Universiteit Leiden
The Netherlands

Plasmodium falciparum and Necator americanus in Gabon: observation, intervention, and controlled human infection

Alabi, A.

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CHAPTER 7

Summarizing discussion: *Plasmodium falciparum* and *Necator americanus* in Gabon: observation, intervention, and controlled human infection

Here, I will discuss the ensemble of previous chapters of this thesis.

In a first part (**chapters 2, 3, and 4**) the thesis covers *Plasmodium falciparum (Pf)* infection in Lambaréné, Gabon. We investigated the local epidemiology of malaria, revealing the continued prominence of *Pf* infection in Lambaréné. We also concluded that the STANDARD™ Q Malaria/ C-reactive protein (CRP) rapid diagnostic test (RDT) as part of disease management was unsuitable as a standalone diagnostic test. Moving from management of *Pf* to prevention, we showed that a $9{\cdot}0 \times 10^5$ dose of irradiated whole *Pf* sporozoite vaccine (*Pf*SPZ) in Gabonese children was safe and well tolerated, but vaccine efficacy was poor.

In a second part (**chapters 5 and 6**) covering *Necator americanus (Na),* we established a controlled human infection study with *Na* in Lambaréné. In preparation, we reported the outcomes of a meeting with stakeholders where different barriers and considerations were successfully addressed. We then conducted the controlled human hookworm infection (CHHI) study for the first time in an endemic area, showing that a dose of 50 Gabonese L3 larvae (G-L3) was safe, tolerable, and infective.

Our observational studies of malaria (**chapters 2 and 3**) indicate that the clinical management of malaria in Gabon should integrate other causes of acute febrile illness due to the frequency of co-infections and poor antimicrobial stewardship. Our interventional studies (**chapters 4 and 6**) showed that pre-exposure to the parasite is possibly consequential to poor malaria vaccine protective efficacy on the one hand, and a trend of lower hookworm egg count after CHHI on the other. Finally, it is discussed how the stakeholder meeting (**chapter 5**) influenced the successful conduct of the CHHI study in Gabon (**chapter 6**).

1. A holistic approach to the diagnosis and management of *Plasmodium falciparum* in Lambaréné, Gabon

For a significant proportion of the local population in Gabon, there remains a paradigm that fever is equal to malaria. However, there are a plethora of causes of acute febrile illness (AFI). When a patient presents to any level of healthcare with symptoms of an acute fever, it could be infectious or non-infectious. If infectious, the fever could be parasitic, it could be a virus, or it could be bacteria. In **chapter 2,** in a collaborative multicentric study, we showed that cases of AFI present similarly, and we showed that they cannot be clinically separated by symptomatology across sites in Lambaréné, Gabon; Rio de Janeiro, Brazil; and Chilumba, Malawi. We also showed that in about half of AFI cases in Lambaréné, *Pf* was identified by malaria slide or RDT. Thus, in moderate-to high malaria prevalence areas, it is important that the clinician can make a fast and accurate diagnosis of whether a case of AFI is due to *Pf* or not and then be able to take adequate steps in treatment and management of the disease, emphasising the importance of high performing point-of-care (POC) tests. In parallel, searching for the cause of AFI does not pose a dichotomous question. The cause is not always mono-pathogenic, malaria or not malaria, a virus or not a virus, or a bacterium or not a bacterium, but rather frequently it could be multi-pathogenic. In Lambaréné, we showed that even when Pf is identified, almost a third of these cases have another causative agent. Besides, it is intuitive that not all co-infected febrile cases in which malaria is detected in a malaria-endemic region is necessarily caused by the parasite, based on a high background prevalence of asymptomatic malaria, although asymptomatic episodes are less likely to occur in young children.[237,228] However, it is important to include both asymptomatic malaria as well as healthy controls from the same areas as the patients for estimating an attributable fraction of disease vs incidental findings.

A conservative prescribing approach, as advocated by D'Acremont et al. in Tanzania, was based on data from outpatients with acute febrile illness, with few cases of malaria. In our study, two out of five cases in which antibiotics were supposed to be prescribed were missed.[239] Approximately, 50% vs 10% of AFI cases were associated with malaria in the Gabonese and the Tanzanian children, respectively. This highlights the importance of considering disease epidemiology per region, as well as the level where recruitment takes

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238 – Moutombi Ditombi BC, M'Bondoukwé NP, Ndong Ngomo JM, et al. Burden and determinants of asymptomatic malaria among adults living in urban and rural areas in Gabon in 2023: a community-based cross-sectional study. Malar J 2025; published online Dec 24. DOI:10.1186/s12936-025-05672-4.

