

Pregnancy-associated Malaria, Challenges and Prospects in Sub-Saharan Africa

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Abstract

Pregnancy-associated malaria remains a major risk to the pregnant woman, her foetus and infants in sub-Saharan Africa. Infection by *Plasmodium falciparum* significantly affects maternal, foetal and neonatal wellbeing. Maternal anaemia, low birth weight, preterm labour, spontaneous abortion, and maternal and neonatal mortalities are some of its consequences. It complicates maternal immunological responses and possibly also selfishly preempts foetal immunological responses by transplacental communications. Therefore, the impacts may extend well beyond the duration of pregnancy and the immediate period post-delivery. Effective case management and prevention continue to yield positive results, but challenges still remains especially in sub-Saharan Africa. The challenges of antenatal service provision, compliance with intermittent preventive treatment at pregnancy with sulfadoxine-pyrimethamine (IPTp-SP), widespread SP resistance, and resistance to insecticide treated nets (ITNs) and insecticides continue to complicate efforts at PAM control in sub-Saharan Africa. Hopefully, the Global Technical Strategy for Malaria 2016–2030 will comprehensively consider these challenges and improve the prospect of every pregnant woman in sub-Saharan Africa.

Keywords: Malaria in pregnancy; *Plasmodium falciparum*; Antenatal care; Antenatal service; Sulfadoxine-pyrimethamine; Insecticide treated nets

Introduction

Malaria, an acute febrile illness caused by protozoa of the genus Plasmodium, continues to constitute a major source of morbidity and mortality globally. Five species of the genus Plasmodium are pathogenic to human, namely, P. falciparum, P. vivax, P. malariae, P. ovale and the recently included P. knowlesi. P. falciparum causes the most virulent cases of human malaria; it is of major importance in sub-Saharan Africa and serves as the species of interest in this review. Presently, malaria poses enormous burden to societies, especially to the developing countries. It is especially regrettable in sub-Saharan Africa. In Nigeria, over 12.0% of the gross domestic product (GDP) is expended on malaria annually [1]. The estimated annual costs (in millions) for the management of malaria in Ghana, Kenya and Tanzania in 2013 were placed at US\$ 37.8, US\$ 109.0 and US\$ 131.9 respectively [2]. This enormous cost of managing malaria further contributes to the negating of developmental efforts in these regions. In 2015, an estimate of 212 million (range 148-304 million) new cases of malaria occurred worldwide. The Africa Region accounted for 90%, South-East Asia Region and Eastern Mediterranean Region accounted for 7% and 2% respectively [3]. From the same estimate, 429 000 malaria mortalities (range 235 000-639 000) occurred worldwide; the African Region accounted for 92%, South-East Asia Region accounted for 6%, and the Eastern Mediterranean Region for 2%. The most vulnerable groups from these estimates are children under five (U5) and pregnant women.

Pregnancy-associated malaria (PAM)-malaria infection during pregnancy, is a major public health concern constituting a serious risk

to the pregnant woman, her foetus and the newborn [4]. This is as infection by malaria parasites especially *P. falciparum* further subjects the pregnant woman to stresses in addition to that arising from pregnancy. This combination of stresses which on one hand is directed at sustaining the foetus and on the other at eliminating parasite, may overwhelm the pregnant woman leading to her death, or abortion of the foetus [5], still birth [6] and low birth weight (LBW) neonates [7]. Wrong drug administration to the gravid woman may have teratogenic consequences if not death to the foetus. Thus, malaria in pregnancy is of critical concern.

