Trends in Parasitology

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Review

Plasmodium vivax Controlled Human Malaria Infection – Progress and Prospects

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Modern controlled human malaria infection (CHMI) clinical trials have almost entirely focussed on *Plasmodium falciparum*, providing a highly informative means to investigate host–pathogen interactions as well as assess potential new prophylactic and therapeutic interventions. However, in recent years, there has been renewed interest in *Plasmodium vivax*, with CHMI models developed by groups in Colombia, the USA, and Australia. This review summarizes the published experiences, and examines the advantages and disadvantages of the different models that initiate infection either by mosquito bite or using a blood-stage inoculum. As for *P. falciparum*, CHMI studies with *P. vivax* will provide a platform for early proof-of-concept testing of drugs and vaccines, accelerating the development of novel interventions.

Controlled Human Malaria Infection

CHMI with *Plasmodium falciparum* is an established method for evaluating new candidate vaccines and antimalarial drugs in early-phase proof-of-concept clinical trials. The controlled nature of these studies enables trials to be undertaken with small numbers of volunteers with power to investigate efficacy against malaria using a variety of defined end-points, thereby accelerating development of antimalarial drugs [1,2] and vaccines [3]. CHMI can be initiated by the traditional mosquito-bite method (still frequently used), by the injection of cryopreserved sporozoites, or by an inoculum of blood-stage parasites, so-called induced blood stage malaria (IBSM) [3–10]. *P. falciparum* strains other than the reference clone 3D7 and its parental strain NF54 are now being tested, including the 7G8 laboratory isolate and the Cambodian clone NF135.C10 [11,12]. Genetically attenuated parasites that arrest development during the liver stage of infection have now been tested in humans [13]. Most of these studies have been carried out in nonendemic settings, but more recently they have also taken place in endemic countries, in particular through the use of cryopreserved sporozoites [14,15].

By contrast, modern CHMI with *Plasmodium vivax* has been less utilized, with only a small handful of studies reported in the last few years. In only two of the studies published to date has efficacy of immunization been assessed (Table 1).

There is an extensive history of deliberate infection with *P. vivax* – most notably in malariotherapy, which was carried out for the treatment of neurosyphilis almost a century ago. The Austrian psychiatrist Julius Wagner-Jauregg later received a Nobel Prize for his work with this treatment [16], and the practice was widely adopted as the only effective treatment available at the time. Malariotherapy provided a wealth of information about *P. vivax* infection, which has been reviewed previously [17]. Deliberate infection with *P. vivax* was also conducted in the USA

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Controlled human malaria infection (CHMI) studies provide a valuable means to test the efficacy of antimalarial drugs and vaccines and to study host–pathogen interactions, but have almost exclusively been used for *Plasmodium falciparum*.

CHMI with *P. vivax* has now been successfully conducted in several studies via mosquito bite (sporozoite); however, logistical challenges remain alongside the potential for relapsing infection.

One vaccine efficacy study has now been completed using mosquito-bite CHMI.

More recently, an alternative method of CHMI using an infected blood-stage inoculum has been developed and successfully tested in QIMR Berghofer, Brisbane.

Induced blood-stage malaria (IBSM) will aid testing of blood-stage drugs and vaccines, overcomes some of the logistical challenges associated with mosquito-bite CHMI, and could enable the study of parasite transmission stages.

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from the 1940s to the 1970s in prisoners involved in the Malaria Research Project at the Illinois State Penitentiary. The studies mainly examined compounds for their potential use as antimalarials [18]. Similar studies were also carried out at the United States Penitentiary, Atlanta, and in both programs the Chesson strain of malaria was used because it was noted to be more likely to relapse and have a shorter latency period than previously utilized strains, meaning that compounds could be assessed more rapidly [18,19]. Key discoveries of the biology of *P. vivax* were made during this period including, for example, the association between Duffy negativity and resistance to *P. vivax* infection [20]. This review focuses on the more recent trials using *P. vivax* CHMI rather than these early studies and treatment programs.

P. vivax Studies Using Sporozoite (Mosquito-Bite) CHMI

Following on from the studies of *P. vivax* infection conducted in Illinois, CHMI experiments were carried out to see if prior exposure to irradiated mosquitoes could confer protection by immunization. Rieckmann *et al.* [21] reported no protection against CHMI in three participants previously exposed to *P. vivax*-infected irradiated mosquitoes on four occasions at intervals of 2–4 weeks (total of <200 mosquitoes).

Three *P. vivax* CHMI studies assessing the ability to 'immunize' with X-irradiated sporozoites also took place in Maryland, USA, during the 1970s. Following immunization, challenge infection was initiated by periodic exposure to the bites of nonirradiated infected mosquitoes in three volunteers in separate experiments, and blood films were taken at least daily for all volunteers

Table 1. Overview of Published *Plasmodium vivax* CHMI Studies

Trial site	Number of volunteers	Pre-patent period (days)[a]	Number of infected mosquitoes OR infective inoculum	Number of volunteers with patent parasitemia	Refs
Sporozoite (mosquito-bite) CHMI studies					
Cali, Columbia	18	9–13	2–10	17/18[b]	[26]
Cali, Columbia	17 Duffy positive 5 Duffy negative	9–16	2–4	17/17 (Duffy positive) 0/5 (Duffy negative)	[27]
Cali, Columbia	7 malaria-naïve 9 semi-immune	11–13	2–4	16/16[c]	[28]
Cali, Columbia	12 Duffy -positive vaccinees 2 Duffy-positive controls 5 Duffy-negative controls	12–13	2–4	7/12 vaccinees 2/2 Duffy-positive controls 0/5 Duffy-negative controls	[31]
WRAIR, USA	27 vaccinees 6 infectivity controls	10–13 10–11	5	27/27 vaccinees 6/6 controls	[32]
Blood-stage CHMI studies (IBSM)					
QIMRB, Australia	2	8–9	13 000 genome equivalents	2/2	[35]
QIMRB, Australia	6	8–9	31 786 (± 11 947) as determined by qPCR (= 15 ± 5 viable *P. vivax* parasites)	6/6	[37]

[a]The pre-patent period refers to the period before malaria diagnosis which was made by blood film in sporozoite (mosquito-bite) studies and qPCR in the blood-stage studies.
[b]One volunteer did not develop parasitemia; the authors of the study suggested that this may have been due to surreptitious self-administration of antimalarial medication, but this was not proven.
[c]One volunteer developed parasitemia detectable by qPCR but cleared it spontaneously within 4 days.

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