239 – D'Acremont V, Kilowoko M, Kyungu E, et al. Beyond Malaria – Causes of Fever in Outpatient Tanzanian Children. New England Journal of Medicine 2014; 370: 809-17.

place; community versus primary health care centre, versus outpatient versus hospitalized patients. Taking a public health point of view, we showed that the surveillance, diagnosis, and management of malaria should not be in silos. To reinforce an integrated approach to malaria management, innovation in diagnostic modalities is critical. A high-performance biomarker of fever for determining the cause/s of AFI, integrated as a POC test, can increase healthcare worker and patient confidence and satisfaction with AFI management in malaria endemic areas.

We investigated the utility of an innovative POC test in Lambaréné in **chapter 3.** The excellent sensitivity and good specificity of the HRP2 component of the RDT means that there is high certainty that a child presenting with AFI in Lambaréné does not have a moderate-to-severe form of malaria if the RDT is negative. This is of importance in rural to remote settings (such as in Lambaréné and her surroundings), where there is little access to other diagnostic methods, and where a clinician is regularly faced with a dilemma of whether to send a child who does not seem particularly unwell home without antimalarial treatment. A growing global problem is that HRP2 is not essential to *Pf* survival, thus the parasite has evolved a loss of the HRP2 gene in response to the selection pressure of HRP2-based malaria RDTs.[240] In 2010, the first reports of HRP2 deletions in real world settings was reported in South America.[241] The HRP2 sensitivity (98%) we reported in Lambaréné is in vast contrast to sensitivities in the horn of Africa, where HRP2/3 deletions were rapidly selected for after initial detection, and up to 80-90% of *Pf* cases can be missed by standard RDTs.[242,243] Gabon currently reports a low prevalence of HRP2 deletions of around 1%,[244,245] which might be due to continued use of microscopy and reliance on clinical symptoms as a primary method for diagnosing malaria in the country, thus lessening RDT-dependent HRP2 deletion selective pressure.[246] However, other yet to be elucidated factors applying selective pressures could also play a role.[247,248] Continued surveillance is required, and can be conducted at reference centres, such as the Centre de Recherches Médicales de Lambaréné (CERMEL). In addition to surveillance, there is R&D of RDTs based on both HRP2 and LDH, which outperform single antigen-based tests, and have good sensitivity in areas with a high prevalence of HRP2 deletions.[249]

240 – Watson OJ, Tran TN-A, Zupko RJ, et al. Global risk of selection and spread of Plasmodium falciparum histidine-rich protein 2 and 3 gene deletions. Nat Med 2025; 31: 3372–9.

241 – Gamboa D, Ho M-F, Bendezu J, et al. A Large Proportion of P. falciparum Isolates in the Amazon Region of Peru Lack pfhrp2 and pfhrp3: Implications for Malaria Rapid Diagnostic Tests. PLOS ONE 2010; 5: e8091.

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243 – Feleke SM, Reichert EN, Mohammed H, et al. Plasmodium falciparum is evolving to escape malaria rapid diagnostic tests in Ethiopia. Nat Microbiol 2021; 6: 1289–99.

244 – Krueger T, Ikegbunam M, Lissom A, et al. Low Prevalence of Plasmodium falciparum Histidine-Rich Protein 2 and 3 Gene Deletions—A Multiregional Study in Central and West Africa. Pathogens 2023; 12: 455.

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248 – Valdivia HO, Anderson K, Smith D, et al. Spatiotemporal dynamics of Plasmodium falciparum histidine-rich protein 2 and 3 deletions in Peru. Sci Rep 2022; 12: 19845.

249 – Mandefro A, Ding XC, Farge J, et al. Performance of a Novel P. falciparum Rapid Diagnostic Test in Areas of Widespread hrp2/3 Gene Deletion. Clin Infect Dis 2025; : ciaf212.