Pathology in PAM is dependent on the localization of the parasiteinfected red blood cells (RBC) in the maternal circulation or maternofoetal interface and the immunological responses elicited. PAM may be considered under the contexts, gestational, placental and congenital [8]; where gestational malaria is interpreted as the presence of Plasmodium sp. in maternal circulation which eventually leads to the distribution of parasitaemia to the placenta, a condition considered as placental malaria. Placental isolations of *P. falciparum* also occur in the absence of parasite detection by microscopy in maternal peripheral blood during sub-microscopic infection [9]. Gestational malaria may be considered to incorporate placental localization, as was used by Fisayo [10]. Congenital malaria as the name implies links neonatal malaria to maternal malaria. In this context, transplacental transmission of Plasmodium from maternal circulation into infant's, and infection resulting from maternal placental and foetal cord bloods mixing during delivery are two widely held views on congenital malaria transmission [11-13]. In this review focus was given to PAM without stringent concern for this contextual framework. Here PAM was reviewed under the headings effects, immunological response, management and prevention, challenges and prospective research solution with sub-Saharan Africa as the focus.

Effects of malaria to pregnant women, foetus and neonates

Malaria is one major determinant of pregnancy outcome (Figure 1). PAM is characterized by modification to maternal physiological and biochemical state. Anaemia [14], interference with liver activity [15], depletion of essential micro-and macro-nutrients [16,17] and alteration of plasma lipid and protein profile [10,18,19] are effects attributable to malaria during pregnancy. Rupturing and dysfunctional modification of infected RBC by the blood dwelling erythrocytic stage of *Plasmodium* parasite, the merozoites, depletes cumulative available RBC surface areas and haemoglobin needed for oxygen transport. In extreme cases, PAM may lead to preterm labour and mortality of the gravid woman. Malaria was the third most common cause of death of women of reproductive age in Africa in 2015 [20].

Spontaneous abortion and low birth weight (<2500 g) are other effects attributable to PAM [18,21] as indirect consequences on the foetus from placental sequestration of *P. falciparum*-infected RBC. These effects on the foetus result from interference with placento-foetal exchange, shortage of glucose, reduction in oxygen supply to foetus and maternal anaemia [18,22]. Disturbance of foetal growth influencing substances such as placental lactogen, placental folate metabolism and insulin-like growth factor (IGF) by placental sequestration of infected erythrocytes have been suggested [23]. Low birth weight (LBW) is associated with high infant and neonatal mortality. The risk for neonatal mortality increases steadily as the birth weight decreases to below the low birth weight threshold [22].

Transfer of Plasmodium from maternal circulation through the placenta into foetal circulation is yet to be fully established, but the possibility of such scenario is greatly favoured by research findings. Bidirectional materno-foetal transfer of nucleated cells and plasma DNA at first, second and third trimester of pregnancy is widely acknowledged [24-26]. Where bidirectional transplacental transmission of nucleated cells is possible, unicellular organisms such as Plasmodium may be able to transverse such medium by virtue of size; molecular adhesion markers of Plasmodium may however constitute a major determinant of transplacental transmission. P. falciparum isolates from cord blood have been shown to be acquired antenatally by transplacental transmission [27]. Several studies have linked neonatal or infant malaria to presence of malaria parasitaemia in mother at delivery [12,13,28]. In an 8-year study at a rural hospital in Kenya, 18 (0.35%) out of 5 114 neonate had P. falciparum malaria parasitaemia, and 11 (61.1%) of these were admitted within the first week of life for malaria [12]. Cord blood localization of parasite presents yet another possibility beyond just interference with foetal growth and survival. Dampening of immunological response of newborn to Plasmodium (more importantly P. falciparum) from placental exposure is yet another problem. P. falciparum infected erythrocytes [29] and Plasmodium yoelii infected reticulocytes [30] have been shown to exude extracellular vesicles. Similar vesicles exuded by Leishmania-infected macrophages originated from the parasite and carried its molecules to other cells [31]. Though not yet reported to the best of my knowledge, it is possible that such vesicles are exuded into the cord blood environment consequently educating and modifying the foetal immune system. Such communication may dampen or prime the foetal immunological response against parasite. Observation in foetal circulation of IgM antibodies that specifically bind P. falciparum [32] may suggest foetal-maternal interface antigen exposure if not direct transfer of parasite. In the same vein, P. falciparum strains from cord blood different from those in maternal circulation have been reported [33]. The prior held view that foetal

haemoglobin (HbF) inhibits *P. falciparum* growth in the first month of neonatal life has been questioned by a recent finding. Sauerzopf et al. [34] reported that HbF-containing erythrocytes were permissive to *P. falciparum* growth in vitro and growth was not significantly different from that in maternal bloods; even though growth rate was reduce by yet unknown factor when cord and maternal plasma were added. This highlights need for further research into post-delivery consequences of PAM on infants and newborns.



endemic or recurrent malaria.

