# Gates Malaria Partnership
# **Publications 2000-2010**

GatesMalariaPartnership

# Contents

# Introduction

The Gates Malaria Partnership (GMP) was established in 2000 with the support of a generous grant from the Bill and Melinda Gates Foundation. An initial five year grant was awarded but GMP activities continued through a no-cost extension until 2009. GMP had four European partners - the Centre for Medical Parasitology, University of Copenhagen, DBL-Institute for Health Research and Development, Copenhagen, Liverpool School of Tropical Medicine and the London School of Hygiene & Tropical Medicine - and many partners in Africa. The activities of GMP covered three main areas (a) conducting applied malaria research with a focus on the optimum deployment of existing malaria control tools (b) supporting a malaria research capacity development programme including a PhD programme for African scientists and (c) bridging the gap between research and policy. The achievements of GMP in each of these areas are summarised in reports which are available on the GMP web site: http://gmp.lshtm.ac.uk/annualreport.htm

Hard copies of the reports are available from Amit Bhasin at:

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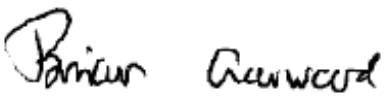
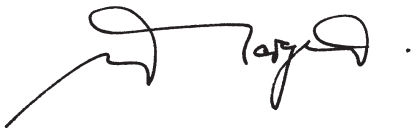
Research undertaken by staff and students supported financially by GMP, either through salary support or through support for their research, has resulted in 401 peer-reviewed publications with a few more still to come. Therefore, we thought that it would be worthwhile compiling a bibliography which brings these publications together. Publications have been categorised, somewhat arbitrarily, into sections to help the reader interested in a particular area of research. Each section is preceded by a brief summary which shows how the individual studies come together in areas deemed at that time to be of particular importance to malaria control. Some of these areas of research have expanded into individual programmes which are now receiving support in different ways.

Review of this bibliography provides an interesting view of how malaria research has evolved during the past 10 years. It also illustrates that malaria will only be finally brought under control through the collaborative work of those working in many different disciplines.

We hope that you will find it useful.



Brian Greenwood



Geoffrey Targett

# Clinical Studies

## Malaria Pathogenesis and Pathology

The Lambaréné Organ Dysfunction Score (LODS) combines the variables coma, prostration and deep breathing and is a simple clinical predictor of fatal malaria in African children[9]. Severe malaria In Yemen had a similar presentation to that in Africa. Here the predictors of mortality were fits, being female, and hyperlactataemia, but not severe anaemia, respiratory distress or hyperparasitaemia[1]. Being female, febrile or a referral, and having low malarial parasitaemia or hepatomegaly were risk factors for severe anaemia in Zambia[20]. There are many cases of severe anaemia in Malawian pre-school children and, even in the presence of malaria parasites, other causes need to be considered[5,24]. Long term, severe anaemia is a risk for child morbidity and mortality in Malawi; treating HIV infection could reduce this [26,21]. The standard three-fold conversion from haematocrit to haemoglobin underestimates the prevalence of haemoglobin < 11g/dl in children under 5 in a malaria setting[6]. A soluble transferring receptor/ferritin (TfR-F) index best predicted iron deficiency[23] and bone marrow examination improved iron assessment in severe anaemia[22].

High levels of pigmented circulating leucocytes were associated with fatal outcome from *P.falciparum* but their predictive value was low[17]. A significant association was shown between Fc gamma receptor IIa (CD32) polymorphism and severe malaria[8] but not between severe malaria and haptoglobin genotypes and phenotypes[2]. Relatives of individuals with hyperactive malaria splenomegaly (HMS) in Ghana were shown to be more likely to have splenomegaly, higher IgM levels and lower haemoglobin than population controls but with no obvious pattern of Mendelian segregation[19].

## Pregnancy

Malaria in pregnancy (in Ghana) is often symptomatic but symptoms are non-specific and overlap with features of pregnancy. Careful history taking may still be helpful in identifying and treating malaria cases[25]. The hazards ratio for infant mortality among women who had been severely anaemic in pregnancy were 3:1[18].