1.1. A role for artificial intelligence in the integrative management of malaria

In **chapter 3,** we investigated the utility of C-reactive protein (CRP) to determine the presence of bacterial infection using artificial intelligence (AI) i.e. machine learning (ML). Due to the number of participants negative for bacterial infection, we had an imbalanced dataset. Thus, a standard Receiver Operating Characteristic curve was susceptible to producing misleading results of better performance of CRP. Precision-Recall Area Under the Curve (PR AUC) provided a suitable alternative as it functions independently of true negative results and is therefore not affected by imbalance.[250] Using a random forest model and CRP, we were able to classify with good PR AUC, participants with bacterial and non-bacterial infection. Despite the development of newer generations of biomarkers such as Alpha-1-acid glycoprotein, Galectin-9, IP-10 (CXCL10), lipopolysaccharide-binding protein, Chitinase 3-like 1, TRAIL (TNF-Related Apoptosis-Inducing Ligand) etc., CRP remains the best performing biomarker in Gabon.[251] CRP performance is only bettered by innate/haematological markers such as white blood cell count and neutrophil count.

AI has potential to be leveraged to provide technological assistance to clinicians. Recent advances in AI allow for the collection of data and looking at the data from a multiclass level; data encompassing clinical signs and symptoms, or/and lab results, or/and biomarkers of fever such as CRP, could be supplied to a ML tool to aid clinical management of AFI. The utility of such an ML tool is dependent on clinical data that is of quality and that is representative e.g. (1) continuous surveillance of AFI epidemiology in malaria endemic settings, (2) creation of high-quality and harmonized datasets that are mindful of patient privacy, (3) integration of ML-based predictive analytics into routine management of AFI, (4) followed by a cycle of optimization of the ML tool. Asides random forest, other ensemble modifiers such as XGBoost, and support vector classifiers are ML tools that can be used to develop diagnostic AI models for accurate classification of AFI.[252–254] These models will of course have to be used with clinical insight.

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2. Deciphering parasite pre-exposure signals following inoculation with *Plasmodium falciparum* sporozoites and *Necator americanus* L3 larvae

2.1. Plasmodium falciparum sporozoites as a vaccine candidate

Whole sporozoite vaccines have been universally shown to be safe and tolerable.[255] Besides safety and tolerability, the co-primary outcome of a pre-erythrocytic malaria vaccine trial could be either the prevention of infection (asymptomatic or symptomatic) or the prevention of clinical disease (symptomatic). Our phase 2 trial in **chapter 4** was designed to investigate the former but showed poor vaccine efficacy (9% protection in the vaccine group). Immunity produced by *Pf*SPZ is primarily dependent on the effector functions of tissue resident CD8+ T cells- induced by γδ T cell- that eliminate infection by recognition of class I MHC on infected liver cells; induced immunity is not dependent on antibodies to circumsporozoite protein (CSP) (although antibodies might also play a role).[256–258] This is corroborated by controlled human malaria infection (CHMI) studies that show 100% protection i.e. sterile immunity for sporozoite based vaccines; similar results are not observed for CSP-based vaccines.[259] Due to the difficulty of studying tissue-resident T cell responses in the liver i.e. they cannot be directly studied in the peripheral blood, and the lack of a correlate of protection (COP) in pre-exposed individuals,[260] improving vaccine efficacy should be done through clinical trials and mechanistic studies conducted in malaria-endemic regions. Theoretically, the optimal *Pf*SPZ vaccination strategy would induce T cell responses in the liver that are above the threshold necessary for protection in pre-exposed individuals.[261] A study in Kenya showed that *Pf*SPZ did not elicit T cell responses in an infant population.[262] It was hoped that older Gabonese children would produce competent γδ T cell responses to induce *Pf*SPZ protective efficacy. Indirect interpretation of our clinical trial results indicates this was not the case.[263]

Pre-existing immunity to malaria represents a compendium of immune responses to malaria antigens; it occurs in endemic areas, beginning in childhood, and aggregating to provide protection from severe disease and death in adults.[264] One explanation for the lack of *Pf*SPZ efficacy in Gabonese children might be that pre-existing immunity in the children eliminated some of the irradiated sporozoites before they could generate a protective immune response, akin to the blocking

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263 – Agnandji ST, Bok J, Alabi A, et al. Safety, tolerability, and protective efficacy of a radiation-attenuated, whole sporozoite malaria vaccine in children in Gabon: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Infectious Diseases 2026; 26: 79–90.