Immunity in PAM

In areas where malaria is endemic, it has been observed that while children above 6 months suffer severe malaria with fatal consequences if left untreated, adults irrespective of sex tend to acquire partial immunity by persistent exposure to *Plasmodium* [34,35]. This immunity acquired is characterized by asymptomatic parasitaemia. In primigravidae and secundegravidae, this acquired partial immunity appear to decline or is completely ineffective [8,36] such that *P falciparum* infection if not carefully managed develops into severe disease state threatening the life of the foetus and its carrier. Immunological responses against *Plasmodium* requires both cellmediated and the humoral arms. The pre-erythrocytic stage is controlled by cell-mediated mechanism while humoral activity ensures immunity against the stages.

Critical regulation of systemic and localized immunological responses is important during pregnancy. This may be why it has been observed that maternal cytokines and soluble cytokine receptors level change throughout the course of pregnancy. Studies have observed that during pregnancy, maternal systemic circulating levels of interleukin (IL)-4, IL-6, IL-10 and IL-13 (Th2 cytokines) increase progressively while the plasma concentration of IL-1 α , IL-1 β , IL-2, IL-12 and INF- γ (Th1 cytokines) take an opposite course even becoming significantly less in the third trimester than that observed in the first [37,38]. Tumor necrosis factor (TNF)- α level in the maternal circulation remains unchanged though soluble tumour necrosis factor receptor (sTNFR) level increases which may interfere with the activity of TNF- α probably

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preventing any negative consequences for the foetus [18,39]. Placenta localized immunological response is also Th2 arm directed [40]. These modifications are attributable to the up-regulation of hormones such as progesterone, oestrogen, testosterone and cortisol during pregnancy [41].

The control of parasitaemia during pregnancy presents a major challenge to the gravid woman. Unlike in the non-pregnant where the different aspects of immunologic responses-humoral and cellmediated arms, may be employed in the control of parasitaemia, the tendency of responses to skew toward the humoral arm during pregnancy may have deleterious consequences. While the maintenance of humoral response characterized by the production of T-helper type 2 (Th2) cytokines such as IL-4, IL-5 and IL-13 is important for the sustenance of the foetus, it may not effectively clear parasitaemia. This condition is similar to that utilized by helminthes for continual survival facilitating chronic infection in host [42,43], where even though such humoral-tilted modulation is effective in prevention of pro-inflammatory responses and destruction of pathogens controlled by humoral responses, those controlled by cell-mediated immunological response thrive. It has, however, been observed that P. falciparum-associated pregnancy is characterized by the sequestration of the parasite-infected erythrocytes to placental endothelia which depending on burden may elicit cell-mediated immunological responses. This response characterized by placental localized production of pro-inflammatory or Th1 cytokines such as interferon (INF)-y, TNF-a, IL-12 and IL-2 may lead to placental tissue damage, spontaneous abortion of foetus, preterm labour and intrauterine growth retardation [8,18].

