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Mini Review

Immunological Perspectives of sub-Saharan Populations under Prophylaxis against Malaria

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Abstract

Immunity is the state of protection against infectious disease conferred either through an immune response generated by immunization or previous infection. Generated immune responses may be long lasting even lifelong or gives immediate, but short-lived protection. In malaria-endemic areas, young children and pregnant women are particularly susceptible to malaria, but with exposures protective immunity against malaria develop although sterile immunity is never achieved. Assuring protection to vulnerable populations, prophylaxis against malaria is advocated to pregnancy women and sickle cell disease children. Unfortunately, prophylaxis has been suggested to cause a decrease in exposure that curtails the development of acquired protective immunity, leaving individuals more susceptible to malaria in future. To describe this event, a review on effects of intermittent preventive therapy in pregnant women primigravidae (first pregnancy) in particular and chemoprophylaxis against malaria in sickle cell disease children was conducted.

Keywords: acquired immunity; chemoprophylaxis; malaria endemic; pregnant women; sickle cell

Background

Malaria especially caused by *Plasmodium falciparum* is one of the leading cause of morbidity and mortality to vulnerable populations such as pregnant women and children under five years of age (1–3). According to World Health Organization (WHO) report of 2018, pregnancy women and children aged below five years contributed more than 80% of all malaria cases (3). Furthermore, malaria has been the mostly recorded infection in children with sickle cell disease (SCD) (4–9).

To ensure protection from the disease burden especially to vulnerable populations living in malaria endemic regions, WHO advocates the use of intermittent preventive therapy in pregnancy women (IPTp) during the second and third trimester (3–5) and use of chemoprophylaxis in SCD children (6,10–12). However, administering prophylaxis to these groups have been reported to impair the acquisition of natural immunity against the disease through decreased exposures, leaving individuals more susceptible to malaria and lack of background immunity to assist antimalarial drug efficacy (13–15).

Therefore, to acquire more knowledge on how prophylaxis affects the natural acquired immunity, a review was conducted to describe the mechanisms behind this phenomenon.

Immunity to malaria

Naturally immunity to falciparum malaria acquired following exposure to malaria parasites protects many people routinely infected by *Plasmodium falciparum* from disease burdens such as severe malaria (cerebral malaria and anaemia) and death (16).

During humans stage various mechanisms are involved in protection these include; anti-disease immunity, by giving protection against clinical disease, which affects the risk and degree of morbidity associated with a given parasite density; anti-parasite immunity, offering protection against parasitemia, which affects the density of parasites; and lastly premunition, by providing protection against new infections through maintaining a low-grade and mostly asymptomatic parasitemia (16,17,18).

In sub-Saharan Africa, most people are usually infected by *P. falciparum*, and the majority of infected adults rarely experience the burden of the disease (16), infected individuals remain asymptomatic while inhabiting parasites in their blood that could become lethal to a malaria naive individuals (19,20). In addition, as compared to children, adults are less affected with malaria, which adds to the evidences of a lower risk of clinical disease conferred to adults through acquired immune protection, which is not present to infants and still developing in young children (18).

Moreover, natural acquired immunity are compromised when the adults migrate from their routine infections and apparently results to a decreased/lose of their natural acquired immunity (21–23). Therefore malaria protection is partial and requires a continues exposure (staying in malaria endemic regions) to malaria parasites to be maintained (21).

Prophylaxis against malaria in pregnancy and SCD patients

Prophylaxis is recommended to save the populations, which bare more risks of malaria infections and their associated health consequences (19,20,24), these groups include but not limited to travellers (from naïve malaria country to malaria areas) (25–28), pregnancy women and sickle cell disease children (13,14,29–31). The current review will focus more on IPTp and chemoprophylaxis in SCD children (10-12).

Intermittent preventive therapy in pregnancy

Pregnant women is a group mostly affected with malaria after children under age of five years (3), for the past decade pregnant women living in malaria endemic region are recommended to take sulfadoxine-pyrimethamine (SP) during the second and third trimesters (3,5) and this has been part of the national malaria control policy in 33 of 45 African countries where malaria is endemic (32). Evidence from studies reported that children born with mothers used IPTp-SP were protected from adverse effects of malaria such as maternal anemia, stillbirth, miscarriage, premature delivery, and low birth weight (32,33). Therefore pregnant women regardless of the presence or absence of malaria living in areas of moderate to high malaria transmission should be treated with at least two curative doses of SP with an interval of at least 1 month between the two doses, starting in the second trimester of pregnancy (14,32).

In addition, current recommendations from WHO to its member states advocates the minimization of these adverse effects through case management and malaria prevention using insecticide- treated bed nets (3,32,34).

