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

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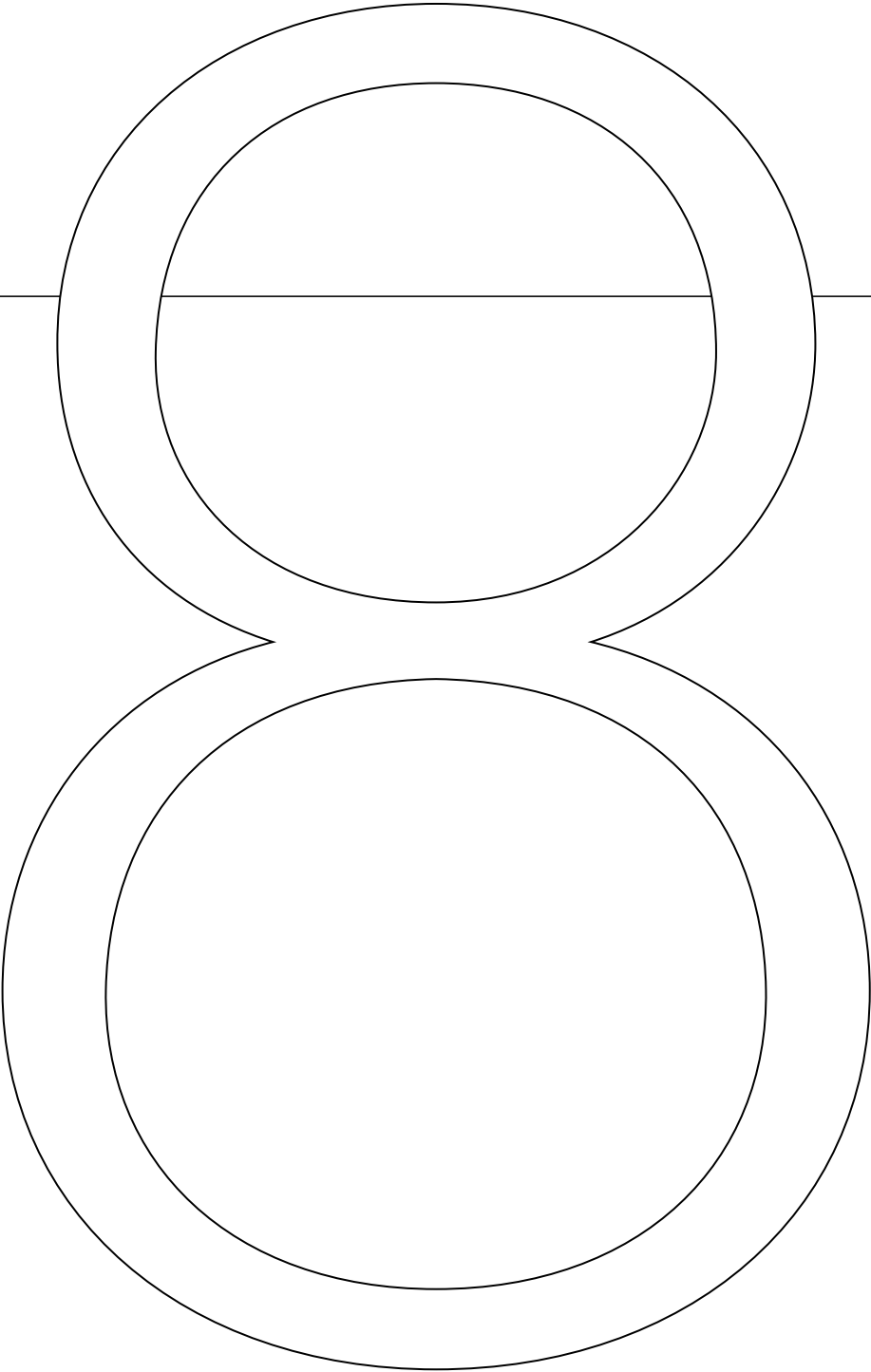
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CHAPTER



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Summary

Chapter 1

This chapter introduces malaria and hookworm as major parasitic diseases that continue to impose significant health and economic burdens in low-resource settings, despite being largely eliminated in high-income countries. It argues that both diseases although associated with poverty, are strongly linked to poor sanitation, limited access to healthcare, and environmental exposure, disproportionately affecting vulnerable populations in sub-Saharan Africa. The chapter highlights the need for integrated control strategies, including improved diagnostics, vaccines, drugs, public health infrastructure, stakeholder engagement, and interventions such as vector control and WASH programmes. It also discusses the challenges of vaccine development, given the complex biology of both parasites and the lack of sterilising immunity after natural infection. A key focus is the introduction of Controlled Human Hookworm Infection (CHHI) in Gabon as a platform for studying host-parasite interactions and testing future interventions. The chapter concludes by outlining the thesis structure, which examines diagnostics, vaccine efficacy, stakeholder engagement, and hookworm research in endemic settings.