Mean birthweight, length, and head circumference were shown to be lower at all gestational ages for Malawian children compared with Swedish counterparts[13]. Improving maternal nutrition on both a short and long term basis helped to reduce adverse pregnancy outcomes[11]. Infant undernutrition was linked to maternal illiteracy[15]. IUGR was associated with maternal short stature, primigravidae, placental or peripheral malaria at delivery, HIV status and maternal anaemia at recruitment[10,15]. Risk factors for post-natal infant mortality included respiratory infections, diarrhoeal diseases, low birth weight, maternal HIV and malaria at first antenatal visit[27]. Active placental *P.falciparum* detected at delivery gave a greater risk of malaria during early life; infants born to infected multigravidae were at greatest risk[4]. Other factors affecting foetal anaemia were birth in the rainy season and pre-term delivery[3]. Foetal anaemia was associated with shorter time to first illness episode but LBW was not associated with higher morbidity incidence[12]. Where prevalence of malaria parasitaemia and anaemia were high in pregnant women (in N. Ghana), targeting interventions to the high transmission season and to primigravidae was reccommended[7].

## Publications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# Diagnosis

Malaria is frequently over-diagnosed and over-treated when diagnosis is based on presentation with fever and clinical symptoms[10,12]. In the absence of diagnostic facilities, it is recommended that febrile children in endemic areas should be given antimalarials as clinical algorithms are not sufficiently accurate[4] but this approach results in major over-use of antimalarials, especially in areas where the incidence of malaria is falling.

Introduction of rapid diagnostic tests (RDTs) can reduce over-prescription without clinical harm, and with better targeting of antibiotics[2], but clinicians often do not follow results of the tests[11]. Research is needed on how to maximize use of RDTs[6] and make health facility and primary health care staff proficient in their use[9]. To build confidence of health workers faced with negative RDTs, a range of support packages and training in alternative causes of disease are required[3]. Economic evaluation of RDTs needs to take account of whether clinician responses are consistent with test results[7].

The diagnostic accuracy of RDTs was shown to be high in pregnant women[13]. They were effective in a trial in low endemicity settings but effectiveness was reduced in higher transmission settings and by age and season[1].

Serological tools allow detection of variations in malaria transmission over time and can be used to monitor trends in endemicity and the effectiveness of control programmes[5].

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# Epidemiology

## Epidemics

Conventional approaches used to assess the burden of malaria epidemics are inadequate and more accurate estimates are required[15]. Epidemic risk is dynamic with changing patterns based on temporal variations in weather and other eco-epidemiological characteristics of the area at risk[2]. GIS have proved useful in stratification to guide selective targeting of interventions. Seasonal climate predictions should focus on early recognition of anomalies, and mass drug administration or selective vector control is recommended[3].

Models of malaria incidence that incorporate monitored or predicted climate can provide early warnings of epidemics[4,14]. A modelling approach to the weather-malaria relationship was developed but the need for mechanisms that also account for temporal variations in immunity to malaria were indicated[1]. During an epidemic in the highlands of W. Kenya, there was spatial clustering of cases, and the risk of malaria was high in children who were underweight and/or lived at low altitudes[8].

To detect epidemic malaria, there is a need to build systems that improve routine collection of confirmed malaria cases, allow rapid investigation of anomalies in clinical data, and translate early warning information into timely targeted control measures[12]. The highland malaria project (HIMAL) established a malaria surveillance system that was devolved to district level. With some provisos, the system proved manageable, effective and sustainable[17].

## Transmission

Systematic reviews were conducted to assess malaria morbidity and mortality and changes over time in sub-Saharan Africa, against a general paucity of data on burden of disease in developing countries[32]. A literature review covering 18 African countries showed a high malaria mortality burden in 2000[31]. These figures are approximations and there is a need for improved methods of determining annual incidences[29]. In The Gambia and Burkina Faso, child mortality declined between 1960 and 2004 but not malaria mortality rates[23]. Later, however, it was shown that a large proportion of the malaria burden had been alleviated in The Gambia[10]. The microscopically detectable parasite prevalences in The Gambia (and Guinea Bissau) had become low, but PCR revealed a three times higher proportion of carriers, and serology provided information on longer term trends[33]. As malaria prevalence falls, there is a problem of over diagnosis at health centres[30]. With these declines in malaria transmission, it is necessary to determine whether disease prevention strategies should still be focussed on very young children[9,25].