hypothesis for the BCG vaccine.[265] *Pf*SPZ presents a range of antigens/epitopes to the immune system. As observed in our placebo group, natural exposure to malaria also elicits anti-CSP and anti-exported protein 1 (EXP1) antibodies. Although these particular antibodies did not associate with vaccine induced protection, it is possible that natural infection induces complex immune responses to conserved immunodominant epitopes on the sporozoite, which can then in turn limit *Pf*SPZ. These immune responses, when augmented above a threshold required for protection, which surpasses titres observed in natural immunity, can provide protection from disease in young children. Indeed, identification of CSP as a conserved immunodominant epitope that induces protection after vaccination with irradiated sporozoites led to its eventual development as the subunit vaccines RTS,S and R21.[266] These anti-CSP based vaccines provide protection by eliciting high levels of anti-CSP antibodies, in contrast to sporozoite antigen-specific CD8+ T-cell responses elicited by *Pf*SPZ.[267,268]

*Pf*SPZ dose has been shown to be important for eliciting sterile immunity and establishing heterologous immunity.[269–272] This could be because a higher dose elicits a stronger response to sporozoite antigens, including responses to cryptic epitopes. The mechanisms of these responses are still poorly understood. Based on CHMI studies in malaria-naïve adults, it was determined that a regimen of three-doses of 9×10^5 *Pf*SPZ given one month apart (1, 8, and 29 days) is optimal and was used in our paediatric trial, but showed poor efficacy in Gabonese children.[273] The vaccination intervals might be of greater importance. This can be portrayed as a biological equivalent of the photoelectric effect- the ability of light to eject an electron from a material is dependent on light's frequency, regardless of its intensity. Increasing vaccine dose does not necessarily guarantee the stimulation of an adequate immune response. Empiric investigation of different *Pf*SPZ time-series (days of vaccination), and booster doses, by CHMI in malaria-exposed individuals might provide translatable vaccine efficacy results in African children.[274] Another factor that appears to affect response to *Pf*SPZ is the length of development of the liver stage. Irradiated sporozoites are non-replicating, meaning they only express early and mid-stage liver proteins. Non-attenuated sporozoites replicate ≈50,000 times in the liver resulting in the expression of ≈2000 proteins.[275,276] Chemo-attenuated *Pf*SPZ (C-vac), in which sporozoites undergo the full development of the liver phase produces sterile immunity at a dose of 2×10^5 *Pf*SPZ.[277] The mechanism of action may be that the prolonged presence and replication in the liver results in a higher probability of

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275 – Shears MJ, Sekhar Nirujogi R, Swearingen KE, et al. Proteomic Analysis of Plasmodium Merosomes: The Link between Liver and Blood Stages in Malaria. J Proteome Res 2019; 18: 3404–18.

generating a protective response. However, promising C-vac efficacy has not translated to African populations.[278] Newer generations of genetically attenuated late-arresting liver stage (-mei2) *Pf*SPZ, which provide ≈90% protective efficacy against CHMI, are yet to be tested in endemic settings, which have challenged outcomes in non-endemic settings[279–281] Finally, an important element for eliciting *Pf*SPZ protection in malaria endemic areas is pre-treatment with an efficacious anti-malarial prior to vaccination. Malian adults and pregnant women who received pre-treatment prior to vaccination with the three-dose regimen of *Pf*SPZ were significantly protected against parasitaemia and clinical malaria (61% and 56% for 9 × 105 Pf SPZ dose) at 2 years post-vaccination, those without pre-treatment were not protected.[282] The three-dose regimen is being studied in pre-treated 6–10-year-old Malian children (NCT04940130).[283] We did not pre-treat in Gabon, meaning concomitant malaria infection/exposure possibly blunted *Pf*SPZ efficacy due to parasite mediated hypo responsiveness.

2.2. Necator americanus L3 larvae for controlled human infection

In **chapter 6,** we showed that CHHI in Gabon is safe, tolerable and with good infectivity of a dose of 50 Gabonese L3 larvae (G-L3). When comparing the Gabonese cohort with a cohort from the Netherlands challenged with 50 Papua New Guinea L3 larvae (PNG-L3), we observed trends along a gradient of previous exposure for both egg production and eosinophilic responses. The less exposed group had higher eosinophilic responses and higher egg counts. This observation must be given careful consideration, bearing in mind the number of study volunteers (22 in challenge group). However, similar approaches with CHMI (comparing malaria naïve vs malaria pre-exposed) have shown protective trends with pre-exposure.[284,285] A degree of induced protective immunity has been observed in CHHI studies in hookworm-naïve individuals in Australia and the Netherlands vaccinated with attenuated larvae.[286,287] As in malaria, one hypothesis for an exposure effect can be that there remains a balance between an inflammatory response and a regulatory response in naïve individuals, and with each subsequent exposure, there is a natural selection of a regulatory response over an inflammatory response.[288] The regulatory response could also be driven by hookworm to create a more conducive environment in the human host; primary hookworm infection in the hookworm-naïve has been shown to enrich CD45RA+Foxp3+CD4+ T cells.[289] This hypothesis can explain our observed trend of less symptomatology, and less

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eosinophilia in previously exposed individuals. Taking a leaf out of our discussion of **chapter 4,** the trend observed in lower egg counts in pre-exposed volunteers may also be explained by antibody responses to immunodominant epitopes of G-L3.

