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... PUBLICATIONS ...

Assessing malaria burden during pregnancy in Mali (Subscription required)

Kassoum Kayentao, Mary Mungai, Monica Parise, Mamoudou Kodio, Abdoul Salam Keita, Drissa Coulibaly, Boubacar Maiga, Boubacar Traoré and Ogobara K. Doumbo

Acta Tropica, Volume 102, Issue 2, May 2007, Pages 106-112

Malaria infection during pregnancy is associated with adverse consequences including low birth weight (LBW) and maternal anemia, particularly in primigravidae and secundigravidae. In preparation for a clinical trial of the efficacy of chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) containing prevention regimens during pregnancy, we conducted a one-year cross sectional study in Koro and Bandiagara, Mali using an assessment methodology developed by the Centers for Disease Control and Prevention (CDC) to generate basic data on malarial burden during pregnancy.

Identification of four members of the *Anopheles funestus* (Diptera: Culicidae) group and their role in *Plasmodium falciparum* transmission in Bagamoyo coastal Tanzania (Subscription required)

E.A. Temu, J.N. Minjas, N. Tuno, H. Kawada and M. Takagi

Acta Tropica, Volume 102, Issue 2, May 2007, Pages 119-125

The role of *Anopheles funestus* group in malaria transmission was investigated in Bagamoyo coastal Tanzania, in the process of characterizing the area as a malaria vaccine testing site.

The presence of four *A. funestus* species in Tanzania emphasizes the relevance to define precisely their spatial and temporal distribution, specific behaviour, ecology and exact role in malaria transmission.

Spatial modelling and risk factors of malaria incidence in northern Malawi (Subscription required)

Lawrence N. Kazembe

Acta Tropica, Volume 102, Issue 2, May 2007, Pages 126-137

Identifying areas of high risk is crucial for providing targeted antimalarial interventions. This study used ecological spatial regression models to profile spatial variation of malaria risk and analysed possible association of disease risk with environmental factors at sub-district level in northern Malawi. The results suggest that the spatial variation in malaria risk in the region is a combination of various environmental factors, both observed and unobserved, and the map only highlights the overall effect of these factors. The results also identified areas of increased risk, where further epidemiological investigations can be carried out. This study, therefore, constitutes an important first step and future models analysed at a sub-district level could be pursued to delineate priority areas for focussing of finite resources.

Molecular surveillance for drug-resistant *Plasmodium falciparum* malaria in Malawi (Subscription required)

Standwell Nkhoma, Malcolm Molyneux and Stephen Ward

Acta Tropica, Volume 102, Issue 2, May 2007, Pages 138-142

We assessed the presence of point mutations associated with resistance to chloroquine (CQ) and sulphadoxine-pyrimethamine (SP) in 178 *Plasmodium falciparum* infections from three geographically distinct sites in Malawi. We confirm that CQ-resistance mutations are now rare in Malawi, being detectable at very low frequencies (2–4%) in infections from two of the three study sites. We also show that over 90% of infections from each of the three study sites carry a set of three dihydrofolate reductase (dhfr) and two dihydropteroate synthase (dhps) mutations strongly associated with SP treatment failure. In this short communication, we present these molecular data and discuss their implications for Malawi's first-line antimalarial treatment policy.

Malarial anemia: of mice and men (Subscription required)

Abigail A. Lamikanra, Douglas Brown, Alexandre Potocnik, Climent Casals-Pascual, Jean Langhorne, and David J. Roberts

Blood 2007;110 18-28

Severe malaria is manifest by a variety of clinical syndromes dependent on properties of both the host and the parasite. In young infants, severe malarial anemia (SMA) is the most common syndrome of severe disease and contributes substantially to the considerable mortality and morbidity from malaria. There is now growing evidence, from both human and mouse studies of malaria, to show that anemia is due not only to increased hemolysis of infected and clearance of uninfected red blood cells (RBCs) but also to an inability of the infected host to produce an adequate erythroid response. In this review, we will summarize the recent clinical

and experimental studies of malaria to highlight similarities and differences in human and mouse pathology that result in anemia and so inform the use of mouse models in the study of severe malarial anemia in humans.

Transcriptome profile of dendritic cells during malaria: cAMP regulation of IL-6 (Subscription required)

Daniel Carapau, Mogens Kruhofer, Allison Chatalbash, Jamie Marie Orengo, Maria Manuel Mota and Ana Rodriguez

Cellular Microbiology, Volume 9 Issue 7 Page 1738-1752, July 2007

Dendritic cells (DCs) have been proposed as mediators of immunity against malaria parasites, as well as a target for inhibition of cellular responses. Here we describe the transcriptomic analysis of spleen DCs in response to Plasmodium infection in a rodent model. We identified a high number of unique transcripts modulated in DCs upon infection. Many cellular functions suffer extensive genomic regulation including the cell cycle, the glycolysis and purine metabolism pathways and also defence responses. Only a small fraction of the regulated genes are coincident with the response induced by other pathogens, suggesting that Plasmodium induces a unique genetic re-programming of DCs. We confirmed regulation of a number of cytokines at the mRNA level including IL-6, IL-10 and IFN- γ . We further dissected a signalling pathway regulating Plasmodium-induced expression of IL-6 by DCs, which is mediated by release of PGE₂, increases in intracellular cAMP and activation of PKA and p38-MAPK.

Effect of the antimicrobial peptide gomesin against different life stages of Plasmodium spp. (Subscription required)

Cristina K. Moreira, Flávia G. Rodrigues, Anil Ghosh, Fernando de P. Varotti, Antonio Miranda, Sirlei Daffre, Marcelo Jacobs-Lorena and Luciano A. Moreira

Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 346-353

While seeking strategies for interfering with Plasmodium development in vertebrate/invertebrate hosts, we tested the activity of gomesin, an antimicrobial peptide isolated from the hemocytes of the spider *Acanthoscurria gomesiana*. Gomesin was tested against asexual, sexual and pre-sporogonic forms of *Plasmodium falciparum* and *Plasmodium berghei* parasites. The peptide inhibited the in vitro growth of intraerythrocytic forms of *P. falciparum*. When gomesin was added to in vitro culture of *P. berghei* mature gametocytes, it significantly inhibited the exflagellation of male gametes and the formation of ookinetes. In vivo, the peptide reduced the number of oocysts of both *Plasmodium* species in *Anopheles stephensi* mosquitoes, and did not appear to affect the mosquitoes. These properties make gomesin an excellent candidate as a transmission blocking agent for the genetic engineering of mosquitoes.

Plasmodium yoelii: Combinatorial expression of variants of the 235 kDa rhoptry antigen during infection (Subscription required)

Henry K. Bayele and K. Neil Brown

Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 354-360

The 235 kDa rhoptry protein Py235 of *Plasmodium yoelii*, has been implicated in erythrocyte invasion by the merozoite forms of the parasite. Py235 is encoded by a large, highly polymorphic gene family, members of which appear to be differentially transcribed. However, it is not clear how many variants are expressed at the protein level during an infection cycle and whether or not these variants are expressed selectively or combinatorially. Certain monoclonal antibodies to Py235 have been shown to attenuate parasite virulence upon passive transfer into mice, suggesting that this antigen or its derivatives may be useful vaccine candidates. To provide a basis for this, we sought to identify those variants that are recognised by the host immune system, and to establish the pattern of expression of the antigen in mice during infection. Using Py235 monoclonal antibodies as probes, we isolated distinct antigenic variants from an expression library, suggesting that the antigen repertoire is potentially large and that different Py235 variants may be produced during infection. The implications of these observations are discussed with respect to the ability of a cloned parasite line to express distinct antigenic variants in vivo.