Malaria morbidity was shown to increase in school children as transmission intensity decreased[11]. Age and level of exposure independently influence clinical presentation and fatal manifestations of severe malaria were shown to be more likely when the overall incidence had become low[27]. In a comparison of lowland and highland malaria transmission areas, parasite thresholds were lower in older individuals and in low transmission areas[22]. Farming communities in Tanzania that use irrigation have greater socio-economic status and less malaria than the ones who practice traditional subsistence agriculture[16].

## Co-infections and anaemia

In Uganda, there was no evidence for an association between the presence of infection with nematode worms and risk of malaria[35]. However, school children may be at high risk of co-infection with hookworms and *P.falciparum* malaria[7], or malaria and intestinal schistosomiasis[18], and these contribute to reduced haemoglobin concentrations. Most episodes of anaemia in Tanzania were shown to be asymptomatic; IMCI should improve case management and EPI may be an appropriate way to deliver tools for controlling anaemia and malaria[34].

# Publications


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# Treatment & Chemoprevention

## Treatment

Recommendations for changeover to ACT for treatment of uncomplicated malaria were made based on demonstration of widespread resistance of *P.falciparum* to the commonly used antimalarials, chloroquine, amodiaquine and sulphadoxine-pyrimethamine[50,59,73,84]. The six-dose regimen of artemether-lumefantrine was effective when taken unsupervised[70] and assessments were made of how to improve home- based treatment as well as improving access to antimalarials through health facilities[19,49,104]. Treating severe malaria with pre-referral artesunate saved lives and prevented CNS damage[30]. Supervising health care workers to improve adherence to a standardized treatment protocol greatly reduced in-hospital mortality[4]. There was concern about the use of oral quinine for treatment of uncomplicated malaria when ACTs are not available[88]. A trial of azithromycin and artesunate showed that this combination could not be recommended for use[95]. There was concern too that it might be too soon to abandon presumptive treatment of malaria in areas where laboratory facilities are not available[26]. The use of a highly effective antimalarial (atovaquone-proguanil) reduced the need for blood transfusion in children with malarial anaemia[68]. When SP was used to treat malaria, it was recommended that high doses of folic acid as an adjunct therapy should not be used[69] (but see below). Experimentally, promising preliminary results were obtained using activated charcoal, which did not impair the efficacy of artesunate, as an adjunct therapy for severe malaria[21]. Artesunate also had beneficial antischistome as well as antimalarial efficacy[6].

Artemisinins are effective against immature gametocytes of *P.falciparum* but sub-microscopic gametocytaemia is common after ACT treatment and the overall effect on transmission is moderate[7]. They can reduce the spread of drug-resistant parasites[23,40,92,94] and it was proposed that protocols measuring evolution of drug resistance should have both therapeutic and transmission endpoints[39]. Effective treatment of asexual parasitaemia in the dry season reduced gametocyte carriage to very low levels[24].

A mass drug administration (MDA) trial with SP and artesunate in The Gambia did not work[106]. It was recommended that combination drugs used for MDA should include one that is gametocyticidal[105].

Larger clinical trials, including pharmacovigilance, are required to determine the safety of artemisinins in pregnancy[22]. There were mixed opinions on whether drug efficacy data from children are appropriate for determining drug regimes in pregnancy[45,71,97]. Amodiaquine, used alone or in combination, was considered appropriate for treatment of malaria in pregnancy in Ghana[96,98].

Chloroquine is safe and effective against *P.vivax* in pregnancy, which does not affect blood concentrations of the drug and its metabolites[54,103]. Antifolate treatment was shown to be effective against *P.vivax* in Pakistan and Afghanistan and in these countries may be used as an alternative to chloroquine where other malaria species occur. An extended 8-week course of primaquine was recommended for radical treatment[56].

Poor quality medicines are a major impediment to improvements in public health[74] and substandard antimalarials are common[47,81]. Fake artesunates compromise use of ACT therapy for malaria control[75]. Two simple field assays have been developed to check the quality of artemisinin-based antimalarials[43].

## Drug Resistance

A series of studies across Africa has revealed the evolution of resistance to chloroquine and antifols that preceded the change to artemisinin combination therapy for treatment of *P.falciparum* malaria[2,25,27,46,48,57,60,66]. The benefits of combining genotypic and phenotypic studies have been recognized[42] and a Worldwide Antimalarial Resistance Network (WWARN) has been established[87]. Drug resistant parasite *dhps* has emerged independently in multiple sites in Africa[85]. Regional rather than national policies would help to prevent spread of drug resistance alleles[8] and continued surveillance for changes in susceptibility are recommended[78].

