PhD defence Hamtandi Magloire Natama

Inter-individual variation of infantsâ€™ susceptibility to malaria: role of in utero environment and host immunogenetic factors

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Dit is de omschrijving

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Summary:

Despite substantial decline of global malaria burden during the past two decades, *Plasmodium falciparum* malaria remains one of the leading global causes of morbidity and mortality, with African children bearing the highest disease burden. The hallmark of *P. falciparum* parasite is the complexity of its interaction with the human host and, the multiplicity of factors driving differential risk of infection resulting in an inter-individual variation in disease manifestation. In infants, while there is strong evidence that placental malaria (PM) increases the risk of malaria during the first months of life, the mechanism underlying this phenomenon is not completely understood. In addition, there is a lack of evidence on whether or not malaria in pregnancy (MiP) preventive treatments may have a long-term benefit in infants as information to date is scarce and inconclusive. Moreover, although the influence of immunerelated polymorphisms on malaria susceptibility is well established in adults and children of various ages, its role and relative importance in infants, especially for genetic loci driving innate immunity, still need to be demonstrated. Therefore the overall aim of this PhD project was to investigate the role of *in utero* environment and host immunogenetic factors in modulating the risk of malaria in infancy. The study was nested to a larger multicentric trial assessing the effectiveness of a community based-scheduled screening and treatment of malaria, in addition to the standard intermittent preventive treatment during pregnancy with sulfadoxine-pyrimethamine (CSST/IPTp-SP), in improving maternal health and birth outcomes in Burkina Faso, Benin and The Gambia (COSMIC trial, NCT01941264). In the first part (**Chapters II-III**), we determined malaria incidence and prevalence in a birth cohort of 734 infants living in Nanoro Health District (NHD), the study site of the COSMIC trial in Burkina Faso. Malariometric indices were determined over 1-year follow-up in which, clinical episodes were determined by passive case detection while asymptomatic malaria infections were identified during 4 cross-sectional surveys at 3, 6, 9 and 12 months of age. *P. falciparum* infections were detected by rapid diagnostic test and/or light microscopy (LM) and quantitative PCR. In addition, we explored the association between cord blood malaria infections as detected by qPCR and clinical outcomes from birth to 59 days. We found high and marked age and seasonal-dependency of malaria infections and disease during the first year of life in NHD, calling for intensified efforts to control malaria in rural Burkina Faso. The overall incidence of clinical malaria was 1.03 per child-year and increased from 0.27 to 1.92 per child-year at 0-3 months and 9-12 months of age, respectively, whereas prevalence of asymptomatic infections increased from 17.7 at 3 months to 30.3% at 12 months of age (**Chapter II**). These *P. falciparum* infections were more likely to be acquired postnatally given the non-clinical relevance of cord blood infections from birth to 59 days of life (**Chapter III**). In the second part, we investigated factors that modulate the risk of malaria during the first year of life (**Chapters IV-V-VI**). The effect of CSST/IPTp-SP combination was compared to the standard IPTp-SP alone to assess the impact of MiP preventive treatments on malaria susceptibility in infancy as well as nonmalarial fevers (NMFs). Additionally, in a subgroup of infants (N=313), we examined the impact of four types of PME (*i.e.* maternal peripheral infection and placental acute, chronic and past infections) on both spontaneous and toll-like receptors (TLRs)-mediated cytokine production in cord blood and how these innate immune responses modulate the risk of malaria during the first year of life. Furthermore, a nested case-control study (N=656) was employed to determine genetic variation in genes driving innate immune response pathways that are associated with malaria susceptibility in infants during the first year of life. Our results showed that the individual risk of malaria during

the first year of life is strongly influenced by *in utero* environment and genetic variations in the immune system. We provided evidence that MiP preventive treatments may provide additional protection against both malaria and NMFs during the first year of life, suggesting that effective malaria control strategies in pregnancy could have long-term benefits in infants (**Chapter IV**). Moreover, we demonstrated that past PM has a profound effect on fetal immune system, and that the differential alterations of innate immune responses by PME categories might drive heterogeneity between individuals to clinical malaria susceptibility during the first year of life. Owing that past PM is a biomarker of early infection during pregnancy, these results suggest that a strategy based on screening and treatment of malaria during pregnancy, which is implemented as early as possible during the first trimester would improve the long-term benefit in infants (**Chapter V**). Finally, the genetic association analysis revealed that, polymorphisms in the immune system genes driving innate immune responses such as IL-1β (rs1143634) and FcγRIIA/CD32 (rs1801274), condition malaria susceptibility during the first months of life, possibly by modulating production of inflammatory mediators (**Chapter VI**). Overall, these findings indicate that, in addition to the inherited genetic background, the differential alteration of fetal immune system by PME categories may have profound implications on immune responses to both malaria and other infections as well as to vaccines formulated with TLR-based adjuvants in infants prenatally exposed to malaria. Therefore, future investigations towards a better understanding of factors driving inter-individual variation of malaria risk in early life are warranted in order to develop rational strategies and/or new tools for preventing malaria cases and related-deaths in infants.