Importance of the Spleen to Survival from *P falciparum*

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Abstract

P falciparum infections carry a considerable mortality risk, but the nature of the 'immunity' gained from infection experience is uncertain. Although anaemia may contribute some protection against mortality, the function of the spleen appears critical to controlling *P falciparum* parasitemia and increasing survival. Melanesian reports suggest that survival advantages of *P vivax* infections and genetic polymorphisms, such as alpha-thalassemia, are expressed through enhanced splenic function. Overwhelming infections in post-splenectomy patients further indicate non-specific splenic immunity. The co-evolution of *P falciparum, P vivax* and *Homo sapiens* has likely devised a rough balance between parasite growth and host survival.

> *While the army of defence is recruited from connective tissue in every part of the body, the spleen seems to have a special function to perform which cannot be assumed by the liver or any other depot of the reticulo-endothelial system.*
>
> L W Hackett 1937[1]

In the Southwest Pacific during World War II, the mortality rate for *P falciparum* malaria in soldiers was usually <1:1000, except in units cut off from medical supplies.[2] 'Australian soldiers retreating from Rabaul, New Britain died at high rates (20%) when their quinine ran out in 1942.[3] Japanese soldiers from the non-endemic island of Nauru fared particularly poorly (26% mortality) after hostilities ceased in 1945 when mixed with their comrades who had survived the war on the highly malarious island of Bougainville.[3] This was despite being treated with quinine by experienced medical officers (see Figure 1). Extraordinary mortality from *P falciparum* appears to be limited primarily to first infections, but there is little understanding of the nature of subsequent tolerance or immunity. Comparison of modern West African and Melanesian populations indicate that mortality in Melanesia is much less than under similar exposures in Africa.[4] Extensive epidemiology studies of malaria in African children still yield highly variable mortality information.[5] Despite significant advances in immunisation against malaria, it is challenging to demonstrate mortality differences directly due to malaria vaccines.[6] Some mortality differences appear to be due to non-specific immune actions.[7] The original indicator of malaria immunity was splenomegaly. Non-specific protection provided by spleen moderating *P falciparum* parasitemia may explain some of these disconnections between historical experience and epidemiological data.

Figure 1. Surrendered Japanese soldiers repatriated from Nauru to the Solomon Islands, where they first encountered malaria in October 1945. Nearly universal infection with *P falciparum* led to more than a quarter dying from malaria within five weeks despite treatment with quinine by experienced medical officers.[2] Australian War Memorial photo P00001.249, now in the public domain.

Classical studies of malaria spleens in the early 20th century indicated two types of splenomegaly.[1] Soft spleens turgid with blood were acute, transitory and usually found in early age groups with few infections. Hard spleens were caused by more chronic infections and mobilisation of phagocytes indicative of immunity. Spleen surveys were done on school children to give some direct indication of malaria infection rates in a geographic area recently. Epidemic malaria with *P falciparum* was marked by high mortality rates occurring in a non-immune population and was associated with low rates of splenomegaly. Thus, the presumed association of

splenomegaly, relative malaria immunity and low mortality.[1]

One key difference between West African and Melanesian malaria is the presence of *P vivax* in Asia. However, doubts about the limitations of *P vivax* prevalence in Africa have been recently expressed.[4,8] The two plasmodium species have co-evolved in Asia, with a third of falciparum infections triggering vivax relapses despite the rarity of simultaneous mosquito infections.[9] Soldiers with chronic vivax infections during World War II developed splenomegaly, although this was suppressed by continuous chemoprophylaxis with mepacrine.[10,11] An enlarged spleen caused by *P vivax* may clear subsequent parasitemias better than one without such experience, as was suggested by studies using heated autologous blood to track the removal of stiff erythrocytes from falciparum malaria patients treated with quinine in hospital.[12] *P falciparum* patients with splenomegaly cleared heated erythrocytes much faster than those without pre-existing splenomegaly, implying a survival benefit from splenomegaly leading to lower peak parasitemias. Malaria patients without splenomegaly did not clear parasites quickly until quinine was given, implying that a shift in splenic function only occurred after the addition of chemotherapy. Co-evolution means a balance of competing interests to maximise transmission of both parasite species and host survival. Splenomegaly induced by early *P vivax* infection protecting against lethal *P falciparum* would be one possible means to achieve such a mutually advantageous outcome.