Chapter 2

This chapter investigates the causes of acute febrile illness (AFI) among outpatients in Gabon, Malawi, and Brazil using a symptom-guided diagnostic approach combining clinical assessment, rapid diagnostic tests, culture, serology, and PCR. The study enrolled 1,915 participants and identified a broad

range of bacterial and non-bacterial causes of fever. Malaria remained a major cause of AFI in Gabon and Malawi, while arboviral infections (dengue, chikungunya, and Zika) were more prominent causes of AFI in Brazil. Respiratory pathogens, bloodstream infections, and co-infections were also identified as causes, demonstrating the complexity of diagnosing the cause of AFI in tropical settings. The study found that diagnostic uncertainty often persisted despite extensive testing, with many cases remaining unclassified. Antibiotic prescribing practices varied significantly across sites, ranging from conservative use in Gabon to widespread use in Malawi, contributing to concerns about inappropriate antibiotic use and antimicrobial resistance. Overall, the chapter highlights the limitations of current diagnostic tools for managing AFI and emphasises the need for improved point-of-care biomarkers to better distinguish bacterial from non-bacterial infections and guide appropriate treatment decisions in low-resource settings.

Chapter 3

Following conclusions from chapter 2, this chapter evaluates the performance of the STANDARD Q Malaria/CRP DUO rapid diagnostic test (S-DUO) in children with acute febrile illness in Lambaréné, Gabon. The test was designed to simultaneously diagnose malaria and measure C-reactive protein (CRP) as a potential biomarker to guide antibiotic prescribing. A total of 415 children were enrolled, with malaria detected in approximately 42% of participants by microscopy. The S-DUO test demonstrated high sensitivity (99.1%) for malaria detection, showed strong agreement with standard malaria diagnostics, and confirmed its usefulness in malaria-endemic settings. However, the CRP component was less effective in distinguishing bacterial from non-bacterial causes of fever. Although CRP levels were significantly higher in bacterial infections, the test's 20 mg/L threshold was not sufficiently accurate for guiding antibiotic prescription decisions. The findings suggest that a higher CRP cut-off (>40 mg/L) may be more appropriate in this setting. Overall, the chapter concludes that while the dual RDT is effective for malaria diagnosis, further optimisation of the CRP component is needed before it can reliably improve antibiotic stewardship in malaria-endemic regions.

Chapter 4

This chapter presents a randomised, double-blind, placebo-controlled phase 2 trial evaluating the safety, tolerability,

immunogenicity, and protective efficacy of the radiation-attenuated *PfSPZ* malaria vaccine in children aged 1–12 years in Lambaréné, Gabon. The study aimed to determine whether the vaccine could safely prevent naturally acquired *Plasmodium falciparum* infection in children living in a malaria-endemic setting. A total of 200 children were enrolled and randomly assigned in a 2:1 ratio to receive either the *PfSPZ* vaccine (134 children) or placebo (66 children). Participants received three doses on days 1, 8, and 29, and all children were given artemether-lumefantrine before the third dose to clear latent parasitaemia. The vaccine demonstrated a strong safety profile, with mostly mild local and systemic adverse events. Serious adverse events occurred in both groups but were unrelated to vaccination, and no treatment-related deaths were reported. Although transient leukocytosis and thrombocytopenia were observed in some vaccine recipients, these resolved without clinical consequences. Despite inducing strong immune responses, the vaccine showed limited protective efficacy. During the primary follow-up period (2–26 weeks after vaccination), 19% of vaccinated children and 22% of placebo recipients developed *P. falciparum* infection, resulting in an overall vaccine efficacy of only 9% (95% CI –75 to 53; $p = 0.78$). The study suggests that the lack of efficacy may be due to pre-existing or submicroscopic malaria infections before vaccination, which may suppress immune responses and reduce vaccine effectiveness. It was concluded that while the *PfSPZ* vaccine is safe and immunogenic in children, pre-vaccination parasite clearance and improved vaccine strategies may be necessary to achieve meaningful protection in malaria-endemic populations.