Plasmodium vivax: Molecular cloning, expression and characterization of glutathione S-transferase (Subscription required)

Byoung-Kuk Na, Jung-Mi Kang, Tong-Soo Kim and Woon-Mok Sohn

Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 414-418

Malaria parasite glutathione S-transferases (GSTs) are postulated to be essential for parasite survival by protecting the parasite against oxidative stress and buffering the detoxification of heme-binding compounds; therefore, GSTs are considered potential targets for drug development. In this study, we identified a *Plasmodium vivax* gene encoding GST (PvGST) and characterized the biochemical properties of the recombinant enzyme. The PvGST contained 618 bp that encoded 205 amino acids and shared a significant degree of sequence identity with GSTs from other *Plasmodium* species. The recombinant homodimeric enzyme had an approximate molecular mass of 50 kDa and exhibited GSH-conjugating and GSH-peroxidase activities towards various model substrates. The optimal pH for recombinant PvGST (rPvGST) activity was pH 8.0, and the enzyme was moderately unstable at 37 °C. The K_m values of rPvGST with respect to GSH and CDNB were 0.17 ± 0.09 and 2.1 ± 0.4 mM, respectively. The significant sequence homology and similar biochemical properties of PvGST and *Plasmodium falciparum* GST (PfGST) indicate that they may have similar molecular structures. This information may be useful for the design of specific inhibitors for plasmodial GSTs as potential antimalarial drugs.

Real-time PCR versus conventional PCR for malaria parasite detection in low-grade parasitemia (Subscription required)

Bianca E. Gama, Felipe do E.S. Silva-Pires, Mauro N'Kruman R. Lopes, Maria Angélica B.

Cardoso, Constança Britto, Kátia L. Torres, Leila de Mendonça Lima, José Maria de Souza, Cláudio T. Daniel-Ribeiro and Maria de Fátima Ferreira-da-Cruz

Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 427-432

We have optimized a faster and cheaper real-time PCR and developed a conventional genus specific PCR based on 18S rRNA gene to detect malaria parasites in low-grade parasitemias. Additionally, we compared these PCRs to the OptiMAL-IT™ test. Since there is no consensus on choice of standard quantitative curve in real-time assays, we decided to investigate the performance of parasite DNA from three different sources: "genome", amplicon and plasmid. The amplicon curve showed the best efficiency in quantifying parasites. Both PCR assays detected 100% of the clinical samples tested; the sensitivity threshold was 0.5 parasite/μl and no PCR positive reaction occurred when malaria parasites were not present. Conversely, if OptiMAL-IT™ were employed for malaria diagnosis, 30% of false-negative results could be expected. We conclude that PCR assays have potential for detecting malaria parasites in asymptomatic infections, in evaluation of malaria vaccine molecule candidates, for screening blood donors, especially in endemic areas, or even in monitoring malaria therapy.

Plasmodium yoelii: Contribution of oocysts melanization to natural refractoriness in Anopheles dirus (Subscription required)

Xu Wen-Yue, Zhang Jian, Zhou Tao-Li, Huang Fu-Sheng, Duan Jian-Hua, Wang Ying, Qiu Zhong-Wen and Xia Li-Sha

Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 433-439

It is well known that *Anopheles dirus* is naturally refractory to rodent malaria parasite, *Plasmodium yoelii*, but the mechanism is still largely unknown. Here, we found that some *P. yoelii* taken into *An. dirus* could develop into oocysts, but oocysts were partially melanized at 7 days and completely melanized at 15 days post-infectious blood meal. Transmission electronic microscopy could find the melanized *P. yoelii* oocysts in *An. dirus* as early as 5 days post-infection, with a few haemocytes attaching to the melanized oocysts, indicating a typical humoral melanization reaction. Although the change of protein pattern at 24 h post-infection suggested that other unknown mechanisms and/or factors might be involved in killing ookinetes, our data implied that oocysts melanization was one of the mechanisms of *An. dirus* to block *P. yoelii* development. In addition, activity of phenoloxidase, such as monophenol oxidase and o-diphenoloxidase, in haemolymph of *An. dirus* fed on infectious blood meal was much higher than that of mosquitoes fed on 5% glucose or normal mouse blood ($p < 0.05$), implying the possible role of PO in oocysts melanization by *An. dirus*.

Plasmodium berghei XAT: Protective 155/160 kDa antigens are located in parasitophorous vacuoles of schizont-stage parasite (Subscription required)

Fumie Kobayashi, Seiji Waki, Mamoru Niikura, Mayumi Tachibana, Takafumi Tsuboi, Motomi Torii and Shigeru Kamiya

Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 450-457

Effective blood-stage malaria vaccine candidates have been mainly developed from the proteins in exposed locations on the parasite such as the surface of free merozoites or infected red blood cells. In the present study, we identified and localized novel protective antigens derived from the blood-stage of *Plasmodium berghei* XAT after establishment of hybridomas producing protective monoclonal antibodies (mAbs) against the parasites. The protective antigens were expressed in schizonts but not in trophozoites, and located in the parasitophorous vacuoles in the infected erythrocyte cytoplasm. The antigens, with molecular weight of 155/160 kDa, were not identical to any merozoite/schizont antigens that have been reported as target molecules recognized by mAbs developed to rodent malaria parasites. The characterization of new malarial antigenic targets of potentially protective antibody responses following infection would give us new insights for the selection of candidate antigens for malaria vaccine.

***Plasmodium falciparum*: mRNA co-expression and protein co-localisation of two gene products upregulated in early gametocytes** (Subscription required)

Alessandra Lanfrancotti, Lucia Bertuccini, Francesco Silvestrini and Pietro Alano
Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 497-503

Genes encoding *Plasmodium falciparum* proteins Pfs16 and Pfpeg3/mdv1, specifically appearing in the parasitophorous vacuole of the early gametocytes, are upregulated at the onset of sexual differentiation. Analysis of asexual development in gametocyte producing and non-producing clones of *P. falciparum* indicated that these genes are also transcribed at a low level in asexual parasites, although their protein products are not detectable in these stages by immunofluorescence. Immunoelectron microscopic analysis of stage II gametocytes indicated that Pfs16 and Pfpeg3/mdv1 proteins co-localise in the parasitophorous vacuole membrane and in all derived membranous structures (such as the multi-laminate membrane whorls of the circular clefts in the infected erythrocyte cytoplasm and the membranes of the gametocyte food vacuoles). In this analysis both proteins were also observed for the first time in the membrane and in the lumen of distinct cleft-like structures in the erythrocyte cytoplasm.

Plasmodium berghei*: Plasmodium perforin-like protein 5 is required for mosquito midgut invasion in *Anopheles stephensi (Open access)

Andrea Ecker, Sofia B. Pinto, Ken W. Baker, Fotis C. Kafatos and Robert E. Sinden
Experimental Parasitology, Volume 116, Issue 4, August 2007, Pages 504-508

During its life cycle the malarial parasite *Plasmodium* forms three invasive stages which have to invade different and specific cells for replication to ensue. Invasion is vital to parasite survival and consequently proteins responsible for invasion are considered to be candidate vaccine/drug

targets. Plasmodium perforin-like proteins (PPLPs) have been implicated in invasion because they contain a predicted pore-forming domain. Ookinetes express three PPLPs, and one of them (PPLP3) has previously been shown to be essential for mosquito midgut invasion. In this study we show through phenotypic analysis of loss-of-function mutants that PPLP5 is equally essential for mosquito infection. Δ pplp5 ookinetes cannot invade midgut epithelial cells, but subsequent parasite development is rescued if the midgut is bypassed by injection of ookinetes into the hemocoel. The indistinguishable phenotypes of Δ pplp5 and Δ pplp3 ookinetes strongly suggest that these two proteins contribute to a common process.

Molecular Analysis of Erythrocyte Invasion in Plasmodium falciparum Isolates from Senegal (Subscription required)

Cameron V. Jennings, Ambroise D. Ahouidi, Martine Zilversmit, Amy K. Bei, Julian Rayner, Ousmane Sarr, Omar Ndir, Dyann F. Wirth, Souleymane Mboup, and Manoj T. Duraisingh
Infect. Immun. 2007;75 3531-3538

The human malaria parasite, *Plasmodium falciparum*, utilizes multiple ligand-receptor interactions for the invasion of human erythrocytes. Members of the reticulocyte binding protein homolog (PfRh) family have been shown to be critical for directing parasites to alternative erythrocyte receptors that define invasion pathways. Recent studies have identified gene amplification, sequence polymorphism, and variant expression of PfRh paralogs as mechanisms underlying discrimination between pathways for invasion. In this study, we find considerable heterogeneity in the invasion profiles of clonal, uncultured *P. falciparum* parasite isolates from a low-transmission area in Senegal. Molecular analyses revealed minimal variation in protein expression levels of the PfRh ligands, PfRh1, PfRh2a, and PfRh2b, and an absence of gene amplification in these isolates. However, significant sequence polymorphism was found within repeat regions of PfRh1, PfRh2a, and PfRh2b. Furthermore, we identified a large sequence deletion (~0.58 kb) in the C-terminal region of the PfRh2b gene at a high prevalence in this population. In contrast to findings of earlier studies, we found no associations between specific sequence variants and distinct invasion pathways. Overall these data highlight the importance of region-specific elaborations in PfRh sequence and expression polymorphisms, which has important implications in our understanding of how the malaria parasite responds to polymorphisms in erythrocyte receptors and/or evades the immune system.

