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Chronic inflammation of blood vessels could help explain high childhood mortality in malaria regions

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Recurrent episodes of malaria cause chronic inflammation in blood vessels that might predispose to future infections and may increase susceptibility to cardiovascular disease, a Wellcome Trust study in Malawian children finds.

The findings could explain the indirect burden of malaria on childhood deaths in areas where the disease is highly prevalent and children experience multiple clinical episodes of malaria in a year.

Malaria is caused by infection with a parasite that starts by infecting the liver and then moves into red blood cells. The most deadly of the malaria parasites is *Plasmodium falciparum* because of its ability to cause inflammation in blood vessel walls, making them more sticky so that the infected red blood cells can cling to the sides. Being able to stick to the blood vessels in vital organs allows the parasite to hide away from the immune system, a process called sequestration. When it occurs in the brain it causes a more severe form of the disease called cerebral malaria, associated with seizures, coma and sometimes death.

It was thought that the changes in the blood vessel walls that enable the infected red blood cells to stick would resolve quickly once the cells had been cleared; however, the new findings show that inflammation is still present up to one month later.

Researchers from the Malawi-Liverpool-Wellcome Clinical Research Programme at the University of Malawi College of Medicine in Blantyre, Malawi, looked at 190 children with uncomplicated, mild or cerebral malaria compared with healthy children of the same age. They found that the changes were most pronounced in children with cerebral malaria, with the levels of one inflammatory molecule remaining 22 times higher than in healthy controls one month after the initial infection.

Dr Chris Moxon, a Wellcome Trust Clinical PhD Fellow and first author of the study, explains: "These findings suggest that children who live in areas of high malaria transmission have persistently inflamed blood vessels, and that could have significant effects on their long term health. It could leave them more susceptible to repeated and more severe infections with malaria, but also with other bacteria and viruses. Chronic changes to the blood vessels like these could an important contributing factor to cardiovascular disease later in life."

Professor Rob Heyderman, lead author and Director of MLW, added: "If follow-up studies in other populations confirm these findings, we should consider whether existing anti-inflammatory drugs such as statins may be able to limit these effects. Short courses of statins could be targeted to children with severe and recurrent disease to try and limit the severity of future infections but this would need to be evaluated in well-conducted clinical trials."

Around 300 million clinical episodes of malaria are caused by infection with the parasite *P. falciparum* each year. The disease is transmitted by mosquitos and children living in areas where the parasite is particularly prevalent may receive more than one infective bite per day, resulting in repeated clinical episodes of malaria over the course of the year.

Studies have shown that reducing malaria transmission in a population

such as this can reduce the number of childhood deaths from any cause by up to 70%, an effect that is much greater than can be explained by reducing malaria alone. The findings from this new study, published today in the *Journal of Infectious Diseases*, could offer some explanation for the unexplained mortality in areas where malaria transmission is high.

More information: C.A. Moxon et al. Persistent endothelial activation and inflammation after Plasmodium falciparum infection in Malawian children. *Journal of Infectious Diseases*, 2013. [epub ahead of print]

Provided by Wellcome Trust

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