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Perspective Piece

Was the First Malaria Vaccine Tested in 1898?

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Abstract. Early trials of killed, whole-cell typhoid vaccine indicated a paradoxical, positive effect on malaria infections. British soldiers in India in 1898 reported > 90% decrease in malaria recurrences after receiving an investigational typhoid vaccine despite no intention or expectation to observe such an outcome. In the 1940s, multiple doses of intravenous typhoid vaccine appeared to control parasitemia and limit reinfection in three syphilis patients purposefully infected with *Plasmodium vivax*. Several modern vaccines (against human papillomavirus, hepatitis B virus, and malaria) use a detoxified lipid A derived from *Salmonella* as an immune adjuvant. Early typhoid vaccines could have plausibly functioned as an innate immune stimulus, leading to some protection against malaria.

The question as to whether any protection against malarial fevers is in reality afforded by an injection of a dead typhoid culture may, in spite of the a priori improbability of such being the case, perhaps be deserving of attention. (Sir Almoth Wright 1900)[1]

The quest for a malaria vaccine has been long and difficult, but it may have started much earlier than is currently understood. In the dawn of the vaccine era, the search for a typhoid vaccine was driven by typhoid fever's military impact during the Spanish American (1898) and Boer (1899–1902) Wars when many more American and British soldiers died of typhoid than from armed conflict.[2,3] With killed, whole-cell cholera vaccine as a model, Almoth Wright began in 1897 to test various formulations of cultured *Salmonella typhi* killed by heat for subcutaneous injection. The first field trials were conducted when Wright was a member of the Plague Commission in India in 1898 when, peripheral to his duties as a commissioner, he inoculated a single dose of heat-killed typhoid vaccine into 2,835 British soldiers.[1]

The protection derived against typhoid fever by Wright's vaccine was disappointing, likely due to reheating of the vaccine to 60°C to insure sterility in the tropical environment. This heating would have destroyed antigenicity of most of the bacterial surface antigens now known to be important for protection. The bacterial cell wall endotoxin, however, withstands such heat treatment. Army medical officers followed the volunteer vaccine–recipient population for 6 months; although typhoid attack rates appeared to decrease, clinical field trials were yet to be standardized, and the results were both ambiguous and disputed. The vaccine was a very reactogenic product, with many men unable to walk for some days after gluteal injection, discouraging further volunteers despite the known lethal risk of typhoid fever in India.[1] A practical vaccine with good disease prevention was still years into the future for both the British (1914) and American (compulsory in 1910) armies.[2,4]

One reported and unexpected finding of the 1898 typhoid vaccine trial was that soldiers remarked on how well the vaccine had stopped "fever and ague" from chronic malaria infections, presumably due to *Plasmodium vivax*. Although reported by several military units, the regimental (nonmedical) officers of one unit counted the apparent protection from malaria after 6 months and reported that 111/121 (91%) men who had previously suffered from malaria and then received the typhoid vaccine had few if any further malaria episodes.[1] Only two of those vaccinated, who had not had previous malaria attacks, "declared themselves to have suffered slightly since." These findings prompted the quoted observation from Almoth Wright that leads this perspective piece, which admits that a causal relationship between typhoid vaccine and prevention of malarial illness seemed improbable.

This was not the only spontaneous and unexpected report of this nature. In 1943, Boyd and Kitchen stated that residents of rural Mississippi had a similar positive effect from typhoid vaccine and that "their malaria experience had much diminished since the introduction of the practice of typhoid vaccination."[5] This so impressed these two classical malariologists that they induced human infection with the McCoy strain of *P. vivax* to study the phenomenon. This was part of a series of experiments with the objective to "hyperimmunize" patients already infected with *P. vivax* as part of fever therapy for syphilis to determine if they could resist subsequent malaria infections. Administering repeated intravenous infusions of killed bacteria seems like an extreme and unusual intervention, but it was an accepted alternative to generate fevers as therapy for syphilis and for some ophthalmological indications.[6–9] One of the original uses of typhoid vaccine as a treatment of acute typhoid fever had largely been abandoned by the 1940s.[10]