Production of High-Affinity Human Monoclonal Antibody Fab Fragments to the 19-Kilodalton C-Terminal Merozoite Surface Protein 1 of Plasmodium falciparum (Subscription required)

Xun-Jia Cheng, Hitoshi Hayasaka, Katsuomi Watanabe, Yan-Lin Tao, Jin-Ye Liu, Hideo Tsukamoto, Toshihiro Horii, Kazuyuki Tanabe, and Hiroshi Tachibana
Infect. Immun. 2007;75 3614-3620

A combinatorial immunoglobulin gene library was constructed from peripheral blood lymphocytes of eight patients infected with *Plasmodium*

falciparum and was screened for the production of human monoclonal antibody Fab fragments to the C-terminal 19-kDa fragment of *P. falciparum* merozoite surface protein 1 (MSP-1₁₉). This is the first report of gene analysis and bacterial expression of human monoclonal antibodies to *P. falciparum* MSP-1₁₉. The combinatorial immunoglobulin gene library derived from malaria patients provides a potential tool for producing high-affinity human antibodies specific for *P. falciparum*.

Inhibition of Dendritic Cell Maturation by Malaria Is Dose Dependent and Does Not Require Plasmodium falciparum Erythrocyte Membrane Protein 1 (Subscription required)

Salenna R. Elliott, Timothy P. Spurck, Joelle M. Dodin, Alexander G. Maier, Till S. Voss, Francisca Yosaatmadja, Paul D. Payne, Geoffrey I. McFadden, Alan F. Cowman, Stephen J. Rogerson, Louis Schofield, and Graham V. Brown
Infect. Immun. 2007;75 3621-3632

Red blood cells infected with *Plasmodium falciparum* (iRBCs) have been shown to modulate maturation of human monocyte-derived dendritic cells (DCs), interfering with their ability to activate T cells. Interaction between *Plasmodium falciparum* erythrocyte membrane protein 1 (PfEMP1) and CD36 expressed by DCs is the proposed mechanism, but we show here that DC modulation does not require CD36 binding, PfEMP1, or contact between DCs and infected RBCs and depends on the iRBC dose.

Neural Cell Adhesion Molecule, a New Cytoadhesion Receptor for Plasmodium falciparum-Infected Erythrocytes Capable of Aggregation (Subscription required)

Bruno Pouvelle, Valery Matarazzo, Christophe Jurzynski, Johannes Nemeth, Michael Ramharter, Genevieve Rougon, and Jurg Gysin
Infect. Immun. 2007;75 3516-3522

The cytoadhesion of *Plasmodium falciparum*-infected erythrocytes (IEs) to the endothelial cells lining the microvasculature, clogging the microvessels of various organs, is a key event in the pathogenesis of certain severe forms of malaria, such as cerebral malaria and pulmonary edema. Studies aiming to identify possible correlations between the severity of clinical cases and the presence of particular cytoadhesion phenotypes have been largely unsuccessful. One of the possible reasons for this failure is that some of the key receptors and/or mechanisms involved have yet to be identified. By combining IE selection, cell transfection, and adhesion inhibition assays, we identified a new cytoadhesion receptor, neural cell adhesion molecule (NCAM).

Effect of Sulfadoxine-Pyrimethamine Resistance on the Efficacy of Intermittent Preventive Therapy for Malaria Control During Pregnancy: A Systematic Review (Subscription required)

Feiko O. ter Kuile; Annemieke M. van Eijk; Scott J. Filler
JAMA 2007;297 2603-2616

To determine the effect of increasing resistance to sulfadoxine-pyrimethamine on the efficacy of IPT during pregnancy in Africa.

In areas in which 1 of 4 treatments with sulfadoxine-pyrimethamine fail in children by day 14, the 2-dose IPT with sulfadoxine-pyrimethamine regimen continues to provide substantial benefit to HIV-negative semi-immune pregnant women. However, more frequent dosing is required in HIV-positive women not using cotrimoxazole prophylaxis for opportunistic infections.

Plasmodium berghei-Infected Primary Hepatocytes Process and Present the Circumsporozoite Protein to Specific CD8+ T Cells In Vitro (Subscription required)

Silayuv E. Bongfen, Ralph Torgler, Jackeline F. Romero, Laurent Renia, and Giampietro Corradin

J. Immunol., Jun 2007; 178: 7054 – 7063

A substantial and protective response against malaria liver stages is directed against the circumsporozoite protein (CSP) and involves induction of CD8+ T cells and production of IFN- γ . CSP-derived peptides have been shown to be presented on the surface of infected hepatocytes in the context of MHC class I molecules. However, little is known about how the CSP and other sporozoite Ags are processed and presented to CD8+ T cells. We investigated how primary hepatocytes from BALB/c mice process the CSP of *Plasmodium berghei* after live sporozoite infection and present CSP-derived peptides to specific H-2Kd-restricted CD8+ T cells in vitro. Thus, it can be hypothesized that infected hepatocytes can contribute in vivo to the elicitation and expansion of a T cell response.

Plasmodium falciparum Infection Causes Proinflammatory Priming of Human TLR Responses (Subscription required)

Matthew B. B. McCall, Mihai G. Netea, Cornelius C. Hermsen, Trees Jansen, Liesbeth Jacobs, Douglas Golenbock, Andre J. A. M. van der Ven, and Robert W. Sauerwein

J Immunol 2007;179 162-171

TLRs are a major group of pattern recognition receptors that are crucial in initiating innate immune responses and are capable of recognizing *Plasmodium* ligands. We have investigated TLR responses during acute experimental *P. falciparum* (*P.f.*) infection in 15 malaria-naïve volunteers. Taken together, *P.f.* primes human TLR responses toward a more proinflammatory cytokine profile both in vitro and in vivo, a characteristic exceptional among microorganisms.

Genome-Wide Expression Analysis of Placental Malaria Reveals Features of Lymphoid Neogenesis during Chronic Infection

(Subscription required)

Atis Muehlenbachs, Michal Fried, Jeff Lachowitz, Theonest K. Mutabingwa, and Patrick E. Duffy

J Immunol 2007;179 557-565

Chronic inflammation during placental malaria (PM) is most frequent in first time mothers and is associated with poor maternal and fetal outcomes. In the first genome-wide analysis of the local human response to sequestered malaria parasites, we identified genes associated with

chronic PM and then localized the corresponding proteins and immune cell subsets in placental cryosections. B cell-related genes were among the most highly up-regulated transcripts in inflamed tissue.

The results suggest that B cells and macrophages contribute to chronic PM in a process resembling lymphoid neogenesis. We propose a model where the production of Ig during chronic malaria may enhance inflammation by attracting and activating macrophages that, in turn, recruit B cells to further produce Ig in the intervillous spaces.

Plasmodium falciparum Intercellular Adhesion Molecule-1-Based Cytoadherence-Related Signaling in Human Endothelial Cells

(Subscription required)

Neil Jenkins, Yang Wu, Srabasti Chakravorty, Oscar Kai, Kevin Marsh, and Alister Craig
The Journal of Infectious Diseases 2007;196:321-327

Cytoadherence of *Plasmodium falciparum*-infected erythrocytes to host endothelium has been associated with pathology in severe malaria, but, despite extensive information on the primary processes involved in the adhesive interactions, the mechanisms underlying disease are poorly understood.