The ability of P. falciparum to express on its surface pregnancyassociated variant surface antigen (VSAPAM) which mediates binding of P. falciparum-infected erythrocyte to chondroitin sulphate proteoglycans in the placental intervillous space defines morbidity [44-46]. VSAPAM also known as VAR2CSA (product of the var2csa gene family) is a conserved member of the P. falciparum-infected erythrocyte membrane protein 1 (PfEMP1). Its association with severity of malaria in primigravidae and secundigravidae has been corroborated by observation of poor anti-VSAPAM antibodies in men and children [47]. Anti-VSAPAM specific IgG antibodies increase by number of pregnancies such that sequestration of P. falciparuminfected erythrocytes to placental chondroitin sulfate A is eventually blocked [48,49]. It is the sequestration of P. falciparum-infected RBC to placental chondriotin sulphate A that characterize severe morbidity and possibly mortality and other inherent deleterious consequences of PAM. Additionally, var2csa gene occur more in infected placentae than in samples of *P. falciparum* from non-pregnant women [50]. Therefore developing vaccine that targets VSAPAM antigen could hold promises against LBW, spontaneous abortion, preterm labour and stillbirth caused by PAM [46,51].

Management and prevention of PAM

Appropriate and prompt diagnosis and chemotherapy requiring stringent consideration for duration of pregnancy remains a standard management procedure for malaria during pregnancy [52]. Chemotherapeutic agents such as chloroquine, clindamycin, hydroxochloroquine, mefluoquine and artemesinin combination therapy are effective depending on virulence. Serious care is recommended in chemotherapy during pregnancy, therapeutic agents could disrupt foetal development especially at the first trimester. In areas of moderate to high malaria transmission such as sub-Saharan Africa, intermittent preventive treatment (IPTp) with sulfadoxinepyrimethamine (SP) administered from the second trimester, accompanied by the use of insecticide treated nets (ITNs) and prompt and effective case management of malaria and anaemia were recommended. As an update to this recommendation, WHO [53] advised that three or more doses of IPTp-SP are more effective than two. This updated recommendation has been supported by observations that women that had three or more doses of IPTp-SP delivered babies with better birth weight than those that had less [54]. However, IPTp-SP is threatened by observations of widespread resistance in several parts of Asia, Americas and Africa [9,55-59]; making replacement of SP as IPTp a matter of when, by what and how. Studies appear to still support the usage of SP as more effective alternatives has not been developed [57,60].

Present research efforts encompass not only the development of appropriate chemotherapeutics but development of both appropriate and cost effective diagnostic procedure especially as most of those afflicted by PAM are in sub-Saharan Africa where poverty rate is high [61]. Improving sensitivity and specificity in the detection of submicroscopic parasitaemia which will facilitate better management of disease before higher and more deleterious parasitaemia develops, remains a major challenge [8]. Even though microscopy remains the standard diagnostic method, and rapid diagnostic tests (RDTs) keeps gaining widespread acceptance in malaria diagnosis [62-64], polymerase chain reaction (PCR) technique which is bedevilled by demand for high technical expertise and cost has been shown to be more sensitive in the detection of sub-microscopic parasitaemia than the former [9,65,66]. An alternative to the detection of parasites or its antigen in the blood is the assessment of plasma or serum biochemical changes [18,67]. This is based on the tendency of the parasitic infection to interfere with the levels of biochemical in circulation. Development of vaccine against the var gene-family products [48,49,68-70] is yet another viable and promising research area targeted at blocking placental adherence of P. falciparum-infected erythrocyte.

Current challenges to PAM prevention and management

Antenatal services: The three pronged-approach (i.e. ITNs usage, IPTp and effective management of malarial cases) to prevention and management of PAM recommended by WHO [71] is greatly dependent on antenatal care provision for effective delivery. Though ITNs distribution, acquisition and usage by pregnant women can happen without interference from antenatal service providers, studies have indicated needs for counselling on ITNs ownership and usage [72]. Promotion of ITNs usage among pregnant women taking together with the other two antenatal care-rooted recommendations during antenatal may be more cost effective than otherwise. As already stated, all three approaches are only employed in area of moderate to high malaria transmission. Possibly, this is why WHO policy for PAM in sub-Saharan Africa was largely dependent on the knowledge that two third of pregnant women in this Region attend antenatal clinics at least once during pregnancy [71]. Therefore appreciable gains in PAM prevention and management are inseparable from antenatal service provision-antenatal care (ANC) and antenatal clinics.