That such co-evolution has occurred in Melanesia was suggested by epidemiology studies in children from Vanuatu.[13,14] The genetic polymorphism alpha-thalassemia produces disordered haemoglobin chains, mild anaemia and splenomegaly. Splenomegaly is more common in homozygous alpha-thalassemia (Relative Risk RR 1.5) and heterozygous alpha-thalassemia (RR 1.2) than controls, as is clinical malaria but not actual parasitemia. The Darwinian selection of alpha-thalassemia strongly indicates a survival advantage possibly generated by early *P vivax* infections protecting against mortality from later *P falciparum*.[4,13,14] Increased filtration of parasitised erythrocytes by the spleen is a plausible mechanism suggesting an evolutionary mechanism justifying earlier infection with a more chronic parasite. Multiple other haemoglobin polymorphisms appear to have been selected in malarious areas such as Southeast Asian Ovalocytosis (SAO), which was shown to protect against cerebral malaria in Papua New Guinea, but the smaller SAO series did not show distinct splenic differences.[15] Additional New Guinea studies showed SAO protection against *P vivax* infection indicates that polymorphism selection could be operating by multiple mechanisms.[16]

Studies from severe malaria in African children are also suggestive that the spleen has a critical role in survival after *P falciparum* infection. In a study of 104 African children with severe malaria, the spleen size (as measured by sonography and standardised by body surface area) in those dying was found to be comparable to community controls and significantly smaller (roughly half) than those who survived severe malaria.[17] The suggestion was that those with larger spleens were more capable of arresting the course of parasitemia, but it was uncertain what this meant regarding previously acquired immunity. Spleen size in severe malaria patients due to severe malaria anaemia was larger than those with cerebral malaria indicating the sequestration of large numbers of erythrocytes in the spleen.[17] In an extensive study from urban Mali, clinically measured splenomegaly was associated with improved survival in children with severe malaria.[18]

That the spleen is important to survival during *P falciparum* infection is most dramatically demonstrated in infections in splenectomised patients.[19] Although the four patients reported from Thailand were all successfully treated with standard chemotherapy, pigmented schizonts in the peripheral blood indicated the lack of normal splenic function of removing such parasites. Further studies from Thailand show that asplenic patients do not clear dead parasites from their circulation, emphasising the spleen's importance in parasite removal.[20] Sickle cell disease (SCD) is a special case similar to surgical splenectomy, as nearly all SCD children become functionally asplenic from repeated splenic infarcts. Epidemiological studies indicate that although SCD does not increase the incidence of malaria, SCD children hospitalised with malaria in East Africa are much more likely to die than those without SCD.[21] The relationship of the spleen to *P falciparum* infection is complex and modified by other immune factors. In a retrospective severe malaria study from Thailand, splenomegaly was roughly twice as common in cerebral malaria patients as those without complicated malaria but still had a high parasite biomass.[22] A previous clinical trial in African children with cerebral malaria showed the opposite finding that those with enlarged spleens cleared *P falciparum* faster, resolved coma quicker and survived at higher rates (each 1 cm increase in spleen size resulted in a decreased mortality ratio of 0.8; CI 0.7-1.0).[23] Bigger, however, is not always better, as in the case of hyperreactive malarial splenomegaly syndrome (HMS).[24] This obscure syndrome likely is generated by chronic malaria antigenic stimulation and carries

a considerable mortality risk, with more than one-third dying of all causes over three years. Splenic function is important, and the size of the spleen is only an indirect and imperfect indicator of the spleen's ability to perform its protective functions.

Is anaemia an indirect measurement of increased splenic activity during malaria infection? Moderate anaemia, often seen with iron deficiency, is common with either splenomegaly or malaria infection. Interestingly, moderate anaemia is one of the few protective factors discovered during a large meta-analysis of severe malaria specifically concerning mortality.[25] Although the mechanism of such protection (Odds Ratio 0.87, CI 0.80-95) is unknown, it is at least possible that moderate anaemia is a marker for increased splenic activity and, as such, may reflect malaria parasites being more effectively removed from circulation. Survival during falciparum infection could, therefore, be a function of decreased peak parasitemia.

Mortality during *P falciparum* infection is a complex interplay of multiple factors, but non-specific protection from the spleen is part of the equation. Increasing splenic activity by various mechanisms may incrementally contribute to host survival. The Darwinian selection of a variety of hemoglobinopathies (Sickle Cell, SAO, alpha-thalassemia) by malaria may be partially explained by the removal of stiffened erythrocytes by the spleen, creating a less permissive environment for *P falciparum*. *P vivax* may contribute to survival by enabling enlarged spleens to better handle *P falciparum*. Rather than specific immunity to certain antigens, the picture resembles a composite of non-specific cellular immunity centred on the spleen, incrementally increasing survival. How might such a mechanism be tested? Mortality studies are inherently challenging, requiring large populations and sound medical surveillance systems that may indirectly lower mortality simply by increasing access to medical care and transportation. However, more efforts to determine what factors genuinely determine malaria mortality are vital, otherwise, costly public health programs may end up expending scarce resources on programs unlikely to influence the most important survival endpoint.[6]

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