A high prevalence of drug resistant parasites and poor access to hospital was shown to increase the risk of severe malaria[65]. Combining artesunate and chloroquine, where chloroquine resistance occurred, was not beneficial[93]. Antibodies to merozoite antigens AMA-1 and MSP-1 were shown to be associated with recovery from chloroquine-resistant *P.falciparum* in The Gambia[86], and the fitness cost of chloroquine resistance was shown to work against the persistence of resistant parasites through the dry season[82]. Artemether-lumefantrine and amodiaquine exerted opposite selective effects on the *Pfmdr1* resistance gene of *P.falciparum*[41].

Decline in resistance to chloroquine has been shown following a decrease in use of the drug[72,77]. In Malawi, a high

degree of susceptibility to quinolines and artemisinins was shown[76]. In other cases, genetic markers of resistance to chloroquine[100,101] and antifols[80] were rare despite being under drug pressure.

## Intermittent Preventive Treatment (IPT)

An overview of IPT in infants (IPTi) has been published[35]. Treatment with sulphadoxine-pyrimethamine (SP) is safe and has efficacy against malaria and anaemia[3]. The protection covers a range of transmission settings[89] but is short lived[9] with some concerns about rebound[12,32]. Modelling data concluded that IPTi is unlikely to shorten the useful life of the drug used[1] but, as resistance to SP is widespread already, new combinations of long-acting drugs are needed[10]; mefloquine is effective[31]. An IPTi strategy was developed in Tanzania[58] and a decision support tool for implementation developed[11].

IPT in children (IPTc)[36] has been shown to be highly effective[14,15,51,91] and it can be effectively provided through community-based or facility-based systems[52]. It is deliverable through schools[16] and was shown to improve health and cognitive ability[18] and growth in weight[79], but caused decrease in anti-malarial antibody responses[6].

IPT in pregnancy (IPTp) is an established intervention. It reduces the risk of malaria infection in primigravidae but has a lesser effect in multigravidae[28,61]. Uptake is not always good[27] but using community-based approaches increases access and adherence[63,64] , though this sometimes reduces antenatal attendance[67]. SP is the standard drug and use of folic acid supplementation did not alter its effectiveness[62]. Other drugs are needed[102] and the possible use of azithromycin-chloroquine has been reviewed[13].

## Publications


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# Social, Economic and Health Access Studies

## Bednet provision and use

Questions remain about the optimum procedures for large-scale provision of insecticide-treated nets (ITNs), to ensure that those most at risk receive and use them. Investigations conducted to establish the determinants of bednet ownership showed that net use is often low due to their cost and a perception that chemicals on the nets are dangerous[33,90]. Knowledge of malaria and the use of anti-mosquito measures may be particularly low in rural or minority communities[37].

There have been extensive studies on the policy options for increasing uptake of ITNs[10]. Social marketing of nets has increased equity in access[47] and is a cost-effective use of scarce health resources[14,84]. It is more costly than relying on the unassisted commercial sector but achieves a higher overall coverage[18]. Social marketing is linked with provision of subsidized nets, and a voucher scheme has been widely tested. There are demonstrable benefits[37] but less so for the poorest quintile as for them nets are still too costly[15,45]. The cumulative effect of modest attrition at several steps in a

national voucher scheme to deliver ITNs greatly diminished overall coverage, especially amongst the poor[24]. Procedures are also needed to ensure the proper distribution and redemption of vouchers[77] and, when given to pregnant women, it is suggested the distribution should be linked to gestational age to ensure they are provided soon enough in pregnancy to provide optimum protection [26].

A national distribution policy is required[25], combined with targeting of the poorest populations[29,75]. There are benefits from linking net distribution to vaccination campaigns[42] and employer-based delivery systems[81]. Providing nets free of charge is increasingly advocated, and integrated free provision of ITNs was proposed as the most efficient way to increase ITN coverage[93]. However, there are concerns that, in some situations, this could damage local commercial markets[7,82].

