Review Article: Hypothesis: Dynamics of Classical Malaria Epidemics Show *Plasmodium falciparum*’s Survival Strategy

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Abstract. Areas of marginal transmission can generate enormous lethal falciparum malaria epidemics when factors favoring the parasite shift only slightly. Although usually described in terms of vectorial capacity, medical scientists working in India in the early 20th century came to the conclusion that “an epidemic of relapses” was the key triggering event of malaria epidemics. This explanation has been largely discarded, because the biology of *Plasmodium falciparum* recrudescence has since been differentiated from *P. vivax* relapse. Using data from the Punjab in 1908 and Ceylon in 1934–1935, the genesis of malaria epidemics has been re-examined to inform current control efforts. The epidemics were focused geographically depending on recent rainfall or drought. Epidemics arose very suddenly and simultaneously in several places. Malaria spleen surveys indicated very little recent malaria transmission, and blood smears showed very few gametocytes just before the epidemic. Population stress as indicated by high grain prices because of a poor harvest caused by drought the previous year was a risk factor for malaria epidemics. Although increased female *Anopheles* survival because of increased humidity played an important part in the magnification of the epidemic, it does not explain its genesis. Human population stress triggering a shift toward gametocytophoresis is hypothesized as the key initiation factor for malaria epidemics. Its evolutionary significance may be that it allows the parasite to match the tropical agricultural cycle.

The epidemic condition appears to be due to an excessive seasonal increase of the normal parasite rate. S. R. Christophers

Malaria epidemics, particularly those caused by *Plasmodium falciparum*, are marked by sudden increases in mortality in areas that are normally of low endemicity. Although endemic malaria causes the bulk of malaria mortality in children and non-immune visitors, lethal malaria epidemics mostly occur in zones of marginal transmission when diverse contributory factors unite to cause infections with severe clinical expressions in immunologically naïve populations. These factors can include meteorological events, such as flood or drought, increases in vector capacity, such as introductions of more efficient *Anopheles* species, and introductions of infected humans who are asymptomatic but carry gametocytes, the plasmodial transmission forms. Only small shifts in these factors are capable of triggering a malaria epidemic. Falciparum malaria has adapted to its human host and *Anopheles* vector over millennia, and the association of epidemics with human stress may possibly have a biological explanation. Examples of classical malaria epidemics of the early 20th century in south Asia are used to illustrate this hypothesis.

PUNJAB 1908 EPIDEMIC

Falciparum malaria epidemics were first appreciated historically and defined epidemiologically by studies done by Samuel Rickard Christophers after an epidemic in Punjab, India in 1908. Sudden disruption of all normal activities, such as railroad travel, occurred when a large proportion of the entire population of Punjab Province became ill with malaria; an estimated 250,000 excess deaths occurred. The government ordered an investigation into this unexpected epidemic, and Christophers arrived in 1909 in the post-epidemic period. Population and taxes were linked in colonial India, and therefore, prospective records of births and deaths were locally maintained, although the catch-all classification of fever allowed little diagnostic differentiation. Through detailed examination of mortality and meteorological records, Christophers was able to determine that preceding heavy monsoon rains were a necessary but insufficient condition to trigger a falciparum epidemic. This was likely because of the increased survival of the *Anopheles* vector with increased humidity in the otherwise arid Punjab. Maps, text, and data are available from the National Library of Scotland (http://digital.nls.uk/indiapapers/browse/pageturner.cfm?id=75058530). All-cause mortality exceeded 10 times the expected number in some areas and was closely linked to the monsoon rains and subsequent canal overflow. From studying the administrative records, Christophers was able to determine that falciparum epidemics were swift in onset, sudden in duration, geographically focal, and centered in distressed human populations with little pre-epidemic parasitemia. The ability of lethal malaria to appear simultaneously over a large diverse area was seen as particularly problematic in terms of both explanation and management. Figure 1 shows seasonal distribution of malaria infections after the mid-year monsoon.