In a preliminary experiment, a syphilis patient was given three intravenous infusions of typhoid vaccine 1 month after inoculation with mosquito-transmitted McCoy strain vivax malaria.[5] It was hypothesized that the typhoid vaccine might induce a recurrence in a resolving infection, but that did not occur. Three subsequent malaria blood challenges were given 110, 273, and 280 days postinfection with between 69 and 370 million parasites. The last two blood challenges only caused brief periods of microscopically detectable parasitemia. On postinfection day 468, a large sporozoite challenge was inoculated with 45 infected mosquitoes; after a prepatent period of 13 days, only 5 days of low-level (10/mm^3) parasitemia were observed. It was concluded that the patient was now "hyperimmunized" against vivax malaria.[5]

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Two additional syphilis patients, whose *P. vivax* infections had already produced sufficient paroxysms for treatment (approximately two months postinfection by mosquitoes) and whose malaria symptoms had spontaneously resolved, were given a series of eight intravenous infusions of killed, whole-cell typhoid vaccine ranging from 63 to 126 days postinfection. Then, on days 147 and 168 postinfection, they were challenged with blood from another person with the same McCoy strain of *P. vivax*, with each inoculum containing 45–89 million parasites. One of the patients had a slight rise in parasitemia (10 parasites/mm^3) after the first challenge, but none after the second challenge. The second patient mirrored the first, except that a slight rise was seen after the second challenge. One cannot make any firm conclusions from the three patients studied, but it can be hypothesized that a stimulus to the innate immune system caused by large infusions of bacterial endotoxin augmented patients' ability to resist blood and mosquito challenges with *P. vivax*.[5]

Modern attempts to immunize against malaria include whole-parasite preparations that have been inactivated by radiation or genetic modification.[11,12] In terms of antigenic exposure, whole-parasite vaccines are very much like a natural infection. Modern immune adjuvants include a variety of products to stimulate the innate immune system. 3-O-desacyl-4′-monophosphoryl lipid A (MPL) is a detoxified version of the bacterial cell wall endotoxin from *Salmonella minnesota* that is used as an adjuvant component in the human papilloma virus, hepatitis B virus, and RTS,S malaria vaccines.[13–15] Monophosphoryl lipid A is known to be a powerful toll-like receptor 4 agonist and in several proprietary adjuvants is key to generating an immune response to otherwise poorly immunogenic proteins. Monophosphoryl lipid A is a derivative what was contained in the killed whole-cell typhoid vaccines discussed previously, but MPL is much less reactogenic, and in usual doses would deliver a smaller immune signal than the whole-cell typhoid vaccine. Even with such adjuvants, the RTS,S malaria vaccine requires four separate doses to achieve modest immunity for a period of some months.[16]

It is plausible that Almoth Wright inadvertently conducted the world's first malaria vaccine trial by using an extraordinary amount of adjuvant to boost immunity in British soldiers with preexisting malaria parasitemias.[1] The points in favor of the malaria protection reported in 1898 representing boosted natural immunity are that there were multiple, spontaneous reports in different military units, immunity appeared to last for several months, and positive effects seemed limited to those known to have histories of "fever and ague." However, formal clinical trials were not conducted in 1898, and there is no proof of either antimalarial efficacy of the typhoid vaccine or of a specific mechanism for efficacy.

Civilians in rural Mississippi concurred with the British soldiers of India about the protective value of typhoid vaccine, even though they could not have expected any effect against malaria and though the American physicians using the typhoid vaccine were unlikely to have been aware of Wright's observations in India.[5] Further searching has not yielded other such reports, but because typhoid vaccine was predominately used by the military and only relatively few American (Panama and the Philippines) or British (India) soldiers were stationed in malaria-endemic areas, this absence might be due to a lack of disease concurrency.[17]

Our scientific predecessors accomplished an enormous amount in the absence of any modern pathophysiologic or genomic understanding of malaria and other diseases. Although it is difficult to look back through archaic literature for historical observations which can offer modern insights, it is likely that more unexpected and useful observations remain to be found in old tropical medicine texts, including those of the *American Journal of Tropical Medicine and Hygiene*.[18] The reader is invited to look for them.

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