## Intermittent preventive treatment (IPT)

IPT in infants (IPTi) shows evidence of efficacy in controlled trials. IPTi with three doses of SP is cost effective[17]; start-up and running costs for Tanzania gave an estimated cost per dose of 23 US cents[22]. IPTi was generally acceptable and there were no negative effect on the EPI with which it was linked[13]. IPT for children (IPTc), administered by school teachers, is also an effective and cost-effective malaria intervention[78]. In an effectiveness study in Tanzania, a per protocol analysis of children who had recently received IPTi showed a parasite prevalence of 22% compared to a control of 41%[5].

Delivery of IPT in pregnancy (IPTp) is a key strategy to reduce the burden of malaria in pregnant women. IPTp coverage is increasing but there are still many factors that hinder further scaling up[23,41] and access to ANC services[40]. Malaria-associated risks in pregnancy, especially anaemia and low birth weight, are not well understood, and may be treated inappropriately[31,34]. SP is perceived as an effective anti-malarial but with negative effects[32]. Evidence on the benefits of treatment is poor, and the economic impact of malaria in pregnancy requires better epidemiological data and better understanding of long-term health and economic costs[92].

## Access to health provision

There can be marked inequities in provision of health care, particularly amongst the poorest quintiles[6].Equity must be a priority in the design of child survival interventions[80] and practical information has been provided on how best to use diaries for data collection in resource-poor settings[83]. Relatively short distances to health facilities and high antenatal and vaccine coverage have the potential to make a big difference to health and survival in rural Tanzania, even with current human resources[4]. Mortality in children <5 years dropped 24% over 5 years as a result of improvements in the Tanzanian health system, including coverage with key child-survival interventions. Further investments and scaling up could produce further rapid gains[28]. Retail outlets for antimalarials have many negative implications but do present opportunities for widening access to good quality drugs[11].

The introduction of IMCI in Tanzania led to improvements in child health that did not occur at the expense of equity[21]. IMCI was shown to be good value for money in terms of case management for children's illnesses, drug and vaccine availability, cost effectiveness and mortality[3,8,27,76].Costs should not be a barrier to the adoption and scaling up of IMCI[1]. However, there were concerns that no criteria were provided for expansion of IMCI from early implementation districts in Brazil, Peru, and Tanzania, and that areas of greatest need were not prioritized[79]. An improved set of tools for measuring child health care in developing countries, supported by both expert and statistical reviews, was developed for use at first level facilities[12]. Removing out of pocket payments for health care was shown to have an impact on health-seeking behaviour in Ghana[2] although, in this study, not on health outcome measures.

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# Parasite Immunobiology

Malaria asexual blood stages are characterized by extensive polymorphism and antigenic variation. Cytoadherence is a feature of *P.falciparum* infections and variants of the parasite compete for adhesion to endothelia[17]. This binding is mediated by the multi-variant erythrocyte membrane protein, PfEMP 1, and a restricted set of these variant surface antigens (Group A VSAs) is associated with severe malaria and high growth rates in non-immune individuals[9]. Expression of variants is not random[8], and there is an ordered acquisition of antibodies to PfEMP 1 domains[3]. Natural antibody responses to domains of PfEMP 1 are mostly variant-specific but there are some cross-reactive epitopes within variants causing severe malaria[7]. A common natural antibody response to one well characterized Group A variant indicated a role in protective immunity[11] .A high throughput assay has been developed to measure the multiplicity of variant responses simultaneously[2]. Binding of parasites to the widely occurring CD36 receptor does not appear to be associated with virulent parasite genotypes[13] but ICAM-1 binding is implicated, and is mediated by conserved parasite residues[16].

Pregnancy-associated malaria involves placental sequestration of parasitized erythrocytes expressing a different set of VSAs mostly binding to chondroitin sulphate A (CSA). VAR2CSA is a well characterized CSA binding molecule[15,21] and naturally induced anti-VAR2CSA antibody protects against the risk of low birth weight[20]. Upstream open reading frames suppress translation of VAR2CSA in children, men and non-pregnant women[1]. There are multiple var2csa genes on different chromosomes[22] and the situation is further complicated because the Duffy binding domains of VAR2CSA thought to be responsible for CSA binding occur elsewhere in other proteins[18]. A second family of variant specific antigens, RIFINS coded by rif genes, form two gene groups rifA1 and rifA2. Their function is unknown but they were transcribed respectively with group A var genes (associated with severe malaria) and VAR2CSA (pregnancy associated) expression[24].