Other factors besides rainfall, particularly in the human population, were involved, such as grain prices (higher during famines) and splenomegaly rates from school surveys (indicative of non-immunity among children). The genesis of malaria epidemics is inherently difficult to study, because one is dealing with unusual events that occur during times of human stress, such as famine. The studies of Christophers noted that the most likely situation in which an epidemic would develop was a drought year driving up grain prices because of scarcity followed by heavy monsoon rains, which would promote vector breeding and survival. Famine-stressed populations were not only more susceptible to poor clinical outcomes when infected with malaria, but also, they seemed to be more infectious to mosquitoes. Epidemics in the Punjab occurred very suddenly, although very few persons had microscopically visible gametocytes. Most deaths occurred in children born since the previous epidemic, in whom low splenomegaly rates
indicated little immunity to malaria. Using a formula consisting of rainfall during the monsoon, immunity based on school spleen surveys, and population distress as indicated by grain prices, malaria epidemics in the Punjab could be predicted with a modicum of accuracy, allowing public health authorities to anticipate these disease disasters. This prediction scheme was successfully used from 1921 until the division of Pakistan from India, although questions about its use continued to be raised.\textsuperscript{5,7} Retrospectively, the El Nino Southern Oscillation may have been the distant explanation for malaria epidemics because of drought generated by failure of the monsoon rains.\textsuperscript{8}

The underlying ecology of the Indo-Gangetic river system is the background against which malaria epidemics in south Asia have been historically generated.\textsuperscript{9} However, huge lethal malaria epidemics no longer occur in India, and subsequent studies suggest that it is the human stress and immunity factors that have changed and not the basic epidemiology of the parasite and vector.\textsuperscript{10} Those epidemics that have occurred in modern times are largely caused by \textit{P. vivax} in refugee populations or in association with major development projects changing the local \textit{Anopheles} ecology.\textsuperscript{11,12} Even when major flood or tsunami events occurred in vulnerable areas, epidemics, such as the one described by Christophers in 1908, did not occur, suggesting that such disasters are not the main triggering event for malaria epidemics.\textsuperscript{13-15}

**CEYLON 1934–1935 EPIDEMIC**

Analogous malaria epidemics to those seen in the Punjab were studied in Ceylon (now Sri Lanka) by C. A. Gill\textsuperscript{16} after a massive lethal epidemic in 1934–1935. Over 7 months, it is estimated that 80,000 excess deaths occurred from a population of 5.3 million\textsuperscript{16,17} (Figure 2). The most remarkable difference between the two south Asia areas was that the proximal event triggering the epidemic in Ceylon was drought and not flood such as in the Punjab, although the same major vector (\textit{An. culicifacies}) was involved.\textsuperscript{13} In the transitional wet/dry areas of Ceylon, which usually have low rates of malaria transmission, drought caused by a failure of the monsoon lead to a large drop in the flow of local rivers, creating isolated pools of water that were excellent mosquito habitat.\textsuperscript{16,17} Similar to in the Punjab, a favorable \textit{Anopheles} habitat for breeding and subsequent survival to time of parasite transmission was a necessary but insufficient condition to generate a malaria epidemic in Ceylon. Drought generated when the monsoon rains failed also caused failure of the rice crop on which most of rural Ceylon depended for survival. The resulting famine weakened the population, especially the most vulnerable at the extremes of the age range, and contributed to the high mortality rate.\textsuperscript{16,17}

The Ceylon epidemic was seen to occur suddenly over a wide area similar to that observed in the Punjab. The 1934–1935 malaria epidemic could be reconstructed from clinical registers showing that onset could often be determined to a single day as well as occurring over a wide area from the beginning, not a narrow focus that spread outward.\textsuperscript{18} Because epidemics occurred from a very low background of transmission, it was the opinion of Gill\textsuperscript{18} that the gametocytes required to trigger the epidemic resulted from “an epidemic of relapses” at least 2 weeks before the epidemic. Relapse in the sense used by Gill\textsuperscript{18} should be understood as recrudescence of previously suppressed falciparum infections from the blood or vivax infections from hypnozoites, because there was no ongoing transmission to generate an epidemic.\textsuperscript{18} Submicroscopic falciparum parasitemia is now known by molecular diagnostic methods to be quite common in hypoendemic areas.\textsuperscript{19,20} The critical epidemic generating event seemed to be the sudden appearance of gametocytes in a low transmission area from many asymptomatic adults at the time that vectorial capacity was rapidly increasing.\textsuperscript{18,21}

The subsequent history of malaria in Sri Lanka has been driven by a memory of the severe epidemic of 1934–1935.\textsuperscript{22} A nearly complete program of dichlorodiphenyltrichloroethane (DDT) malaria eradication lead to a nadir of only six locally transmitted cases in 1963. When the malaria eradication program was pre-maturely ended, however, malaria resurfaced to again become a major public health problem, with 0.5 million malaria cases reported in 1969. After another long and difficult antimalarial campaign complicated by an armed insurgency in the north, malaria has now apparently been eliminated in Sri Lanka, because there have been no locally transmitted cases since 2012.\textsuperscript{22} Although one may eliminate the parasite, the mosquito vector remains, even if the risk of a major epidemic reoccurring is now vanishingly small.