Infectivity of G-L3 was 100% and did not seem to be affected by heterogeneity in pre-exposure to *N. americanus* in the volunteers. Future work with larger number of participants should determine whether egg output following infection with 50 L3, is robust enough for vaccine testing. Adaptive immune mechanisms (antibody and cell mediated) are likely important in supporting innate immunity e.g. eosinophilia, in the response to hookworm infection in the peripheral blood and mucosal microenvironment.[290,291] Previous CHHI studies in the Netherlands in hookworm-naïve individuals have pointed to a significant role for eosinophils and IgG1 in protection.[292] This needs to be confirmed or disputed once data from CHHI in Gabon are analysed. One of the advantages of CHHI is that we know the exact moment of inoculation with L3 larvae, which then allows us to follow the evolution of infection and make detailed investigations into the human response at different timepoints of infection. CHMIs have been shown to be a better platform for studying the effect of pre-exposure to malaria on host immunity, in comparison to field trials.[293] CHHI in Gabon also allows us to study host adaptation to hookworm infection in pre-exposed individuals. The importance of this was highlighted during the development of the first hookworm vaccine candidate, *Necator americanus* Ancylostoma-secreted protein 2 (*Na*-ASP-2), an L3-secreted activation-associated protein. In a phase I trial in the United States, *Na*-ASP-2 was shown to be safe and immunogenic.[294] However in a second Phase I trial in an endemic region of Brazil, pre-exposed volunteers developed IgE mediated generalized urticaria and the trial had to be halted prematurely.[295]

If we can identify a phenotype of protection in pre-exposed individuals, a level or some signal of protection, this will allow for translation to COPs (mechanistic or non-mechanistic), thus reducing dependency on large scale clinical trials for drug and vaccine development. With CHHI we can control the production and viability of L3 larvae, we can control when volunteers receive the challenge material, we can characterize the immunological background of the volunteers in terms of hookworm exposure; and in the case of an intervention we are aware of the time interval between intervention and challenge, samples can be collected over multiple timepoints, and these samples can contribute to a variety of analyses (clinical data, antibody, B-cell, and T-cell assays). In addition,

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296 – Amoah AS, Agnandji ST, Bengtson M, et al. Tackling vaccine hyporesponsiveness through global collaboration, diverse population studies, and data integration. The Lancet Microbe 2025; 0. DOI:10.1016/j.lanmic.2025.101263.

it is important to develop the genetic tools that will allow the distinction to be made between infection with the trial dose versus infection acquired from the environment. Importantly, these investigations will require a strong collaboration between different scientific groups. International consortia, such as HypoVax Global, which seek to investigate population-level variation in immune responses and vaccine hyporesponsiveness are excellent platforms that can be leveraged for such collaboration.[296]

3. Connecting stakeholder dialogue to clinical trial implementation

Prior to the conduct of CHHI in Gabon in **chapter 6;** in **chapter 5,** we reported the proceedings from a stakeholder meeting where the need for CHHI in an endemic area, its risk/benefit balance in Lambaréné, and how best to conduct it were deliberated upon. These themes were important to the success of CHHI.

3.1. CHHI in Gabon: Risk profile

Regarding the calculus of the ethics of CHHI in Gabon, it is important to emphasize that endemicity of hookworm in Lambaréné does not reduce the risk profile for volunteers in endemic areas. CHHI volunteers experience a similar level of personal risk for the benefit of others in society. Yet, for this pilot study, it was decided not to include individuals with high risk of exposure to hookworm infection. It can be considered that individuals living with high exposure to infection are exposed due to a socio-economic vulnerability that we should be prudent to not seem to exploit. Including educated individuals with prior exposure to research was to limit the social context of misinformation spreading in the community whilst preparing for and conducting the trial. This was not done to "protect" individuals, but rather to protect the social integrity of the study. First enrolling educated individuals with less exposure and with less socio-economic fragility also helps establish a normative baseline of risk for volunteers in Lambaréné and its environs and encourage future participation of the target population. After establishing a baseline, the robustness of the informed consent process remains the same, as any literacy gaps in a highly exposed population should not pose a challenge in communication. The system of community engagement in Gabon means that we approached individuals and introduced the opportunity to participate in our studies to them, unlike in

the Global North where most recruitment is via advertisement and social media outreach. Our inclusion and exclusion criteria were based on assuring minimal health risk to volunteers, by ensuring participants were in good health prior to enrolment. Including participants with health abnormalities might distract from the scientific aims of CHHI in Gabon.

