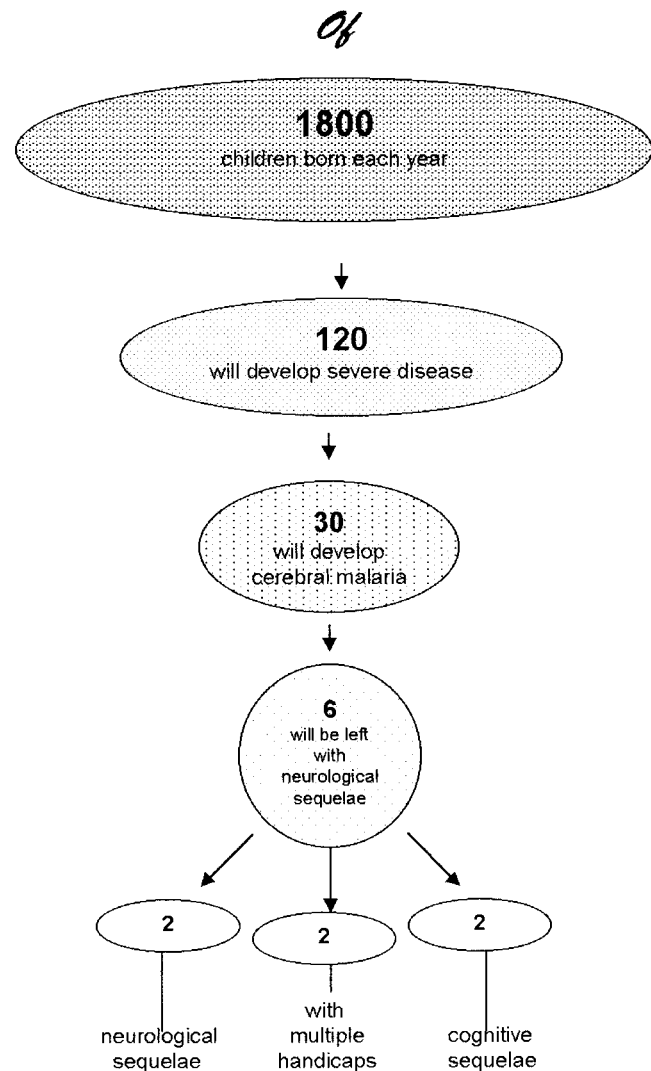


FIGURE 1. The pathways for poor outcome by levels of malaria.

who had seizures go on to develop either neurological or cognitive impairments, although all children who had cognitive impairments had also had at least one seizure.<sup>17</sup> Only a small number of our study children ( $n = 5$ ) were recorded as having had status epilepticus, and not all of these developed sequelae, either cognitive or neurological. Interestingly, neither of the children whose cognitive development was most globally impaired had incurred > 3 seizures during the course of their illness, nor had they been in status epilepticus. They did both later develop epilepsy. To explain the variations encountered in the literature on seizures in childhood suggests that account needs to be taken of both the nature of the seizures experienced and preinsult history. Current investigations are describing the former (Newton C, unpublished data; Holding P and others, unpublished data), but no birth cohort studies exist to shed light on the latter issue.

**Indirect consequences of malaria infection and mild disease on cognitive performance.** *The effects of parasitization.* Most children living under stable endemic conditions are chronically infected with the *P. falciparum* parasite. This state begins soon after birth and continues throughout childhood until antiparasitic immunity develops much later in life,