Chemoprophylaxis in SCD patients

Sickle-cell trait (SCT) confers partial protection against malaria while homozygote SCD patients are at greater risk of malaria infection because once the infection occur is always severe (35), hence the use of malaria chemoprophylaxis in SCD patients especially children living in malaria endemic region is recommended (36). Unlike IPTp-SP use where it has been universally recommended, information on use of chemoprophylaxis in SCD children has remained to be scarce (3) i.e. Tanzania is a third leading country in sub-Saharan Africa after Nigeria and Congo with high number of SCD (7,12), still there is no functioning policy which guide the use of chemoprophylaxis against malaria in SCD patients, children in particular (37,38). However, some sub-Saharan African countries still advocates the use of chemoprophylaxis in SCD children (6,11,12).

Immunological consequences as a result of IPTp use

Despite the reported health benefits to babies born with mothers used IPTp-SP during pregnancy (32,33), this good intention has been reported to compromised the development of natural protective immunity especially in primigravidae (13,14,29).

P. falciparum is capable of inhabiting the placenta by expressing variant surface antigens (VSA) which results to a so-called pregnancy associated malaria (PAM) (39). Expressed VSA has good affinity to protein such as chondroitin sulfate A in the placental intervillous space (40,41). Exposure to this VSA proteins cause the development of natural acquired protective immunity to PAM and primigravidae are therefore particularly susceptible to PAM (39,42). However, giving IPTp to primigravidae prevent the acquisition of protective PAM immunity (13).

Although information is scarce but evidence from the current study conducted in Kenyan women found that primigravidae received IPTp-SP had significantly lower levels of VSA-PAM immunoglobulin G (IgG) than those women received a placebo. Furthemore, this study found an association between IPTp doses received and VSA-PAM-specific IgG levels and low IgG levels were recorded among multidose recipients (14). Support from the study by Rogerson et al 2007, pregnant women lacked immunity to this pregnancy-specific VSA protein rendered them susceptible to PAM (43). Other studies documented that, levels of VSA-PAM specific IgG increase with parity and are associated with protection against placental parasitemia, low birth weigh, and anemia (39,42).

Immunological consequences for using chemoprophylaxis

If SCT heterozygotes are protected from malaria through i) the establishment of blood-stage infection, ii) the development of high densities of parasites, iii) the progression of infection to symptomatic malaria (44), unfortunately, this is not the case to sickle cell anemia (SCA) individuals (35). One important reason is that malaria will make the anemia of SCA more severe, to the point of it becoming life-threatening; another reason is that spleen which normally plays great roles in filtering and removing parasitized red blood cells is often impaired in its functions in patients with SCA (35).

Both innate and acquired mechanisms protect children with sickle cell from malaria and this provide an evidence that SCT heterozygotes in malaria endemic areas have an increased probability of surviving until acquired immunity is sufficient to protect them, and others, regardless of their hemoglobin status (44,45).

However, acquisition of protective immunity can be compromised by the use of chemoprophylaxis. Although information regarding the effect of malaria chemoprophylaxis for development of acquired immunity is scarce in SCD but evidence from review on penicillin prophylaxis to prevent pneumococcal infection in SCD children indicated. That rate from infection has been reduced following penicillin prophylaxis but a there was a concern on altered immunological response and penicillin-resistant Streptococcus pneumoniae (46).

Conclusions

A successful regime of intermittent preventive therapy in pregnancy especially primigravidae shield the exposure to placental malaria. More importantly, with reduced exposure to placental malaria, primigravidae might not produce antibodies or develop memory B cells to VSA-PAM. Additionally, if intermittent preventive treatment in pregnancy curtails development of specific immunity, susceptibility to placental malaria could extend to women in their second and even subsequent pregnancies and later to their children during the first year of life due to lack of passive acquired immunity. Furthermore, use of IPTp would results into a compromised background immunity to assist antimalarial drug efficacy.

On the other hand, SCD children and pregnant women especially primigravidae from sub-Saharan Africa countries who live in areas with low malaria transmission, other approaches such as case management and malaria prevention using insecticide- treated bed nets should be prioritized to save the purpose of acquisition of natural protective immunity which has the sustainable health consequences.

Moreover, this review recommends further follow-up studies to be conducted on the effect of protective acquired immunity in the populations under prophylaxis. For the mean time malaria vaccination programme particularly to vulnerable populations should be advocated.

Abbreviations

IgG: Immunoglobulin G; IPTp: Intermittent Preventive Therapy in Pregnancy; PAM: Pregnancy Associated Malaria; SCD: Sickle Cell Disease; SCT: Sickle Cell Trait; SP: Sulfadoxine Pyrimethamine; VSA: Variant Surface Antigens.

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