Studies on the genetic complexity of the gametocytes of *P. falciparum* responsible for transmission to mosquitoes indicated that meiotic recombination between different genotypes was a common event[23]. A detailed genetic analysis showed that genomes of *P. falciparum* are in linkage disequilibrium, which would act to slow emergence of drug resistance and vaccine sensitivity[14]. Natural immune responses to sexual stages measured by serology commonly recognized the Pf230 and Pf48/45 antigens. However, different methods of assessment of transmission-blocking activity gave variable results which might be a consequence of variation in sexual stage antigens and/or the nature of the immune response[4]. Flow cytometry was used to detect antibodies recognizing the surface of cultured erythrocytes infected with mature (but not immature) gametocytes of *P. falciparum*. The gametocyte surface antigens were distinct from antigens on the surface of asexual stage parasites[19].

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# Vaccination and Immunity

The *P.falciparum* circumsporozoite protein (CSP)-based RTS,S malaria vaccine candidate is now undergoing multi-centre phase 3 clinical trials having been tested sequentially in adults, children and infants, with different proprietary adjuvants, for safety and efficacy[3,5,10,11,19]. Five-year follow – up studies in Gambian adults demonstrated the long-term safety and the persistence of anti-CSP antibodies[4]. The protection afforded by RTS, S is not strain-specific[1] and, while RTS,S reduced the multiplicity of infection, it did not,not induce parasite CSP T-cell epitope selection[6] or act preferentially against pfcsp alleles with sequence similarity to the 3D7 strain pfcsp sequence employed in the vaccine construct[30].

Early trials of other vaccines have been conducted including a prime-boost strategy with multi-epitope and thrombospondin-related adhesion protein (ME-TRAP)[18] or CSP[15] recombinants. The potential of a PCR assay for detection of very low level infections in the vaccines was demonstrated[14] . Allele-specific immunity to TRAP was predicted to be important for protection, but this was not so with CSP[33].

The MSP 3 blood stage vaccine was shown to be safe in children and induced cytophilic IgG responses thought to be protective[16]. Natural antibody responses to MSP 3 are allele-specific so a vaccine would need to incorporate the major allelic types[22]. On the other hand, there is extensive cross-reactivity between allelic variants of another blood-stage vaccine candidate, MSP 2[9], and serum IgG responses to MSP 2 are associated with a reduced prospective risk of malaria. Target sequences of MSP 1 and of CSP that correlate with protection have been identified[21,23]. Potential targets for development of a *P.vivax* blood stage vaccine have been reviewed[20]. A novel approach to malaria protection involved re-vaccinating children with BCG; it was not successful[25].

There are marked differences in the requirements for vaccination as part of an elimination strategy as opposed to its use in control programmes[12,26]. Detecting and eliminating sub-microscopic infections is one important difference. These were shown to elicit or maintain humoral immune responses in Tanzania; there was no demonstrable modulation by G6PD deficiency or alpha+ thalassemia[25]. In developing vaccines for both control and elimination, there are important requirements of effectiveness and cost-effectiveness[1].

New developments in vaccine-related research are progressing[29]. Innate immune responses in malaria-naïve adults give very heterogeneous cytokine responses that have far-reaching effects on control of parasite growth and disease outcome[32]. Regulatory- T cells are produced rapidly following blood-stage infection, associated with up-regulation of TGFβ, decreases in pro-inflammatory cytokines, decreased antigen-specific immune responses, and higher rates of parasite growth[31]. The isotype/subclass of immunoglobulin determines antibody function. IgG1/IgG3 class switching is affected by the nature of the antigen, exposure, and maturity in mice of the immune system[28,] and a defined T- cell epitope that drives IgG2b subclass switching was identified[27]. Malnourished children who are underweight or stunted were not more or less susceptible to malaria but wasted children were at lower risk, perhaps as a consequence of immunomodulation[7, 8].