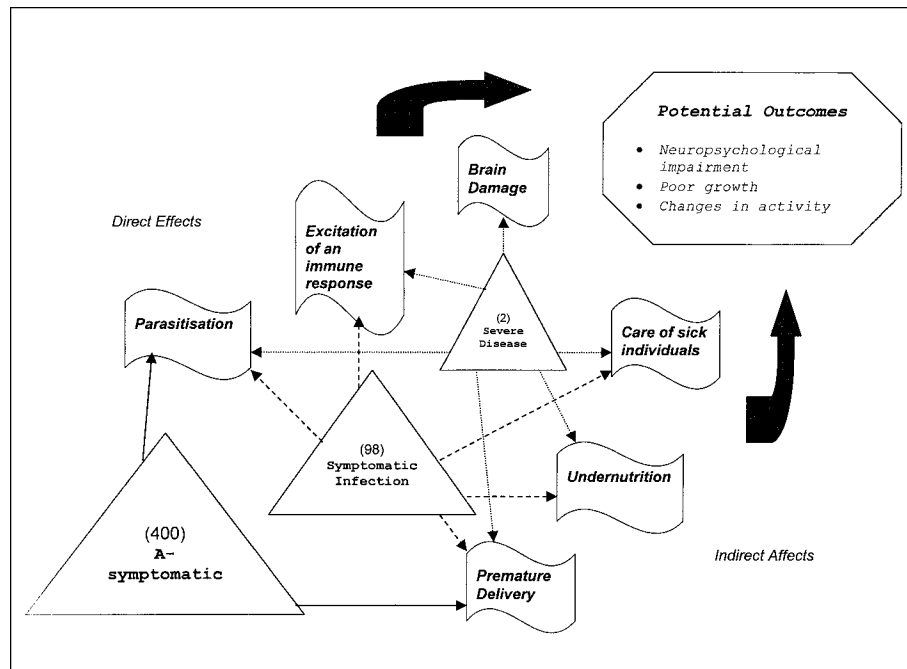


FIGURE 2. Direct impact on the community of malarial disease: the example of the Kilifi study area.

during early adulthood. During this early period, repeated new infections lead rapidly to a functional immunity against the severe and fatal consequences of infection, and immunity to the milder forms of clinical disease develop in later childhood. Nevertheless, the immunological, clinical, and indirect effects of persistent infection and reinfection remain poorly defined.<sup>36,37</sup>

For macroparasites, such as helminths, several mechanisms have been identified through which infection might affect cognition and cognitive development. The relative importance of each mechanism is likely to vary according to the parasite involved, the level of parasitization, the intensity of infection, and the age of the host at infection.<sup>38,39</sup> The mechanisms include a toxicity effect, leading to biochemical changes in the central nervous system; excitation of the immune system, leading to changes in behaviors related to appetite and reaction time; and physiological effects, such as discomfort and disturbed sleep, leading to reductions in activity levels or causing behavioral change.<sup>40–44</sup> Processes similar to these could be envisaged after malaria infection, although the current evidence is inconclusive (see section below on school-age children).

**Anemia and cognitive sequelae.** Anemia is a physiological state that can result from multiple processes. Although anemia is a common feature of both chronic infection and acute illness due to *P. falciparum*, the mechanisms involved are likely to be a result of a combination of the destruction of existing red blood cells and the failure to produce sufficient replacement cells. These processes themselves may not lead to a concomitant loss of iron, as is common with helminths that directly remove iron from the body.

Most anemia is associated with a reduction in oxygen-carrying capacity. This could affect physical performance or compound the effects of cerebral insult by reducing still further the available oxygen supplies to brain tissue. The as-

sociation between malarial anemia and performance has been little studied, and indirect evidence is limited. Studies in adults suggest no relationship between work capacity and malaria infection, measured by the relationship between heart rate after exercise and parasite infection.<sup>45,46</sup> Furthermore, an association between malarial anemia and the development of neurological sequelae after cerebral malaria has only been reported in a few small-scale studies.<sup>11,47</sup> Those that studied a much larger series have found no such association.<sup>10,27</sup>

The association between chronic anemia and cognitive deficits is attributed to the iron deficiency that causes the anemia, rather than the anemia per se.<sup>48–52</sup> Studies have shown that performance on developmental tests is lower in infants with iron deficiency anemia and that this difference persists some years after the period of deficiency.<sup>49,51</sup> But this is an inappropriate model for understanding the effects of severe malaria.

**Other nutritional effects.** Malnutrition and infection frequently coexist; however, the nature of the interrelationship between severe malaria and undernutrition has been the source of disagreement.<sup>53</sup> Studies with more limited series have suggested that malnutrition might be protective against malaria-related morbidity or mortality.<sup>54–56</sup> In contrast, in a large series in Kilifi (> 2,000 children), nutritional status (designated by either weight for height or mid-upper arm circumference) was found to be a risk factor for the development of disease (Marsh K and others, unpublished data). In a series of > 1,000 children with cerebral malaria in The Gambia, worsening nutrition (designated by weight for age) was associated with increasing mortality.<sup>57</sup> Others have suggested that although there is no association with morbidity, there is an association between worsening nutritional status and poor outcome (measured as death or neurological sequelae).<sup>58,59</sup> No study has yet looked in detail at the relation-

ship over time between nutritional status, severity of disease, and the recovery process, or with poor outcome, including the development of cognitive impairment and behavioral problems.