Signaling via apposition of *P. falciparum*-infected erythrocytes with host endothelium is dependent, at least in part, on the cytoadherence characteristics of the invading isolate. An understanding of the postadhesive processes produced by cytoadherence may help us to understand the variable pathologies seen in malaria disease.

Clinical efficacy of chloroquine versus artemether-lumefantrine for Plasmodium vivax treatment in Thailand (Open access)

Srivicha Krudsood, Noppadon Tangpukdee, Sant Muangnoicharoen et al.
Korean J Parasitol. 2007 Jun;45(2):111-114

Chloroquine remains the drug of choice for the treatment of vivax malaria in Thailand. Mixed infections of falciparum and vivax malaria are also common in South-East Asia. Laboratory confirmation of malaria species is not generally available. This study aimed to find alternative regimens for treating both malaria species by using falciparum antimalarial drugs.

We concluded that the combination of artemether-lumefantrine and primaquine was well tolerated, as effective as chloroquine and primaquine, and can be an alternative regimen for treatment of vivax malaria especially in the event that a mixed infection of falciparum and vivax malaria could not be ruled out.

The genetic diversity of Plasmodium vivax: a review (Open access)

Souza-Neiras, Wanessa Christina de; Melo, Luciane Moreno Storti de; Machado, Ricardo Luiz Dantas

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.245-254

The genetic diversity of *Plasmodium vivax* has been investigated in several malaria-endemic areas, including the Brazilian Amazon region, where this is currently the most prevalent species causing malaria in humans. This review summarizes current views on the use of molecular markers to

examine *P. vivax* populations, with a focus on studies performed in Brazilian research laboratories. We emphasize the importance of phylogenetic studies on this parasite and discuss the perspectives created by our increasing understanding of genetic diversity and population structure of this parasite for the development of new control strategies, including vaccines, and more effective drugs for the treatment of *P. vivax* malaria.

A population genetics study of *Anopheles darlingi* (Diptera: Culicidae) from Colombia based on random amplified polymorphic DNA-polymerase chain reaction and amplified fragment length polymorphism markers (Open access)

González, Ranulfo; Wilkerson, Richard; Fidel Suárez, Marco; García, Felipe; Gallego, Gerardo; Cárdenas, Heiber; Elisa Posso, Carmen; Cristina Duque, Myriam
Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.255-262

The genetic variation and population structure of three populations of *Anopheles darlingi* from Colombia were studied using random amplified polymorphic markers (RAPDs) and amplified fragment length polymorphism markers (AFLPs).

Urban malaria in the Brazilian Western Amazon Region I: high prevalence of asymptomatic carriers in an urban riverside district is associated with a high level of clinical malaria (Open access)

Tada, Mauro Shugiro; Marques, Russimeire Paula; Mesquita, Elieth; Martha, Rosimeire Cristina Dalla; Rodrigues, Juan Abel; Costa, Joana D'Arc Neves; Pepelascov, Rosario Rocha; Katsuragawa, Tony Hiroshi; Pereira-da-Silva, Luiz Hildebrando
Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.263-270

Cross sectional studies on malaria prevalence was performed in 2001, 2002, and 2004 in Vila Candelária, an urban riverside area of Porto Velho, Rondônia, in the Brazilian Western Amazon, followed by longitudinal surveys on malaria incidence.

It was concluded that asymptomatic carriers represent an important reservoirs of parasites and that the carriers might contribute to maintaining the high level of transmission. Comparing our findings to similar geo-demographic situations found in other important urban communities of the Brazilian Amazon, we propose that asymptomatic carriers could explain malaria's outbreaks like the one recently observed in Manaus.

Urban and suburban malaria in Rondônia (Brazilian Western Amazon) II: perennial transmissions with high anopheline densities are associated with human environmental changes (Open access)

Gil, Luiz Herman Soares; Tada, Mauro Shugiro; Katsuragawa, Tony Hiroshi; Ribolla, Paulo Eduardo Martins; Silva, Luiz Hildebrando Pereira da
Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.271-276

Longitudinal entomological surveys were performed in Vila Candelária and adjacent rural locality of Bate Estaca concomitantly with a clinical

epidemiologic malaria survey. Vila Candelária is a riverside periurban neighborhood of Porto Velho, capital of the state of Rondônia in the Brazilian Amazon. High anopheline densities were found accompanying the peak of rainfall, as reported in rural areas of the region. Moreover, several minor peaks of anophelines were recorded between the end of the dry season and the beginning of the next rainy season. These secondary peaks were related to permanent anopheline breeding sites resulting from human activities. Malaria transmission is, therefore, observed all over the year. In Vila Candelária, the risk of malaria infection both indoors and outdoors was calculated as being 2 and 10/infecting bites per year per inhabitant respectively. Urban malaria in riverside areas was associated with two factors: (1) high prevalence of asymptomatic carriers in a stable human population and (2) high anopheline densities related to human environmental changes. This association is probably found in other Amazonian urban and suburban communities. The implementation of control measures should include environmental sanitation and better characterization of the role of asymptomatic carriers in malaria transmission.

Microsatellite characterization of Plasmodium falciparum from symptomatic and non-symptomatic infections from the Western Amazon reveals the existence of non-symptomatic infection-associated genotypes (Open access)

Martha, Rosimeire Cristina Dalla; Tada, Mauro Sughiro; Ferreira, Ricardo Godoi de Mattos; Silva, Luiz Hildebrando Pereira da; Wunderlich, Gerhard
Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.293-298

In Western Amazon areas with perennial malaria transmission, long term residents frequently develop partial immunity to malarial infection caused either by Plasmodium falciparum or P. vivax, resulting in a considerable number of non-symptomatically infected individuals. For yet unknown reasons, these individuals sporadically develop symptomatic malaria. In order to identify if determined parasite genotypes, defined by a combination of eleven microsatellite markers, were associated to different outcomes - symptomatic or asymptomatic malaria - we analyzed infecting P. falciparum parasites in a suburban riverine population. Despite of detecting a high degree of diversity in the analyzed samples, several microsatellite marker alleles appeared accumulated in parasites from non-symptomatic infections. This result may be interpreted that a number of microsatellites, which are not directly related to antigenic features, could be associated to the outcome of malarial infection. The result may also point to a low frequency of recombinatorial events which otherwise would dissociate genes under strong immune pressure from the relatively neutral microsatellite loci.

Man biting rate seasonal variation of malaria vectors in Roraima, Brazil (Open access)

Barros, Fábio Saito Monteiro de; Honório, Nildimar Alves

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.299-302

Malaria control has been directed towards regional actions where more detailed knowledge of local determinants of transmission is of primary importance. This is a short report on range distribution and biting indices for *Anopheles darlingi* and *An. albitarsis* during the dry and rainy season that follows river level variation in a savanna/alluvial forest malaria system area in the Northern Amazon Basin.

Vector bionomics and malaria transmission in the Upper Orinoco River, Southern Venezuela (Open access)

Magris, Magda; Rubio-Palis, Yasmin; Menares, Cristóbal; Villegas, Leopoldo

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.303-312

A longitudinal epidemiological and entomological study was carried out in Ocamo, Upper Orinoco River, between January 1994 and February 1995 to understand the dynamics of malaria transmission in this area.

The present study was the first longitudinal entomological and epidemiological study conducted in this area and set up the basic ground for subsequent intervention with insecticide-treated nets.

Adjuvant requirement for successful immunization with recombinant derivatives of Plasmodium vivax merozoite surface protein-1 delivered via the intranasal route (Open access)

Bargieri, Daniel Y; Rosa, Daniela S; Lasaro, Melissa Ang Simões; Ferreira, Luis Carlos S; Soares, Irene S; Rodrigues, Mauricio M

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.313-318

Recently, we generated two bacterial recombinant proteins expressing 89 amino acids of the C-terminal domain of the *Plasmodium vivax* merozoite surface protein-1 and the hexa-histidine tag (His6MSP119). One of these recombinant proteins contained also the amino acid sequence of the universal pan allelic T-cell epitope (His6MSP119-PADRE). In the present study, we evaluated the immunogenic properties of these antigens when administered via the intra-nasal route in the presence of distinct adjuvant formulations.

Considering the limitations of antigens formulations that can be used in humans, mucosal adjuvants can be a reliable alternative for the development of new strategies of immunization using recombinant proteins of *P. vivax*.

