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Commentary

Anemia, Iron Supplementation and Susceptibility to *Plasmodium falciparum* Malaria

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Anemia and malaria constitute major health problems worldwide, especially in tropical countries with low resources (WHO, 2008a, 2008b; Black et al., 2003). Although there are several potential causes of anemia, iron deficiency constitutes approximately half of all cases (WHO, 2008a, 2008b). Other important causal factors include parasitic infections such as malaria or helminth infections, hemoglobinopathies and G6PD deficiency, traumatic childbirth, as well as other nutritional deficiencies (WHO/UNICEF/UNU, 2001). Most severe malaria infections are caused by *Plasmodium falciparum*, and this remains a leading cause of morbidity and mortality among children in sub-Saharan Africa (WHO, 2008a, 2008b). Malaria causes anemia primarily through haemolysis, the destruction of red blood cells (RBCs), although other factors can be involved, such as long term subclinical malaria infection inducing anemia of inflammation. (Gasim and Adam, 2016). In truth, the relationship between the host iron status and malaria susceptibility is quite complicated.

It has been suggested that iron deficiency may offer protection against malaria infection (Gwamaka et al., 2012; Kabyemela et al., 2008; Jonker et al., 2012). Furthermore, it has been documented that providing iron supplements to young children living in a malaria endemic area who are iron replete may increase the risk of malaria-related hospitalization and mortality (Sazawal et al., 2006), among other studies, suggesting possible increased morbidity following iron supplementation in malaria endemic areas. Subsequently, the WHO now recommends that in malaria endemic regions, iron supplements should only be given where malaria management and preventive measure are available (Neuberger et al., 2016; World Health Organization, 2016). However, a complete understanding of the cellular relationship between iron and malaria susceptibility has been lacking, and iron supplementation trials are not possible to conduct without providing appropriate antimalarial countermeasures which could mask results and make interpretations difficult. Furthermore, the degree of protection against malaria infection offered by iron deficiency is not definitively understood. Given its prevalence and health consequences, there remains an important need to address anemia in children in the developing world – in fact this has become one of WHO Global Targets For Nutrition 2025. The current policy of the WHO does not reflect the difficulties of measuring an individual's iron status in the developing world, nor does it provide practical, tangible guidelines for what constitutes adequate antimalarial health services or for how long malaria risk may be elevated following iron administration.

Goheen et al. (2016) have recently assessed the magnitude of protection from anemia against erythrocytic stage malaria and the safety of iron supplementation using *in vitro* assays conducted on RBCs from children in The Gambia undergoing iron supplementation in a malaria endemic area where sickle-cell trait is common. They have systematically characterized *P. falciparum* growth before, during, and after 12 weeks of iron supplementation. Their method of using *in vitro* growth assays provided an optimal procedure to thoroughly examine the cellular determinants of parasite growth in anemic and iron-supplemented children, as they simultaneously tracked measurements of several hematological, iron, and inflammatory markers over the supplementation period. Furthermore, this strategy allowed for researchers to eliminate potential confounding factors such as malaria exposure, antimalarial treatment and prevention services, and variable follow-up periods. The authors observed that invasion and growth of various *P. falciparum* strains were less efficient in RBCs from anemic children. The authors went on to compare the population level impact of protection against malaria from anemia *versus* from sickle-cell trait. The study reports a greater influence on population level parasite growth reduction from anemic RBCs, and an overall prevalence of anemia over four times that of sickle-cell trait. Interestingly, the documented deficits in invasion and growth for erythrocytic stage *P. falciparum* were reversed when anemic children received iron supplementation.

It has previously been hypothesised that iron supplementation increases malaria susceptibility by increasing the availability of *P. falciparum*'s preference for young RBCs (Clark et al., 2014). Goheen et al. (2016) observed significant shifts in RBC populations following iron

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supplementation, finding younger RBCs are most prevalent at Day 49 post iron supplementation – the exact same period at which parasite growth increases the most. This finding supports the hypothesis of increased erythropoietic drive and young RBC population dynamics influencing overall malaria susceptibility. Results from this work concur with WHO recommendations cautioning iron supplementation in malaria endemic areas without extensive health monitoring and antimalarial preventative services and reveal the need for short-term malaria prophylaxis during iron supplementation campaigns. Furthermore, this study provides one possible explanation for why other researchers may have observed conflicting results regarding the malaria-related risks of iron supplementation, given the transient window of increased malaria susceptibility the authors observed here. Finally, as the authors observed a direct correlation between *in vitro* parasite growth rates and hemoglobin levels of the RBC donors, this provides a simple and practical measurement for healthcare workers to take into consideration regarding evaluation of malaria susceptibility and iron supplementation, as opposed to more laborious, less straightforward, and often unavailable measurements of iron status using other iron related biomarkers.

Given the degree of protection afforded by anemia against malaria invasion and growth, the widespread prevalence of anemia in malaria endemic areas, and the well-known observation that people of African descent have lower normal hemoglobin and MCV values, as the authors put forth, it is worth questioning whether these altered hematological values among Africans have a stronger genetic basis than previously appreciated (as opposed to being solely environmentally related). Thus, much like the other hemoglobinopathic signatures, could anemia be an adaptation to live under significant malaria pressure?

Declaration of Interests

I declare that I have no conflicts of interest.

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