In the absence of malaria, malnutrition is associated with deficits in school achievement, performance on cognitive tests, poor attention, apathy, poor organizational behavior, and poor emotional control.<sup>48,60,61</sup> Undernutrition experienced prenatally and in the early years produces observable structural and functional changes in the brain, but brain damage alone does not fully explain these associations.<sup>62</sup> Undernutrition is also associated with the presence of multiple infections and with poor environmental stimulation; and it has not been possible to separate the effects of poor nutrition from those that are a consequence of a generally poor environment. This may also be the case with the effects of malarial infection and disease.

*Low birth weight and prematurity.* The effects of malaria infection during pregnancy on the weight and outcomes of newborn children have been well described.<sup>1</sup> Low birth weight is a well-documented risk factor for poor neurosensory, cognitive, and behavioral development, as well as limited school performance and academic achievement (Taylor HG and others, unpublished data).<sup>63,64</sup> However, there are subgroups with varying risk, the most vulnerable being children born prematurely (< 37 weeks' gestation). Between 2 to 4 times more children born prematurely will experience failure in school (compared with normal birth weight children) and will need specialist support or educational services.<sup>65</sup>

In studies in Europe and North America of low birth weight children born at term, the children appear to have less of a risk of developmental sequelae. This was not always found to be the case, and it is suggested that improvements in outcome for these children are directly attributable to improvements in perinatal care. Without specialist care at birth, the risk of a poor developmental outcome increases significantly. Furthermore, longer term follow-ups of both groups (preterm and full-term low birth weight children) have revealed that the pattern of difficulties changes over time, with more subtle learning difficulties emerging in late childhood and early adolescence that had not been revealed before.<sup>66</sup>

*Clinical malaria among school-age children.* In most endemic populations, the clinical consequences of malaria infection are concentrated among preschool children. There remains a risk of morbidity during the school-age period, but these risks are 30% lower compared with the preschool period for primary school children and 400% lower for secondary school children (Snow RW, unpublished data). Clinical attacks during school may create an indirect impact on performance through an impact on school attendance. However, a recent review of the evidence suggests that only 3–8% of all school absences are directly due to malaria in schoolchildren (between 13–50% of all medical reasons for absence; Brooker S and others, unpublished data). Clearly, a far greater proportion of absenteeism from schools in areas endemic for malaria are due to reasons unrelated to malaria. Furthermore, the effect of successful malaria suppression on improvements in attendance rates in school children, investigated during the 1950s, produced inconclusive evidence

that suppressing malaria improved school attendance.<sup>67,68</sup> The limited effects of clinical malaria on school attendance and performance underlies the basic acquisition of immunity before school age.

The caveat to this position is that disease risks among communities located along the fringes of stable transmission is likely to be much lower, resulting in significant risks persisting through late childhood and adulthood. These risks would be balanced against a risk of infection per se. We currently know very little about these disease risks in Africa.<sup>69</sup> In addition, among the alternative reasons for school absence may be included absences to care for younger siblings who are sick.

#### DISCUSSION

Cross-country studies of economic development and percentages of school-age children in school have both been inversely linked to the prevalence of malaria.<sup>70,71</sup> Such associations have led some to speculate on the role of *P. falciparum* in productivity, performance, and cognitive development. Indeed, it was suggested that the future economic and educational development of the colonial states of preindependence Africa critically depended on the eradication of malaria.<sup>72</sup> The obvious burden of malaria includes the economic implications of managing clinical disease and the psychological effects of bereavement associated with death, but there is a paucity of studies that have examined the consequences of malaria on learning and performance. The effects of *P. falciparum* on neuropsychological development and performance could potentially operate at all levels of the disease continuum. Figure 1 summarizes this relationship.