So far, appreciable benefits due to this policy direction have been achieved globally against PAM, and PAM-associated pregnancy outcomes but more still needs to be done. Targets set against PAM were only partly achieved [73]. One reason for the failures is antenatal service provision and patronage. In some settings, pregnant women attend antenatal clinics for the first time during the third trimester [72], thereby greatly reducing the chances of receiving three or more IPTp-SP as recommended. In some settings where antenatal attendance is high, availability of SP to serve three or more doses recommended intake by pregnant women becomes another limiting factor [74]. Based on available data from UNICEF database, for the duration 2004 to December 2017, only in Zambia among all the sub-Saharan African countries listed did 50% or more of pregnant women receive 3 or more doses of IPTp-SP (Figure 2A). Overall mean percentage compliance with three or more doses of IPTp-SP for this duration in the sub-Saharan countries listed was $12.03 \pm 1.14\%$ (range 0-52%) [75].

Antenatal care in some regions are ineffective at preventing PAM [72]; PAM is either not effectively incorporated as a major target of ANC, or commitment to existing policy is poor [75]. Where antenatal service provision is poor, the objectives of WHO and other partners will not be achieved. Therefore, antenatal service provision is a major challenge to attaining objectives set against malaria during pregnancy. Studies evaluating antenatal service provision are relevant. This will help guide policy direction for future interventions. Evaluating other alternatives to IPTp-SP that will better employ antenatal services is needed. Intermittent screening and treatment in pregnancy (ISTp) using rapid diagnostic tests (RDTs) and ACTs during antenatal care is one alternative that was considered by WHO but it was less effective compared to IPTp-SP giving during ANC [60]. Provision of ITNs during ANC is needed in some areas. Also reviews of aspects of counselling and sensitizations during ANC to incorporate malaria preventive strategies may be needed in some settings as was the case in our study at District Hospital, Ogrute, Enugu State, Nigeria [72]. At that hospital, not only was there need for provision of ITNs, there was need for sensitization on benefits of ITNs usage. Based on data from UNICEF global databases 2016, compliance with ITNs usage by pregnant women was higher than 3+ IPTp-SP compliance (Figure 2B). Based on the data available for 2004 to 2016, for sub-Saharan African countries with more than one year report of ITNs usage by pregnant women, the numbers of pregnant women using ITNs were generally on the increase except for Benin. However, mean percentage ITNs usage for the Region within this duration for countries listed was 32.70 \pm 2.31% (range 1-79%); and 34.2% of the countries listed had greater than 50% ITNs usage by pregnant women in at least one of the years under consideration [75].

Sensitizations to reduce the impacts of some belief systems that compromise effectiveness of ANC are also needed. In a study in Democratic Republic of Congo, cultural beliefs negatively affected times of first antenatal visits and attendance for ANC; other determinants included the cost of the service, distance to health facilities, individual income status, religious prohibitions, time of waiting for service, and stigmatization from other women during conception at late ages, young ages or while still lactating [76].

Drug, ITNs and IRS resistances

Resistance to antifolates such as SP by *P. falciparum* is a major setback to PAM control globally, sub-Saharan Africa inclusive. Resistance of *P. falciparum* to SP have been extensively reviewed elsewhere [56,77] and geo-referenced database of SP resistance markers in Africa created [78]. SP-resistant makers in *P. falciparum* occur from substitutions in the enzymes dihydrofolate reductase (DHFR) and dihydropteroate synthase (DHPS) by point mutations in the *dhfr* and *dhps* genes [79-83].



Figure 2: Compliance with 3+ IPTp-SP and ITNs usage by pregnant women in sub-Saharan Africa. (A) Percentage compliance with 3+ IPTp-SP by pregnant women in sub-Saharan African countries, 2004-2017. (B) Percentage compliance with ITNs by pregnant women in sub-Saharan African countries, 2004-2016. The ITNs compliance was based on number of women who used ITNs a night before the surveys from national surveillance. Green line indicates 50% level [75].