Population genetic structure of the major malaria vector Anopheles darlingi (Diptera: Culicidae) from the Brazilian Amazon, using microsatellite markers (Open access)

Scarpassa, Vera Margarete; Conn, Jan E

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.319-328

The population genetic structure of *Anopheles darlingi*, the major human malaria vector in the Neotropics, was examined using seven microsatellite loci from nine localities in central and western Amazonian Brazil.

Taken together, these data suggest little genetic structure for *An. darlingi* from central and western Amazonian Brazil. These findings also imply that

the IBD model explains nearly all of the differentiation detected. In practical terms, populations of *An. darlingi* at distances < 152 km should respond similarly to vector control measures, because of high gene flow.

Antimalarial drugs disrupt ion homeostasis in malarial parasites

(Open access)

Gazarini, Marcos L; Sigolo, Carlos AO; Markus, Regina P; Thomas, Andrew P; Garcia, Célia RS

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.329-334

Plasmodium chabaudi malaria parasite organelles are major elements for ion homeostasis and cellular signaling and also target for antimalarial drugs. By using confocal imaging of intraerythrocytic parasites we demonstrated that the dye acridine orange (AO) is accumulated into *P. chabaudi* subcellular compartments.

The addition of antimalarial drugs chloroquine and artemisinin resulted in AO release from acidic compartments and also affected maintenance of calcium in ER store by using different drug concentrations.

Comparative recognition by human IgG antibodies of recombinant proteins representing three asexual erythrocytic stage vaccine candidates of *Plasmodium vivax* (Open access)

Barbedo, Mayara B; Ricci, Ricardo; Jimenez, Maria Carolina S; Cunha, Maristela G; Yazdani, Syed S; Chitnis, Chetan E; Rodrigues, Mauricio M; Soares, Irene S

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.335-340

In previous immuno-epidemiological studies of the naturally acquired antibody responses to merozoite surface protein-1 (MSP-1) of *Plasmodium vivax*, we had evidence that the responses to distinct erythrocytic stage antigens could be differentially regulated. The present study was designed to compare the antibody response to three asexual erythrocytic stage antigens vaccine candidates of *P. vivax*.

Our results further confirm a complex regulation of the immune response to distinct blood stage antigens. The reason for that is presently unknown but it may contribute to the high risk of re-infection in individuals living in the endemic areas.

Clinical spectrum of uncomplicated malaria in semi-immune Amazonians: beyond the " symptomatic " vs " asymptomatic " dichotomy (Open access)

Silva-Nunes, Mônica da; Ferreira, Marcelo U

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.341-348

We analyzed prospectively 326 laboratory-confirmed, uncomplicated malarial infections (46.3% due to *Plasmodium vivax*, 35.3% due to *P. falciparum*, and 18.4% mixed-species infections) diagnosed in 162 rural Amazonians aged 5-73 years. Thirteen symptoms (fever, chills, sweating, headache, myalgia, arthralgia, abdominal pain, nausea, vomiting, dizziness, cough, dyspnea, and diarrhea) were scored using a structured questionnaire.

We found significant differences in the prevalence and perceived intensity of fever and other clinical symptoms in relation to parasite load at the time of diagnosis and patient's age, cumulative exposure to malaria, recent malaria morbidity, and species of malaria parasite. These factors are all likely to affect the effectiveness of malaria control strategies based on active or passive detection of febrile subjects in semi-immune populations.

An ecoregional classification for the state of Roraima, Brazil: the importance of landscape in malaria biology (Open access)

Rosa-Freitas, Maria Goreti; Tsouris, Pantelis; Peterson, A Townsend; Honório, Nildimar Alves; Barros, Fábio Saito Monteiro de; Aguiar, Ducinéia Barros de; Gurgel, Helen da Costa; Arruda, Mércia Eliane de; Vasconcelos, Simão Dias; Luitgards-Moura, José Francisco

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.349-358

Understanding the different background landscapes in which malaria transmission occurs is fundamental to understanding malaria epidemiology and to designing effective local malaria control programs. Geology, geomorphology, vegetation, climate, land use, and anopheline distribution were used as a basis for an ecological classification of the state of Roraima, Brazil, in the northern Amazon Basin, focused on the natural history of malaria and transmission.

Such ecoregional mappings are important tools in integrated malaria control programs that aim to identify specific characteristics of malaria transmission, classify transmission risk, and define priority areas and appropriate interventions. For some areas, extension of these approaches to still-finer resolutions will provide an improved picture of malaria transmission patterns.

In vitro inhibition of Plasmodium falciparum by substances isolated from Amazonian antimalarial plants (Open access)

Andrade-Neto, Valter F de; Pohlit, Adrian M; Pinto, Ana Cristina S; Silva, Ellen Cristina C; Nogueira, Karla L; Melo, Márcia RS; Henrique, Marycleuma C; Amorim, Rodrigo CN; Silva, Luis Francisco R; Costa, Mônica RF; Nunomura, Rita CS; Nunomura, Sergio M; Alecrim, Wilson D; Alecrim, M das Graças C; Chaves, F Célio M; Vieira, Pedro Paulo R

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.359-366

In the present study, a quassinoid, neosergeolide, isolated from the roots and stems of *Picrolemma sprucei* (Simaroubaceae), the indole alkaloids ellipticine and aspidocarpine, isolated from the bark of *Aspidosperma vargasii* and *A. desmanthum* (Apocynaceae), respectively, and 4-nerolidylcatechol, isolated from the roots of *Pothomorphe peltata* (Piperaceae), all presented significant in vitro inhibition (more active than quinine and chloroquine) of the multi-drug resistant K1 strain of *Plasmodium falciparum*. Neosergeolide presented activity in the nanomolar range. This is the first report on the antimalarial activity of these known, natural compounds. This is also the first report on the isolation of aspidocarpine from *A. desmanthum*. These compounds are good candidates for pre-clinical tests as novel lead structures with the aim

of finding new antimalarial prototypes and lend support to the traditional use of the plants from which these compounds are derived.

Prevalence and level of antibodies to the circumsporozoite protein of human malaria parasites in five states of the Amazon region of Brazil (Open access)

Arruda, Mercia E; Zimmerman, Robert H; Souza, Renata MC; Oliveira-Ferreira, Joseli
Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.367-372

The aim of this study was to determine the prevalence of malaria infection and antibodies against the repetitive epitopes of the circumsporozoite (CS) proteins of *Plasmodium falciparum*, *P. malariae*, *P. vivax* VK210, *P. vivax* VK247, and *P. vivax*-like in individuals living in the states of Rondônia, Pará, Mato Grosso, Amazonas, and Acre.

The high frequency of reactions to *P. malariae* in most of the areas suggests that the infection by this *Plasmodium* species has been underestimated in Brazil.

Effect of fosmidomycin on metabolic and transcript profiles of the methylerythritol phosphate pathway in *Plasmodium falciparum* (Open access)

Cassera, María B; Merino, Emilio F; Peres, Valnice J; Kimura, Emilia A; Wunderlich, Gerhard; Katzin, Alejandro M

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.377-384

In *Plasmodium falciparum*, the formation of isopentenyl diphosphate and dimethylallyl diphosphate, central intermediates in the biosynthesis of isoprenoids, occurs via the methylerythritol phosphate (MEP) pathway. Fosmidomycin is a specific inhibitor of the second enzyme of the MEP pathway, 1-deoxy-D-xylulose-5-phosphate reductoisomerase. We analyzed the effect of fosmidomycin on the levels of each intermediate and its metabolic requirement for the isoprenoid biosynthesis, such as dolichols and ubiquinones, throughout the intraerythrocytic cycle of *P. falciparum*. This is the first study that compares the effect of fosmidomycin on the metabolic and transcript profiles in *P. falciparum*, which has only the MEP pathway for isoprenoid biosynthesis.