**Figure 1.** Seasonal malaria incidence in Amritsar city in Punjab Province, India in 1900–1908 shown as a percentage of all malaria cases in the city (\(N = 34,265\)) occurring per month.\textsuperscript{1}

**Figure 2.** Malaria-associated deaths (\(N = 47,317\) in 1935) in Ceylon (Sri Lanka) during the epidemic of 1934–1935.\textsuperscript{17}
STRESS AND GAMETOCYTES

The multiple factors that control parasitemia at low concentrations and promote gametocytogenesis are poorly understood. Famine stress seemed to increase malaria transmission in the Punjab and Ceylon. Extreme traumatic stress, such as seen in landmine injuries, is another event that also apparently promotes falciparum recrudescence. During armed conflict in Cambodia, persons in the border areas who survived the severe trauma of a landmine explosion often developed falciparum malaria in less than six weeks, indicating recrudescence of a pre-existing infection. Similar observations have been claimed for surgical stress, but this has been indifferently documented, despite surgeons' interest in post-operative fever. Intercurrent infections not related to malaria, such as diarrhea or dysentery, have been thought by some to cause malaria recrudescence, but this too is largely a matter of expert opinion and not an observed fact. Rural Vietnamese militia units raised largely as armed guards for their own villages could not be used in combined military operations, because within a few days of marching away from their villages, most would be ill with malaria. Because this occurred in less time than an incubation period, the conclusion was that the militiamen had subpatent falciparum infections that recrudesced when placed under the stressful conditions of mobile military operations. The common denominator across these examples seems to be that famine- or trauma-stressed human populations become ill with and transmit malaria better than those who are not involved in such adverse events.

Although the process of gametocytogenesis is poorly understood, it is related to parasite stress in addition to changes in the human population. Anemia and other seasonal effects on parasite growth have been shown to increase gametocytes in Thailand. Sublethal treatment with antimalarial drugs, especially antifolates, such as sulfadoxine/pyrimethamine, and recrudescent infections also increase the number of people with gametocytes. Increased cyclic adenosine monophosphate (cAMP) is a common intracellular second messenger molecule and one of the few chemical signals known to initiate falciparum gametocytogenesis. Although the biology is uncertain, stress of either the human or parasite population seems to promote the formation of gametocytes.

P. FALCIPARUM’S ADAPTATION TO AGRICULTURAL POPULATIONS?

A speculative explanation for these observations is that falciparum malaria has evolved to match the tropical agricultural cycle when intense work for ploughing and planting must be done in a short period after the seasonal rains. Seasonal appearance of gametocytes after the monsoon is known to occur in Thailand. Falciparum malaria and its most efficient Anopheles vectors have coevolved with humans during the agricultural development of west Africa that followed the migration of Bantu peoples over the previous millennia. Malaria is largely a rural disease in areas where there are relatively few children born into an agricultural village each year. Where the non-immune population is limiting, P. falciparum requires a means of maintaining itself in a small population between rainy seasons, likely in the blood of immune adults. Although relapsing malarials, such as P. vivax, have developed a latent hepatic stage known as hypnozoites, falciparum malaria can only hide in the blood or possibly, the bone marrow. If this line of reasoning is correct, then malaria epidemics might be the occasional unintended consequences of a parasite survival strategy that evolved when human populations were much smaller and less mobile. The outcome is that, when recrudescent falciparum malaria is combined with competent mosquito vectors and a large stressed human population, such as during famine, lethal malaria epidemics may result.

If this speculation is correct, the conclusion is that malaria epidemics are highly likely to occur in socially unstable tropical areas dependent on marginal agriculture. An ancillary conclusion is that greatly reduced malaria transmission over a wide area in a large population may not always be a good thing, especially when this population is stressed in times of famine. One strong argument for pushing a malaria control program through to eventual elimination of the parasite is that only by eradicating the parasite will the risk of lethal malaria epidemics be removed.

Received August 28, 2014. Accepted for publication December 7, 2014. Published online January 26, 2015.

Acknowledgments: The author thanks Colonel (retired) John F. Brundage, US Army, for his comments on an early draft of this manuscript and the many unnamed historians, medical librarians, and archivists who have unselfishly provided data and ideas for this work.

Disclaimer: The author is an employee of the Australian Defence Organization and a retired US Army medical officer but did not receive any specific funding for this study. The opinions expressed are those of the author and do not necessarily reflect those of the Australian Defence Force or the US Department of Defense.

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