Immunological defense mechanism leaves malaria patients vulnerable to salmonella infections

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The link between malaria and salmonella infections has been explained for the first time, opening the way to more effective treatments.

Malaria patients are at high risk of developing fatal bacterial infections, especially salmonella infections. This is commonly believed to be due to generalised immunosuppression by malaria, whereby the entire immune system is weakened and compromised.

However, researchers at the London School of Hygiene & Tropical Medicine have discovered that the increased vulnerability to salmonella infections is a side effect of the body's attempts to protect itself from the damaging effects of the malaria infection.

The researchers describe this defence mechanism as a trade-off, where the body fights one enemy but exposes itself to the other. This was demonstrated in their study exploring the connection between malaria and non-typhoid salmonella (NTS)- an infection which is particularly dangerous for children.

Children with malaria can develop anaemia, which puts them at higher risk of developing severe bacterial infections of the blood, caused in up to 70% of the cases by NTS. This infection is fatal in up to 25% of the infected children. To prevent these bacterial infections, or develop an effective treatment, scientists needed to understand the mechanism

behind this connection between malaria and salmonella.

Professor Eleanor Riley, one of the lead authors of the study, says: "It is a widespread belief that malaria is an immunosuppressive disease; that once the disease is contracted, the patient will be susceptible to several other infections because of a compromised immune system. However, this study shows that increased susceptibility to salmonella infections is due to a very specific immunological effect which does not affect the immune system as a whole."

Infection by the malaria parasite periodically causes red blood-cells to burst, releasing the parasite offspring, but also releasing heme – a breakdown product of haemoglobin – which is extremely toxic once outside the red blood cell.

The Medical Research Council (MRC) funded study, published in *Nature Medicine*, found that in malaria-infected mice (which show exactly the same susceptibility to salmonella as is seen in humans) the body's natural response to defend itself from the dangers of heme, an enzyme that degrades it (heme oxygenase-1 or HO-1), very selectively affects the immune system, crippling the production of white blood-cells (neutrophils) that are essential to fight NTS. These crippled cells are unable to kill the bacteria, allowing them to spread freely.

"The key is in the rupture of the red-blood cells," says Dr Aubrey Cunnington, Clinical Research Fellow at LSHTM and co-author of the study. "Sickle-cell anaemia patients, where similar red cell damage occurs, are also more susceptible to NTS. But, numerically speaking, malaria is the most common cause of NTS. Where the incidence of malaria is decreasing, so are the salmonella infections."

The team identified Tin Protoporphyrin (SnPP) as a candidate for the prevention of salmonella infection. SnPP inhibits the activity of the

heme oxygenase enzyme, reversing the susceptibility to salmonellosis in malaria infections.

But the authors say that careful testing will be needed before considering SnPP use in humans, as blocking the action of HO-1 may leave the heme free to cause tissue damage.

More information: A.J. Cunnington, J.B. de Souza, R-M. Walther, E.M.Riley; Malaria impairs resistance to Salmonella through heme- and heme oxygenase–dependent dysfunctional granulocyte mobilization, *Nature Medicine*, (2011), dx.doi.org/10.1038/nm.2601