Mutant *dhfr* alleles of different types code for varied levels of resistance to pyrimethamine ranging from intermediate to high depending upon the points and number of mutations present [78]. A change in serine to asparagine at point 108 (S108N) characterize resistant isolates, with more resistant isolates possessing additional mutations at codons 51 (N511), 59 (C59R), and 164 (I164L) [55,77]. Marked tolerance to SP is conferred by the triple mutant haplotype (S108N+N51I+C59R) which presently has a pan-African distribution [84]. Mutations to *dhps* gene at codons S436A/F, A437G, K540E, A581G and A613T/S confer resistance to sulfadoxine [77,82,83]. In Africa, a combined presence of the triple dhfr mutations (S108N+N51I+C59R) and the double dhps mutations (A437G+K540E) resulting in quintuple mutation haplotypes is associated with significant SP *P*.

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falciparum treatment failure [55,85]. Additional dhfr mutations at codon 1164L and/or dhps mutation at codon A581G tends to abrogate the effect of SP; and reports of these mutations are widely emerging from Africa [78,85-87].

Resistance to SP is widespread in sub-Saharan Africa; prevalence of resistant phenotypes that are responsible for SP treatment failure is greater than 50% in several sub-Saharan African countries, especially eastern regions [58,85,86,88]. From studies conducted in Africa from 1988 to 2009 prevalence of mutations at codons K540E, A581G and I164L was highest in East Africa (i.e. Southeast and Northeast); Central, West, Southwest and Islands had lower prevalence [78]. No recommendation has so far been made about the level of SP resistance for which the drug should be withdrawn as IPTp. SP is still favoured as IPTp in sub-Saharan Africa for several reasons despite reported high prevalence of triple dhfr (S108N+N51I+C59R), double dhps (A437G +K540E), quintuple (S108N+N51I+C59R + A437G+K540E, and other combinations) and other mutations. The reasons include: (i) more effective alternative to SP is not yet available; one of the drug candidates, dihydroartemisinin-piperaquine considered the likely alternative to SP for IPTp [89] was not better than SP administered during ANC [60]. (ii) SP appear to retain some levels of effectiveness despite widespread resistance. Widespread usage of IPTp-SP in Malawi despites reported cases of SP resistance did not potentiate P. falciparum malaria morbidity in a nine years serial cross-sectional study; also prevalence of SP-resistant haplotypes increased from 17%-100% and proportion of women receiving IPTp-SP increased from 25%-82% within the study period [57]. (iii) Field detection in sub-Saharan Africa of field isolates of *P. falciparum* with deletion of histidine-rich protein gene (Pfhrp) [90] may compromise effective delivery of possibly the most advanced futuristic alternative to IPTp-Sp, which is ISTp. These deletions may interfere with the ability of RDTs to detect infection. An effective delivery of ISTp is more likely to rely on RDTs for detection of malaria before treatment commences. In addition, cases of submicroscopic P. falciparum malaria with undetectable parasitaemia by microscopy, and disappearance of *P. falciparum* from peripheral circulation by sequestration in placentae further complicates chances of widespread ISTp implementation in sub-Sahara Africa.