Chapter 5

This chapter describes the preparatory steps taken to establish a Controlled Human Hookworm Infection (CHHI) model in Gabon, aimed at accelerating hookworm vaccine and drug development in sub-Saharan Africa. Given the high burden of hookworm infection, limitations of mass drug administration, and high reinfection rates, the chapter argues that CHHI could provide a faster and more effective platform for testing new interventions. To support this, a stakeholder meeting was held in Lambaréné, Gabon (November 2019) involving researchers, regulatory authorities, ethicists, clinicians, social scientists, and community representatives. Discussions focused on the regulatory, ethical, socio-cultural, and operational requirements for safely implementing CHHI in an endemic African setting. Key issues included developing appropriate ethical guidelines,

ensuring informed consent, addressing community concerns about deliberate infection, determining participant compensation, and strengthening regulatory oversight. The chapter also emphasised the importance of community engagement and public education to address mistrust and cultural concerns surrounding clinical research. Operational discussions focused on establishing local capacity to produce hookworm challenge material, using a local *Necator americanus* strain, and ensuring quality assurance. Overall, the chapter demonstrates that establishing CHHI in Africa is feasible but requires strong ethical oversight, regulatory preparation, local infrastructure, and sustained stakeholder collaboration to ensure safe implementation.

Chapter 6

This chapter reports the first controlled human hookworm infection (CHHI) trial conducted in a hookworm-endemic population in Africa, assessing the safety and infectivity of locally derived *Necator americanus* larvae in Lambaréné, Gabon. The phase I trial enrolled 15 healthy adult males: 10 received 50 hookworm larvae and 5 received a placebo. Participants were followed for 24 weeks. All challenged participants developed patent hookworm infection by week 9, confirming that the locally derived larvae were highly infectious. Egg counts remained within the range of light-to-moderate natural infections, though higher egg burdens were observed in the two hookworm-naïve European participants compared with the eight hookworm-exposed Gabonese participants, suggesting possible naturally acquired immunity in endemic populations. The infection was generally well-tolerated. Most adverse events were mild and transient, including local skin reactions at inoculation sites and gastrointestinal symptoms such as abdominal pain, nausea, and bloating. Eosinophil counts increased following infection and then gradually returned to baseline, reflecting expected immune responses. The magnitude of eosinophilic response was greater in the two hookworm-naïve European volunteers compared with the eight hookworm-exposed Gabonese participants. No serious adverse events related to hookworm infection were reported. By demonstrating the safety and feasibility of CHHI in an endemic African setting, this chapter establishes an important platform for future hookworm vaccine development, drug testing, and studies of host immune responses in populations most affected by the disease.

Chapter 7

This final chapter synthesises the thesis's findings and links the malaria-focused studies (**Chapters 2–4**) to the hookworm-focused studies (**Chapters 5–6**). It argues that both diseases require integrated, context-specific strategies that address diagnostics, prevention, immunity, and implementation challenges in endemic settings such as Gabon. For malaria, the chapter highlights that management of acute febrile illness should move beyond treating fever as synonymous with malaria, as co-infections are common and diagnostic uncertainty remains high. It emphasises the need for improved point-of-care diagnostics, biomarker development, and the potential role of artificial intelligence in improving clinical decision-making and antibiotic stewardship. The chapter also reflects on the limited efficacy of the *PfSPZ* malaria vaccine, suggesting that prior malaria exposure and existing immunity may reduce vaccine effectiveness. It proposes further research into alternative vaccination strategies, dosing schedules, and pre-treatment approaches to improve vaccine-induced protection in endemic populations.

For hookworm, the chapter highlights the successful establishment of Controlled Human Hookworm Infection (CHHI) in Gabon and discusses how prior exposure may influence immune responses, symptom severity, and parasite burden. It emphasises CHHI as a valuable platform for studying immunity and accelerating vaccine and drug development in endemic settings.

Finally, the chapter underscores the importance of stakeholder engagement, ethical oversight, local capacity building, and strong health systems in translating scientific advances into sustainable disease control efforts. Overall, it concludes that addressing malaria and hookworm in endemic regions requires multidisciplinary collaboration that integrates biomedical research, public health systems, and community engagement.