Coadaptation and malaria control (Open access)

Tosta, Carlos Eduardo

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.385-404

Malaria emerges from a disequilibrium of the system 'human-plasmodium-mosquito' (HPM). If the equilibrium is maintained, malaria does not ensue and the result is asymptomatic plasmodium infection. The relationships among the components of the system involve coadaptive linkages that lead to equilibrium. A vast body of evidence supports this assumption, including the strategies involved in the relationships between plasmodium and human and mosquito immune systems, and the emergence of resistance of plasmodia to antimalarial drugs and of mosquitoes to insecticides. Coadaptive strategies for malaria control are based on the following principles: (1) the system HPM is composed of three highly

complex and dynamic components, whose interplay involves coadaptive linkages that tend to maintain the equilibrium of the system; (2) human and mosquito immune systems play a central role in the coadaptive interplay with plasmodium, and hence, in the maintenance of the system's equilibrium; the under- or overfunction of human immune system may result in malaria and influence its severity; (3) coadaptation depends on genetic and epigenetic phenomena occurring at the interfaces of the components of the system, and may involve exchange of infectrons (genes or gene fragments) between the partners; (4) plasmodia and mosquitoes have been submitted to selective pressures, leading to adaptation, for an extremely long while and are, therefore, endowed with the capacity to circumvent both natural (immunity) and artificial (drugs, insecticides, vaccines) measures aiming at destroying them; (5) since malaria represents disequilibrium of the system HPM, its control should aim at maintaining or restoring this equilibrium; (6) the disequilibrium of integrated systems involves the disequilibrium of their components, therefore the maintenance or restoration of the system's equilibrium depend on the adoption of integrated and coordinated measures acting on all components, that means, panadaptive strategies. Coadaptive strategies for malaria control should consider that: (1) host immune response has to be induced, since without it, no coadaptation is attained; (2) the immune response has to be sustained and efficient enough to avoid plasmodium overgrowth; (3) the immune response should not destroy all parasites; (4) the immune response has to be well controlled in order to not harm the host. These conditions are mostly influenced by antimalarial drugs, and should also be taken into account for the development of coadaptive malaria vaccines.

Anti-malaria humoral responses in children exposed to Plasmodium falciparum and Schistosoma haematobium (Open access)

Mutapi, F; Roussilhon, C; Mduluzza, T; Druilhe, P

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.405-410

Antibody responses directed against the Plasmodium falciparum antigens, total extract, anti-merozoite surface protein-3 (MSP3b) and glutamate-rich protein (Glurp-R0) were studied in 42 children exposed to both Schistosoma haematobium and P. falciparum infections. The association between levels of the anti-malaria IgG subclasses and IgM with host age, sex, schistosome infection intensity and schistosome specific antibodies was studied before chemotherapeutic treatment of schistosome infections. The results suggest cross reactivity between schistosome and malaria antigens in this population.

Plasmodium vivax thrombospondin related adhesion protein: immunogenicity and protective efficacy in rodents and Aotus monkeys (Open access)

Castellanos, Angélica; Arévalo-Herrera, Myriam; Restrepo, Nora; Gullosio, Leonel; Corradin, Giampietro; Herrera, Sócrates

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.411-416

The thrombospondin related adhesion protein (TRAP) is a malaria pre-erythrocytic antigen currently pursued as malaria vaccine candidate to *Plasmodium falciparum*. In this study, a long synthetic peptide (LSP) representing a *P. vivax* TRAP fragment involved in hepatocyte invasion was formulated in both Freund and Montanide ISA 720 adjuvants and administered by IM and subcutaneous routes to BALB/c mice and Aotus monkeys.

These results suggest that this TRAP fragment has protective potential against *P. vivax* malaria and deserves further studies as vaccine candidate.

Short communication: Enhancement of the antimalarial efficacy of amodiaquine by chlorpheniramine in vivo (Open access)

Sowunmi, Akintunde; Gbotosho, Grace O; Happi, Christian T; Adedeji, Ahmed A; Bolaji, Olayinka M; Fehintola, Fatai A; Fateye, Babasola A; Oduola, Ayoade MJ

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.417-420

Resistance in *Plasmodium falciparum* to amodiaquine (AQ) can be reversed in vitro with with antihistaminic and tricyclic antidepressant compounds, but its significance in vivo is unclear. The present report presents the enhancement of the antimalarial efficacy of AQ by chlorpheniramine, an H1 receptor antagonist that reverses chloroquine (CQ) resistance in vitro and enhances its efficacy in vivo, in five children who failed CQ and/or AQ treatment, and who were subsequently retreated and cured with a combination of AQ plus CP, despite the fact that parasites infecting the children harboured mutant *pfcrT76* and *pfmdr1Y86* alleles associated with AQ resistance. This suggests a potential clinical application of the reversal phenomenon.

Short communication: Merozoite surface protein 2 allelic variation influences the specific antibody response during acute malaria in individuals from a Brazilian endemic area (Open access)

Sallenave-Sales, Selma; Faria, Clarissa Perez; Zalis, Mariano Gustavo; Daniel-Ribeiro, Cláudio Tadeu; Ferreira-da-Cruz, Maria de Fátima

Mem. Inst. Oswaldo Cruz, June 2007, vol.102, no.3, p.421-425

The antibody response to *Plasmodium falciparum* parasites of naturally infected population is critical to elucidate the role of polymorphic alleles in malaria. Thus, we evaluated the impact of antigenic diversity of repetitive and family dimorphic domains of the merozoite surface protein 2 (MSP-2) on immune response of 96 individuals living in Peixoto de Azevedo (MT-Brazil), by ELISA using recombinant MSP-2 proteins. The majority of these individuals were carrying FC27-type infections. IgG antibody responses were predominantly directed to FC27 parasites and were correlated to the extension of polymorphism presented by each MSP-2 region. This finding demonstrated the impact of the genetic polymorphism on antibody response and therefore, its importance on malaria vaccine efficacy.

Bedlam in the Blood: Malaria (Open access)

Michael Finkel

National Geographic Magazine July 2007

The rapidly spreading disease affects more people than ever before. But until recently, the outcry has been muted.

It begins with a bite, a painless bite. The mosquito comes in the night, alights on an exposed patch of flesh, and assumes the hunched, head-lowered posture of a sprinter in the starting blocks. Then she plunges her stiletto mouthparts into the skin.

Genetic linkage and association analyses for trait mapping in *Plasmodium falciparum* (Subscription required)

Xinzhuan Su, Karen Hayton & Thomas E. Wellems

Nature Reviews Genetics 8, 497-506 (July 2007)

Malaria is a major cause of mortality in the developing world. Genetics and genomics are now greatly assisting our understanding of this disease, through linkage and association studies of the malaria parasite, *Plasmodium*.

Reports: Evolutionary Dynamics of Immune-Related Genes and Pathways in Disease-Vector Mosquitoes (Subscription required)

Robert M. Waterhouse, Evgenia V. Kriventseva, Stephan Meister *et al.*

Science 22 June 2007: Vol. 316. no. 5832, pp. 1738 - 1743

Mosquitoes are vectors of parasitic and viral diseases of immense importance for public health. The acquisition of the genome sequence of the yellow fever and Dengue vector, *Aedes aegypti* (Aa), has enabled a comparative phylogenomic analysis of the insect immune repertoire: in Aa, the malaria vector *Anopheles gambiae* (Ag), and the fruit fly *Drosophila melanogaster* (Dm). Analysis of immune signaling pathways and response modules reveals both conservative and rapidly evolving features associated with different functional gene categories and particular aspects of immune reactions. These dynamics reflect in part continuous readjustment between accommodation and rejection of pathogens and suggest how innate immunity may have evolved.

Examining the evidence of under-five mortality reduction in a community-based programme in Gaza, Mozambique (Subscription required)

Anbrasi Edward, Pieter Ernst, Carl Taylor, Stan Becker, Elisio Mazive and Henry Perry
Transactions of the Royal Society of Tropical Medicine and Hygiene, Volume 101, Issue 8, August 2007, Pages 814-822

Effective implementation of programmes with the community Integrated Management of Childhood Illness model has demonstrated improvements in care-seeking behaviours and utilisation of health services. These findings suggest that effective community-based partnerships that support the delivery of health services can contribute to mortality reductions.