However, reports on effectiveness of SP against P. falciparum and associated pregnancy outcome in the wake of widespread high prevalence of resistance have not been conclusive. There appear to be some grave risks resultant from widespread high percentage resistance haplotypes P. falciparum for pregnant women and infants. In Muheza, Tanzania, IPTp-SP was associated with increase fraction of parasites carrying the resistance allele DHPS-581, increased level of parasitaemia, and more intense placental inflammation than those who had no IPTp-SP [91]. In the population DHFR 108 and DHPS 437 prevalence had attained a fixation, mixed parasite population occurred only at codons DHFR 51 and 59 and at codons DHPS 540 and 581; and all population fully wide type at codons DHFR 50, DHFR 164 and DHPS 436 [91]. Also in Muheza, IPTp-SP did not confer benefit in an area of widespread SP resistance. IPTp-SP was not associated with reduced risk of placental malaria, or increased mean maternal haemoglobin or mean birth weight; it resulted in decreased cord blood haemoglobin and increased odds of foetal anaemia [92]. In yet another study conducted in Tanzania at Korogwe District in Tanga Region, where P. falciparum population had 9.3%, 46.3% and 44.4% of quadruple or less, quintuple and sextuple mutated haplotypes, infection with the sextuple mutated haplotypes compared with the less mutated haplotypes were associated with reduced birth weight [93]. Muheza District is also in Tanga Region of Tanzania. In Uganda, a country that share border with Tanzania, when compared to pregnant women that had no chemoprophylaxis, IPTp-SP compliance resulted in no significant *P. falciparum* infection reduction; it was also not associated with reduction in maternal anaemia, low birth weight and preterm delivery [94]. In their study population, *P. falciparum* with quintuple and sextuple mutations occurred in 93% and the additional DHFR 164L in 36% [94]. In Northern Tanzania where SP-resistant mutant haplotypes prevalence was high, infants administered SP experienced unacceptable high failure rate and mortality of a child occurred [85].

Contrastingly, Desai et al. [95] reported that IPTp-SP was associated with 22% reduction in the risk of LBW in a study covering six sub-Saharan African countries (Mali, Burkina Faso, Zambia, Malawi, Uganda and Kenya). In these countries they noted P. falciparum DHPS mutations at codons 437, 540 and 581 in the ranges 27.5%-100%, 0%-100% and 0%-5.7%. In Tanzania where IPTp-SP practice despite high SP resistance have been linked to exacerbation of virulence markers, a study covering areas of high and low malaria transmission made some contrasting observations. IPTp-SP was associated with a lower risk of placental malaria especially in the high transmission area; however, it was not associated with reduced risk of maternal anaemia and LBW irrespective of transmission setting [96]. Whether the contrasting reports resulted from difference in host immunologic responses, geographical difference in parasite strains and virulence, duration of morbidity and compliance rate to SP dosage as IPTp, constrains of study designs, or other sources is yet to be resolved. Therefore more researches and harmonization of research findings in these areas of interest are urgently needed in order to guide policy decisions in PAM prevention and management.

Resistance to ITNs and indoor residual sprays (IRS) by mosquitoes, the vector of human malaria, is another challenge bedevilling malaria control and prevention generally and not only at pregnancy. Several studies have reported mosquito resistance to insecticides and ITNs in sub-Saharan Africa [97,98]. Challenges posed to sub-Saharan Africa by mosquitoes resistance has been recently reviewed elsewhere [99]. The Nigerian Institute of Medical Research on 20 June 2017 announced cases of widespread resistance to Long Lasting Insecticide Treated Nets in Nigeria [100,101,102]. This could greatly reduce the gains of malaria control efforts in this sub-Saharan country with over 200 million persons at risk of malaria infection annually, and 45% and 27% national malaria prevalence from RDTs and microscopy respectively [103]; also 60% outpatient visits to health facilities, 30% childhood death, 25% death of children under 1 year and 11% maternal death are due to malaria, and financial cost of over 132 billion naira (US\$ 367 million) is expended annually for treatment, prevention, loss of man hour, etc. [104]. A similar unfortunate scenario plays out in other sub-Saharan African countries bedevilled with the scourge of malaria.