Despite the widely held view that chronic anemia leads to a decreased performance overall, there appears to be little evidence to support this position with respect to malaria-induced anemia. The links between anemia and cognitive development appear to be a result of the iron deficiency associated with the physiological state of anemia.<sup>48–52</sup> Assuming, then, that malaria infection is not associated with iron deficiency and that malarial anemia is not associated with a negative neurological outcome, the presence or absence of anemia during the course of infection is, in our opinion, unlikely to be an important risk factor for cognitive impairment. However, direct evidence is required before this assertion can be substantiated or refuted. Because the evidence suggests that malaria does not significantly contribute to school absenteeism, it is also unlikely to significantly impact the acquisition of skills taught in school. Finally, although there is evidence that persistent parasitization with macroparasites such as helminths impacts cognitive development, performance, and behavior, there is no evidence of such effects with plasmodial infections.

Malaria may make an indirect contribution to impaired development. For example, malaria infection and clinical disease are both likely to effect gross nutritional development. A suboptimal nutritional environment has been shown to affect brain development. By extension, it may be argued that malaria contributes to delayed cognitive development and function, mediated through its effects on undernutrition. This remains speculative, and long-term studies of cognition nested within long-term control programs would be neces-

sary to establish these hypothetical links. Perhaps of greater significance are the well-established links between malaria infection during pregnancy on intrauterine growth and subsequent birth weight, as the association between low birth weight and subsequent cognitive problems is well documented. The evidence for the indirect consequences of *P. falciparum* on cognition, performance, and behavior remains weak, largely because of the paucity of studies that have been able to tease out the relative contribution of malaria infection against the range of other confounding factors affecting development. It is difficult to separate the individual effects of potential risk factors from each other. Their influence on development is, in fact, likely to be better explained by a multiple risk model, with improvement in developmental potential coming from a reduction in total risk, rather than one individual element.

What has been easier to establish, albeit from only 2 small, published series, has been the effects on cognitive and neuropsychological development after brain insult. Certain patterns of impairment are suggested and accord with the different physiological mechanisms of damage. First, there were those children whose developmental problems were generalized, in whom impairment appears to follow directly from the effects of brain damage. The children comprising this group would often be identified as children with some gross neurological impairment such as spasticity. Second, there were other children whose impairments were more specific, and similarly, their impairments are also likely to be directly related to brain damage. Specific impairments, such as temporal lobe epilepsy and hippocampal dysfunction (leading to impairments of language and memory function and to behavioral disorders), are supported by animal models of cerebral malaria and seizures and by case study reports.<sup>26,73</sup> Finally, there were suggestions that in some children, impairment may only emerge in assessments of higher order functioning, where the origin of these problems may be disrupted development, rather than direct brain damage, and then lead to behavioral and social problems.

In much of sub-Saharan Africa, most severe and complicated outcomes of *P. falciparum* infection occur during the first 5 years of life. Cerebral malaria and status epilepticus are conditions unlikely to spontaneously resolve without intervention. Those who survive cerebral malaria have anything up to a 1 in 20 chance of developing long-term debilitating sequelae. Direct and developmental effects of brain insults on cognition and behavior have nevertheless been less well defined. From studies in The Gambia and Kenya, impairments of motor skills and information processing among children without obvious gross neurological dysfunction could affect 5–10%. Figure 2 gives speculative figures, on the basis of current evidence, of how these proportions translate into the numbers of children affected in one community in East Africa. Both gross physical and subtle cognitive and behavioral impairments are likely to appear before the child begins school. Among communities with few financial resources, any signs of developmental impairment will limit these children's chances of ever going to school.

Previously, we estimated that ~3,000 children < 10 years of age will, each year, survive cerebral malaria in African hospitals but be left with some gross and persistent neurological disability.<sup>69</sup> It is tempting to try to re-estimate the

burden malaria poses on cognition and other residual neurological sequelae in Africa; however, this review has highlighted that our understanding of the wider impacts of malaria on cognitive development and performance is scanty at best. At present, we can at least claim that the effect of malaria in childhood is likely to have from subtle to profound effects on cognition, behavior, and performance well beyond those previously described. These effects will often be lifelong and will result in children and adults who require special support from family, community, health services, and education services.

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