It was of vital importance for the ethics committees that a curative dose of albendazole would be given to all volunteers, and that there would be no lasting consequences of challenge infection. The pathophysiology of hookworm infection is well described, meaning investigators could easily identify and manage any variability from the expected norm in the course of infection. The study was conducted under good clinical, laboratory, and manufacturing practices.

3.2. CHHI in Gabon: Benefit profile

A benefit of volunteering in the CHHI was the follow-up medical care provided during the period of the trial. Stakeholders strongly recommended a robust system of volunteer compensation for the cost of trial participation and medical insurance coverage. It is important that the compensation does not represent an exchange for the donation of biological samples, but rather a cover for the incurred costs of participation. It was decided to compensate volunteers at the rate of the minimum wage for Gabon, one of the highest minimum wages on the African continent.[297,298] Gabon has a national health insurance system that provides a safety net. This was in addition to a private health insurance to cover any health risk of trial participation. We enrolled males, from the local population as well as Caucasians with a history of short-term residence in Gabon. There was 'default exclusion' of female participants in this pilot phase, like in previous challenge studies in The Gambia and Tanzania.[299–301] In future studies, female participants will be enrolled. This is necessary to ensure that the benefit of CHHI is available, and the results applicable, to both genders. Benefits to local researchers are in terms of capacity building. Researchers have been able to provide equitable independent contributions to the establishment of CHHI in Gabon. A hookworm laboratory for the isolation and preparation of the challenge material to a GMP-like standard was established. This meant that staff developed the capacity to locally prepare G-L3 from a donor pool living in Lambaréné. Local production was preferable to relying on the transport of PNG-L3 from collaborators in Leiden, the Netherlands. The use of G-L3 for CHHI in Gabon facilitates its future use as an attenuated hookworm vaccine candidate.

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CHHI in Gabon: Burden of participation

The burden of participation in the CHHI was a visit to the clinical trial site once a week for 24 weeks for clinical assessments, and exposure to hookworm infection for a period of 16 weeks. It was decided that confinement of volunteers would not be necessary, meaning volunteers were able to successfully conduct their normal daily activities, including work. However, an outpatient follow-up introduced the problem of third-party risk, as it would be impossible to control volunteer behaviour and ensure they would not transmit their hookworm infection to the community. Volunteer precaution was advocated to limit this possibility. This included educating on preventive methods against transmission. If a volunteer would exercise his right to withdraw, investigators would abrogate infection prior to exit from the study. Most volunteers in Gabon did not experience severe disease, with one isolated case of severe itching occurring. This means the burden of disease for a dose of 50 G-L3 in our endemic population is less in comparison to studies conducted in the Netherlands, where a proportion of participants experienced severe gastrointestinal symptoms. CHHI in Gabon had a high retention rate; one Caucasian participant had to move out of the study area at 16 weeks of follow-up for work-related reasons, but all other participants attended all study visits.

Epilogue

In this thesis, we have made important strides in the fight against malaria and hookworm infection in Gabon. We have highlighted the limitations of current malaria management in a malaria-endemic region and propose an innovative approach. Alongside standard malaria RDTs and continued biomarker development, there is increasing value for the integration of predictive analytics in patient care and the holistic management of malaria.

Overcoming any effect of pre-exposure to malaria or hookworm infection might involve either empiric investigations such as controlled human infection studies where ambitious screening of interventions (such as dose, time-series, boosters) is undertaken, in-depth high-dimensional investigations to understand the mechanisms of natural immunity and hypo responsiveness, or a combination. Researchers taking either approach will benefit from collaboration. These studies are to be performed in endemic areas, enrolling primarily pre-exposed individuals to obtain context-specific results. It will be important to integrate the perspectives of local stakeholders, including government, researchers, community, and study volunteers. The combination of expertise in medical, biomedical, and social science areas will be vital for R&D and sustainability in the control of these diseases. Importantly, the ultimate success of these efforts will be reliant on the existence of functioning health systems at the point of implementation.