Relapsing malaria infection in an adolescent following travel to Mozambique (Subscription required)

Cameron B. Oswald, Andrea P. Summer and Philip R. Fischer

Travel Medicine and Infectious Disease, Volume 5, Issue 4, July 2007, Pages 254-255

Infection with *Plasmodium ovale* is uncommon in travelers. We describe a case of *ovale* malaria in a traveler to Mozambique who initially presented several weeks after completion of his trip. Species identification was ultimately achieved with a PCR-based diagnostic method.

Haemoglobinuria in a 38-year-old French expatriate man living in Cameroon following artemisinin-based antimalarial treatment

(Subscription required)

Khaled Ezzedine, Thierry Pistone, Marie-Catherine Receveur, Thomas Cressend, Céline Diéval and Denis Malvy

Travel Medicine and Infectious Disease, Volume 5, Issue 4, July 2007, Pages 256-258

Massive haemoglobinuria is encountered rarely during the course of malaria. It is usually considered a diagnostic criterion for severe malaria, together with anaemia, acute renal failure and jaundice. Haemoglobinuria can also present among expatriates travelling to endemic areas following repeated exposure to quinoline or arylaminoalcohol drugs. A case is described of haemoglobinuria developing in a 38-year-old French expatriate diagnosed concurrently with numerous tropical infections, and treated on presumptive basis with an antimalarial regimen containing artemisinin derivatives. Haemoglobinuria resolved spontaneously within a few days. Although this case does not definitely indicate a causal link between haemoglobinuria and artemisinin derivatives, the risk of such infrequent side-effects should be taken into account in pharmacovigilance monitoring. Moreover, the patient illustrates the multifaceted pathology that can be encountered with tropical infections.

Measurement of malaria vaccine efficacy in phase III trials: Report of a WHO consultation (Subscription required)

Vasee Moorthy, Zarifah Reed and Peter G. Smith

Vaccine, Volume 25, Issue 28, 9 July 2007, Pages 5115-5123

In October 2006, the World Health Organisation (WHO) convened a meeting of experts to discuss appropriate methods for evaluating the efficacy of malaria vaccines in pivotal phase III trials. The participants included regulatory, industry and donor representatives and clinical trialists, epidemiologists and statisticians from both developed and developing countries. The consultation also considered the regulatory requirements for registration of a malaria vaccine and public health issues that clinical development plans need to address before deployment of a malaria vaccine in developing countries. This report summarizes the discussions and conclusions reached during the course of the meeting.

Immunogenicity and in vitro protective efficacy of a polyepitope *Plasmodium falciparum* candidate vaccine constructed by epitope shuffling (Subscription required)

Qiliang Cai, Guiying Peng, Lingyi Bu, Yahui Lin, Lianhui Zhang, Sara Lustigmen and Heng Wang

Vaccine, Volume 25, Issue 28, 9 July 2007, Pages 5155-5165

A polyepitope chimeric antigen incorporating multiple protective and conservative epitopes from multiple antigens of *Plasmodium falciparum* has been considered to be more effective in inducing multiple layers of immunity against malaria than a single stage- or single antigen-based vaccine. By modifying the molecular breeding approach to epitope shuffling, we have constructed a polyepitope chimeric gene that encodes 11 B-cell and T-cell proliferative epitope peptides derived from eight key antigens mostly in the blood stage of *Plasmodium falciparum*. Our studies indicate the potential of M.RCAg-1 recombinant protein as malaria candidate vaccines as well as the rationale of the epitope shuffling technology applied in designing malaria vaccines.

Immunogenicity of *Plasmodium vivax* combination subunit vaccine formulated with human compatible adjuvants in mice (Subscription required)

Yengkhom Sangeeta Devi, Paushali Mukherjee, Syed Shams Yazdani, Ahmad Rushdi Shakri, Suman Mazumdar, Sunita Pandey, Chetan E. Chitnis and Virander S. Chauhan
Vaccine, Volume 25, Issue 28, 9 July 2007, Pages 5166-5174

An effective malaria vaccine will probably require the delivery of multiple antigens that induce several layers of immunity. Malaria antigens expressed on the surface and in apical organelles of blood-stage merozoites are potential vaccine candidates given their importance in the invasion of erythrocytes. The present study examined the kinetics of humoral response in BALB/c mice following immunization with combination of two blood-stage *Plasmodium vivax* invasion related molecules, the N-terminal, cysteine-rich region II of *P. vivax* Duffy binding protein (PvRII) and the 19 kDa C-terminal region of merozoite surface protein 1 (PvMSP119) formulated with Montanide ISA 720 and alhydrogel. The results of the present study provide a rationale for a combination vaccine against *P. vivax* malaria based on PvMSP119 and PvRII.

... BOOKS ...

Guidelines for the Elimination of Residual Foci of Malaria Transmission

World Health Organization, *EMRO Technical Publications Series*, No. 33

Order Number 14500033; Price CHF 10.00/US\$ 9.00; Developing countries: CHF 7.00

Elimination of the residual foci of malaria transmission is a dynamic process, taking place mainly during the late stage of the attack and consolidation phases of malaria elimination. This approach is suitable for countries or areas that are targeting interruption of malaria transmission in their territories. Countries can plan for a selective elimination of *P. falciparum* foci in the first stage, to be expanded to *P. vivax* at a later stage when more resources and a stronger programme are available.

During the past 15 years several national malaria programmes in the WHO Eastern Mediterranean Region adopted elimination strategies. It is the vision of the Regional Office for the Eastern Mediterranean to expand malaria-free areas at sub-regional level and to support new initiatives wherever feasible. These guidelines on the elimination of malaria transmission foci provide information on identification of foci of malaria transmission, epidemiological classification, selection and application of appropriate measures and monitoring and evaluation of implemented interventions. The publication is targeted at policy and decision makers, malaria programme managers at national and sub-national levels, and field staff. It can also be used in training courses on planning and management of malaria elimination.

Guidelines on Prevention of the Reintroduction of Malaria

World Health Organization, EMRO Technical Publications Series, No. 34

Order Number: 14500034; Price CHF 10.00/US\$ 9.00; Developing countries: CHF 7.00

Many countries have succeeded in eliminating malaria from their territories. However, they are still at risk of reintroduction from endemic countries and areas. The malaria programmes in these countries face many challenges for prevention of malaria reintroduction, including weak malaria surveillance and vigilance systems, lack of malaria awareness among health professionals and travellers, uncontrolled population movement and lack of cooperation among countries. In the WHO Eastern Mediterranean Region 13 countries either eliminated malaria many years ago or are very close to malaria elimination. The main priority for these countries is to prevent re-establishment of local malaria transmission in receptive and vulnerable areas in their territories. These guidelines on prevention of reintroduction of malaria provide information on malaria surveillance and vigilance, malaria early warning system, prevention and control of re-introduced malaria, emergency preparedness for malaria outbreaks and monitoring, and evaluation of activities. The publication is targeted at policy and decision makers, health authorities responsible for malaria at national and sub-national levels and field staff. It can also be used in training courses on planning and management of malaria elimination.

--- GRANT & RESEARCH OPPORTUNITIES ---

Call for Proposals: Translational research in major infectious diseases: to confront major threats to public health

Deadline: 18 September 2007 at 17:00:00 (Brussels local time)

Budget: € 549 000 000

Further to its publication in the Official Journal of the European Union, the call FP7-HEALTH-2007-B is now available on CORDIS.

FP7 is the short name for the Seventh Framework Programme for Research and Technological Development. This is the EU's main

instrument for funding research in Europe and it will run from 2007 to 2013.

More information

Reminder: Career Development Grants on bioinformatics and functional genomics research

Application deadline: 1 July 2007

The CDG is designed for support of early career investigators to foster novel applications of bioinformatics tools and functional genomics in DECAs and to establish a new cadre of young scientists working in collaboration and networks. Grant recipients are expected to develop their research in association with the TDR-supported Regional Training Centres in an effort to expand the critical mass in this field.

More information

--- JOB OPPORTUNITIES ---

Research Associate x 2, Division of Cell and Molecular Biology, Faculty of Natural Sciences, Imperial College, London, UK

Closing Date: 23 July 2007

Imperial College London invites applications for the following vacancies in the joint group of Prof. Fotis C. Kafatos and Dr. George K. Christophides at Imperial College London.