Prospective research solutions

The current procedures for malaria prevention and management adopted by WHO have been largely effective [104,105]. This certainly should result in significant benefits to pregnancy outcome; but direct or indirect measures of the present, medium and long term impacts of the gains leaves no room for celebrations yet. This is because millions of pregnancies are still threatened by malaria especially in sub-Saharan Africa and policies have not completely met targets set; therefore more efforts are needed. The WHO Malaria Policy Advisory Committee continues to make continuous improvements on policy directions for malaria generally including malaria in pregnancy depending on research findings. Therefore, studies designed on the bases of progressively current findings on PAM are needed. These studies should encompass:

Antenatal care: Assessment of patterns and determinants of antenatal care attendance in different settings are needed. The present ANC-oriented PAM prevention and management procedures for sub-Saharan Africa are rooted on the assumption that over 60% pregnant women attend antenatal clinics at least once during pregnancy. Therefore in settings where antenatal attendance is low, the goal to reduce morbidity and mortality due to malaria adopted by different policy makers may never be achieved. Therefore widespread localized and nationwide evaluation of ANC effectiveness against PAM is needed; a template may be taking from Brentlinger et al. [74]. Factors such as compliances with at least 4 times ANC attendance, provision of minimum 3 doses of SP drug on target during ANC; and ITNs usage pattern and determinants among pregnant women are needed. Antenatal care linked design to enhance effective usage of ITNs by pregnant women, infants and newborn is another aspect that may be explored; non-patronage of ITNs and skewed usage pattern has been observed in some settings. In some settings, younger ladies usually primigravidae and secundigravidae who are also at greater risk for severe malaria health outcome were less likely to own and use ITNs [72]. Thus, localized studies incorporating into ANC designs to improve ITNs usage by pregnant women, such as counselling on why and how to use ITNs, may help improve pregnancy outcomes.

Drug formulation and trial: Provision of alternative or complimentary drugs to SP is urgently needed. Though dihydroartemisinin-piperaquine [89], mefloquine and azithromycinbased combination [106], and others drug candidates are being considered as alternatives or complimentary regimen to SP as IPTp and IPTi, several studies are needed prior to and after adoption of any of them. Provision of alternative drugs to SP may help reduce SP drug burden and upset the spread of resistance due to SP as was the case for chloroquine [107,108]. Though no reduction in SP resistance haplotypes prevalence occurred in Malawians 5 years after reduction of SP pressure [109]. Studies covering a longer period or a different geographical area may indicate contrasting results. Effects of complimentary administration of SP with azithromycin during ANC are also being evaluated. Therefore, monitoring of outcomes of such intervention is indispensable.

Vaccine development against *P. falciparum* gene associated with sequestration of infected RBC to placentae endothelia are the focus of some research groups. Such research efforts are laudable.

ITNs and IRS: Patterns and determinants of ITNs and IRS usage are other research areas important to malaria prevention generally. Patterns and factors responsible for malaria vectors resistance to ITNs and IRS are research areas needing attention.

Countering the occurrence and effects of *P. falciparum* resistance to SP and other antifolates such as chlorpyguanil-dapsone (whose production has been suspended due most likely to reports of partial cross-resistance) are areas requiring research attention currently. Histidine-rich protein gene deletion in *P. falciparum* has been reported in South America and sub-Sahara Africa [90,110,111], assessing the implications of such observations in malaria control is important. Futuristically, replacing SP administration without diagnosis by the alternative, screening before treatment in sub-Sahara Africa is expected when incidence of malaria burden in pregnancy is appreciably reduced.

Commitment at national levels to health interventions and policies are always needed for success to be achieved. The same is consistently required in sub-Saharan Africa for success against malaria generally and PAM specifically. Progressive evaluation of sources of policy inefficiencies that arise from national and/or political instabilities, inabilities and indifference are required.

Conclusion

PAM still remains a major public health concern in sub-Saharan Africa. The recently released Global Technical Strategy for Malaria 2016–2030 [112] carries with it a great deal of optimism, promises, plans, demands and certainly challenges. Hopefully, according to the strategy the burden of malaria globally will be lowered by 90%. How the challenges confronting malaria in pregnancy in sub-Saharan Africa will be effectively addressed in the near future will determine how much gains is achieved against PAM. If any organism is resilient, the malaria parasite is one; we can only hope that its retaliatory strategies will be favourable to our course. And very importantly, individual, groups, national and international commitments to this global strategy will be the more important determinant of goals attainment.

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