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# Vectors and Vector Control

Insecticide treated nets (ITNs) and long lasting insecticide treated nets (LLIN), developed and evaluated through collaborations with the WHO Pesticide Evaluation Scheme (WHOPES), have become the primary method of vector control and are contributing to major reductions of malaria burden[48-52]. Scale-up of ITN distribution and maintenance of high coverage requires complementary public and private sector involvement[15,24]. LLINs were shown to be tolerant of washing procedures in multi-country field trials[12] and remained effective even after withstanding soot, dirt or smoke[18]. The long lasting treatment kit, K-O Tab 1-2-3, converts polyester or polyethylene nets into LLIN[47] but treatment of cotton nets is less effective[41]. There was demonstrable loss of protection against resistant *culicine* or *anopheline* mosquitoes[17,40] by holed nets even when pyrethroid treated. Olyset LLIN remained fully effective after 7 years of use if kept in good condition[25].

There are wide differences in the association between the effectiveness of pyrethroids and occurrence of molecular markers of resistance. In Ghana, an 8.5 fold increase in resistance to pyrethroids was demonstrated[2] but, elsewhere, only low levels of resistance to pyrethroids and DDT were detected in *An.gambiae* and *An.funestus*[22]. In Benin, multiple insecticidal resistance mechanisms were identified in *An.gambiae* and *Cx quinquefasciatus* which with kdr resistance greatly compromised ITN and IRS effectiveness[7]. By contrast, in Côte D'Ivoire, mosquitoes with high frequencies of just kdr and Ace.IR (organophosphate) resistance genes were still controllable with the pyrethroid lambdacyhalothrin, with chlorpyrifos-methyl, and with a combination of the two[5]. The kdr mutation occurs mainly in West Africa but is increasingly found in *An.arabiensis* in East Africa[23]. Pyrethroids were shown to be variable in effectiveness in Tanzania and combination with a second insecticide has been proposed[32]. A cautionary paper showed that health facility-based case-control studies of ITN effectiveness had the potential for selection bias[46].

Alternative insecticides are being developed for IRS and ITNs to sustain control where pyrethroid resistance has become a serious problem[44,26]. A new formulation of chlorpyrifos-methyl demonstrated high effectiveness for IRS and was active for over a year [35]. IRS with the pyrrole, chlorfenapyr, has proved highly effective against pyrethroid and DDT-resistant *An.gambiae*[34] but like many alternatives should be considered in combination with pyrethroids for ITNs to manage resistance[33,31,36]. PermaNet 3.0, a deltamethrin-piperonyl butoxide combination net, was only marginally better than deltamethrin alone against pyrethroid-resistant mosquitoes[45]. Indoxacarb has potential as a larvicide or adulticide where

mosquitoes are pyrethroid resistant[37]. The insect growth regulator pyriproxifen had no effect on *An.stephensi* fecundity but did affect mosquito egg fertility[3].

Full screening of window, doors and eaves of houses, or ceiling screening, reduced mosquito numbers indoors and anaemia in children[20]. Insecticide-treated plastic sheeting (ITPS) or durable lining as it is now called – a long lasting alternative to IRS – could give long-term community protection in homes[8], and as ITPS in refugee camps, could reduce vectorial capacity if widely deployed[13].

In The Gambia, breeding of *An.gambiae* complex was almost entirely restricted to the alluvial areas of the river even at the peak of the rainy season[1]. In semi-urban areas in Tanzania the EIR showed large variation in time and space[11]. Routine entomological surveillance was not feasible for epidemic monitoring or prediction in areas of low endemicity; unusual increases in temperature and rainfall should be used to initiate rapid vector surveys to assess transmission risk[21]. The IgG response to Anopheles salivary peptide - g SG6-P1 is a valuable marker of level of exposure to bites and is useful for surveillance[42].

For vectors such as *An.darlingi* which bite early, additional protection other than ITNs is required[14,43]. Repellents can be effective[16], but not all traditional plant based repellents can provide significant indoor protection[28,29]. Large numbers of early biting mosquitoes have been caught in living areas in houses[30], and mosquitoes can be diverted from repellent users to non-users[27]. *An.gambiae* biting behaviour did not change in favour of early biting in seven years before and after achievement of high bednet coverage[19]. A slow release formulation of the repellent DEET enhanced residual efficacy of bednets against mosquitoes and use of repellents in this way merits further investigation[38,39].

Use of insecticide-treated curtains (ITC) was not associated with greater circulation of drug resistant parasites or higher risk of treatment failure[10], as children protected by ITCs readily clear drug-resistant parasites[9].

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