The successful applicants will be members of a large research team working on innate immunity and functional genomics of the malaria vector *Anopheles gambiae*. You will work on a programme aiming to understand the mosquito innate immune system and its interactions with *Plasmodium* parasites capitalizing on a variety of postgenomic tools. Required skills include standard molecular biology techniques with emphasis on protein biochemistry, including 2D-PAGE, mass spectrometry, purification of secreted proteins and protein expression. Experience in cell culture techniques is preferred.

You will also be skilled molecular biologists with a PhD in a relevant field and a track record of publications.

These positions are available immediately and funding is available for up to 3 years. For further details please contact Rabeya Sultana, email:

r.sultana@imperial.ac.uk

More information

.....

Part-time Project Manager Communications Malaria Genomic Epidemiology Network, The Wellcome Trust Centre for Human Genetics

Closing date for applications: Friday 6 July 2007

Grade 7: £25,889- £31,840 p.a. (pro-rata)

Applications are invited for the post of part-time Project Manager (50%) to co-ordinate communications within Malaria Genomic Epidemiology Network as well as its external image, at a strategic and a functional level. This international network which is based at the Kwiatkowski laboratory in Oxford University consists of scientists in more than 17 countries who are working to better understand malaria, one of humankind's most persistent and deadly foes.

A detailed job description quoting reference H5-07-030-DK is available from the Personnel Administrator (tel: 01865 287508, email: personnel@well.ox.ac.uk).

More information

... NEWS ...

RBM News E- Update May 2007

With news on the G8 Summit Declaration, Tanzania Country Report: innovative communication campaign to raise awareness and promote understanding of the new malaria case management policy, recent events and quick updates

▪ 24 June 2007, mediLexicon

Jeffrey Sachs Calls For Mass Distribution Of Insecticidal Bednets To Fight Malaria

Jeffrey Sachs, director of the Earth Institute and one of the world's leading economists, has, along with other global experts, called for mass distribution of insecticidal bednets to fight malaria. The call is made in a Comment published early Online and in an upcoming edition of the Lancet.

▪ 22 June 2007, MIM News and Opportunities

Africa Malaria Day Becomes "World Malaria Day"

Awareness of malaria as a global problem remains low. Malaria transmission is still poorly understood by those at risk and they therefore often do not know how to protect themselves and their families against infection. In order to ensure that advocacy is sustained globally, it is proposed that Africa Malaria Day, which is observed on 25 April, be declared World Malaria Day.

▪ 22 June 2007, SciDev.Net

Knowledge for natural resources: a fair exchange?

China and Africa are forging links using Africa's resources, but is it an even deal? Talent Ngandwe investigates the situation in Zambia. China agreed at the FOCAC summit in 2006 to build 30 hospitals and pledged US\$37.5 million to help Africa combat malaria by providing the drug artemisinin and building 30 malaria prevention and treatment centers, according to the Chinese news agency Xinhua.

- 21 June 2007, News-Medical.Net

More effective treatment for malaria control during pregnancy in Africa

A review of previous studies indicates that two doses of a malaria preventive therapy during pregnancy provides substantial benefit to HIV-negative women in Africa, with more frequent dosing apparently necessary for HIV-positive women, according to an article in the June 20 issue of JAMA.

- 21 June 2007, Medical News Today

Immtech Completes Dosing Protocol Of Malaria Prevention Trial

Immtech Pharmaceuticals, Inc. (Amex: IMM) announced today that it has completed the dosing and exposure protocol for a Phase II malaria prevention trial in the United States of its oral drug candidate pafuramidine (DB289). The study is designed to determine whether pafuramidine would be effective in preventing malaria infections for travelers.

- 21 June 2007, Nigerian Tribune

Lemon grass, antidote to malaria, typhoid, pains

Before the advent of orthodox medicine in the treatment of malaria, typhoid fever and other ailments, the traditional African society had devised various means of combating such ailments.

- 21 June 2007, Agencia de Informacao de Mocambique

Mozambique: Public Must Be Involved in Anti-Mosquito Spraying

The public must be involved in anti-mosquito spraying campaign, if Mozambique's fight against malaria is to be successful, according to Elsa Nhamntumbo, of the Maputo Provincial Health Directorate.

- 21 June 2007, New Vision

Uganda: Malaria Still Killing Most IDPs

MALARIA remains the leading killer disease and health threat among the internally displaced persons (IDPs) in northern Uganda.

- 20 June 2007, AMANET

AMANET Launches Clinical Trial of Candidate Malaria Vaccine AMA1 in Mali

The African Malaria Network Trust (AMANET) has launched a Phase Ib candidate malaria vaccine trial in Mali, marking an important milestone in its quest to contribute to the development of effective tools against malaria.

- 20 June 2007, SciDev.Net

Pregnant HIV patients need extra antimalarials

Research suggests that a commonly used antimalarial drug still prevents the adverse effects of malaria in pregnant women, but that women with HIV need more frequent doses.

▪ 20 June 2007, ScienceDaily

More Effective Treatment For Malaria Control During Pregnancy In Africa Identified

A review of previous studies indicates that two doses of a malaria preventive therapy during pregnancy provides substantial benefit to HIV-negative women in Africa, with more frequent dosing apparently necessary for HIV-positive women, according to an article in the June 20 issue of JAMA.

▪ 20 June 2007, Reuters

Fever in travelers often a sign of serious problem

Fever in travelers returning home is a marker of potentially grave illness, according to researchers who report the findings from global surveillance of travel-related illnesses.

▪ 20 June 2007, the Monitor

Uganda: Anti-Mosquito Plan for the Queen's Visit

With only four months left for Uganda to host the Commonwealth Heads of Government Meeting, the Ministry of Health is planning to carry out an indoor residual spray in Makindye Division, to protect visitors from mosquito bites.

▪ 20 June 2007, GlobalHealthReporting.org

CARE Zambia Program Aims To Reduce Childhood Deaths From Malaria, Other Diseases

A program run by CARE Zambia aims to reduce deaths among children in the country from diseases such as malaria by operating mobile clinics and providing health advice through a network of trained volunteers, VOA News reports.

▪ 19 June 2007, Reuters

Ethiopia: Taking the malaria battle to rural areas

Asham Musa had to wait for hours before her two children could be vaccinated against measles at a local clinic in Sherkole town, Benishangul region, in western Ethiopia.

▪ 19 June 2007, New Vision

Uganda: Barclays Raises Sh55m for Malaria Fight

Barclays Bank in partnership with the Uganda National Association of Community and Occupational Health (UNACOH) has raised sh55m in a car washing exercise towards the prevention of malaria in Bujenje sub-county, Masindi district.

▪ 18 June 2007, Daily Monitor

Katakwi, Amuria lack Malaria drugs

Health units in Katakwi and Amuria districts have complained of lack of Coartem, the new recommended drug for malaria treatment.

▪ 18 June 2007, New Vision

Uganda: Kids Engage in Malaria Prevention Games

Over 250 children from Naguru in Kampala, participated in games about the prevention of malaria, reports Francis Emorut.

▪ 18 June 2007, GlobalHealthReporting.org

New York Times Examines U.S. Business' Efforts To Fight Malaria in Africa

New York Times columnist Joe Nocera on Saturday examined the U.S. business community's efforts to eradicate malaria in Africa. According to Nocera, two recent events suggest that the business community is "finally getting serious about eradicating" the disease.

▪ 18 June 2007, GlobalHealthReporting.org

Thailand Works With Mali Company To Produce Malaria Drugs

The Royal Thai Embassy in Dakar, Senegal, has been helping the Mali pharmaceutical company Usine Malienne de Produits Pharmaceutiques produce malaria drugs, the Thai News Service reports.

▪ 17 June 2007, New Vision

Uganda: Malaria Spraying Begins This Month

The Government will start indoor residual spraying of a mosquito insecticide, Icon, in Kampala district this month, ahead of the Commonwealth Heads of Government Meeting (CHOGM) slated for November.

▪ 17 June 2007, Daily Democrat

Dancing for mosquito nets

A two-day fundraising drive coordinated by a UC Davis doctoral student raised \$1,400 to purchase life-saving mosquito bednets for malaria-ravaged Africa.

K&S Consulting, an independent consultancy firm concerned with medical information provision and training activities, provides this free service.

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