Summary

Members of the Malaria Centre members are involved in Pharmacokinetics studies, phase II and III efficacy & safety trials, phase IV studies and large intervention trials involving Rapid Diagnostic Tests (RDTs), antimalarial drugs, and vaccines in Africa and Asia.

WHO now recommends test-based management of malaria across all age groups and transmission settings. The national malaria programs in sub-Saharan Africa are at various stages of implementing the revised guideline. However, there is a need for more evidence on the effectiveness and safety of this strategy. A study conducted by our staff in Tanzania showed that application of malaria RDTs to determine the use of anti-malarial drugs in young children did not result in any missed diagnoses of malaria. A cluster randomised controlled trial to evaluate the effect of restricting Artemisinin-based Combination Therapy (ACT) to RDT-positive malaria in under-five children is underway in Ghana.

Ensuring adherence to the treatment guidelines based on RDT result is a challenge. A trial of a complex intervention consisting of 3 sessions of interactive small-group training, feedback of prescribing results and motivational SMS messages is underway in Tanzania. Another cluster-randomized controlled trial in Uganda is evaluating the effectiveness and cost-effectiveness of training of registered drug shop owners using participatory approach in applying RDTs for diagnosis and rational drug use in case management of malaria. A trial in Afghanistan is assessing the effectiveness of different strategies to provide accurate diagnosis and treatment for malaria and non-malarial fevers, and another trial in Uganda is evaluating the effects of a package of interventions involving training of health workers and supplementing supply of antimalarials and diagnostics on health outcomes of <5 year old children.

Several studies of safety and efficacy of Intermittent Preventive Treatment for malaria in children (IPTc) have been completed or nearing completion. WHO now recommends IPTc, renamed as Seasonal Malaria Chemoprevention (SMC), in areas of highly seasonal malaria transmission. Sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) is the regimen recommended by WHO for SMC. However, the pharmacokinetics data of this combination of drugs in children are very limited. In Burkina Faso, a study to determine the pharmacokinetic profile of SP+AQ and a trial comparing the safety, tolerability and efficacy of dihydroartemisinin+piperaquine (DHA+PQ) with suphadoxine-pyremithamine+amodiaquine (SP+AQ) when used for SMC in children, were recently completed. A large study to confirm the safety and feasibility of SMC using SP+AQ for children 3 months to 10 years of age is underway in Senegal.

Although SMC has been shown to provide substantial reductions in malaria morbidity, there is limited evidence on the additional benefit of SMC when implemented along with prompt treatment of malaria in their communities. Members of the Malaria Centre are investigating the additional benefits of SMC in communities using home-management of malaria in Ghana and Senegal.

Although the risk of malaria is greatest in early childhood, significant numbers of school-aged children remain at risk from malaria. Previous research, in an area of intense perennial transmission, showed that Intermittent Preventive Treatment, given once each term, can reduce malaria-related anaemia and increase sustained attention in class. Members of the Malaria Centre are now investigating the impact of Intermittent Preventive Treatment in school children in highly seasonal transmission area in Senegal.

Pregnant women and their unborn children are vulnerable to malaria, increasing the risk of maternal anaemia, low birth weight, abortion and stillbirth. Intermittent Preventive Treatment in pregnancy (IPTp) and Insecticide Treated Nets (ITNs) have proven benefits. However there is little evidence on the impact and cost-effectiveness of these approaches in areas of low and unstable transmission areas. A randomised controlled trial undertaken in the highlands of Uganda showed that there is no difference

Man and child in the Gambia.

in the effects of IPTp using SP given in combination with ITNs, IPTp-SP alone or ITNs alone on maternal anaemia and low birth weight.

As the incidence of malaria is declining in some parts of Africa and the resistance to SP is increasing, there is a need to identify appropriate interventions to replace IPTp-SP for control of Malaria in Pregnancy (MiP). A trial of Intermittent Screening and Treatment (IST) of parasitaemia at scheduled antenatal clinic visits in the second and third trimester was undertaken in The Gambia, Mali, Burkina Faso and Ghana. A similar study of IST is underway in India. Results of these studies will inform the MiP control policies in Africa and India. Although ACT is recommended to treat MiP in the second and third trimester there is a need to generate further evidence on the safety of these drugs during pregnancy. A study to assess the efficacy and safety of artesunate +mefloquine or artesunate+SP for treatment of MiP is underway in India.

In some other parts of Africa, there has recently been a sharp decline in the incidence of malaria, coinciding with increased control efforts. This raises the prospect that malaria could be eliminated, but despite scaling up of control methods transmission persists in foci which provide a continuing source of infection. Members of the Malaria Centre are investigating different tools and strategies to interrupt transmission. A study to evaluate the efficacy and safety of lower doses of PQ to clear gametocytes is underway in Uganda. Another study in Senegal is evaluating the effectiveness of targeted application of Indoor Residual Spraying and chemotherapy, delivered by district health staff to villages reporting clinical cases, on transmission reduction. Members of Malaria Centre are involved in several vaccine trials. Phase 1 trials have shown that the MSP3-LSP vaccine is safe and immunogenic in adults and children and provided preliminary evidence of efficacy. A phase2b efficacy trial of this vaccine is underway in two sites in Mali. We are involved in another phase 2b trial to determine whether the GMZ2 vaccine, a recombinant fusion protein of *Plasmodium falciparum* Glutamate Rich Protein and Merozoite Surface Protein 3, adjuvanted with aluminum hydroxide, can protect against clinical attacks of malaria in children aged 1-5yrs that is conducted in Uganda, Burkina Faso, Ghana and Gabon. Finally, as malaria control improves, it is important to understand the cause of non-malaria febrile illness. This has been evaluated in an inpatient setting in Northern Tanzania and studies are ongoing in several additional outpatient settings in Africa and south-east Asia.

Effects of restricting the use of artesunate plus amodiaquine combination therapy to malaria cases confirmed by a dipstick test: a cluster randomised control trial.

***LSHTM Investigators**: Daniel Chandramohan, Jayne Webster & Seth Owusu-Agyei.*

***External Investigators/Collaborators:** Frank Baiden (Kintampo Health Research Centre, Ghana).*

Meeting of the study team and staff of study health centres held in Kintampo in April 2010.

***Funding Body:** The Bill & Melinda Gates Foundation through the ACT Consortium.*

The WHO now recommends test-based management of malaria across all age groups and transmission settings. The national malaria programs in sub-Saharan Africa are at various stages of implementing the revised guideline. However, there are concerns that restricting Artemisinin-based Combination Therapy (ACT) to Rapid Diagnostic Test (RDT)-positive malaria could lead to increased frequency of malaria and as a result, anaemia in children who are denied ACT on account of negative RDT results. On the other hand, uncurtailed use of ACT has the potential to accelerate the development of resistance to ACT. The Kintampo-ACT study is a cluster randomised controlled trial to evaluate the effect of restricting ACT to RDT-positive malaria in under-five children in rural Ghana. In June 2010, a cohort of 3061 under-five children from 32 clusters was randomly allocated to RDT-based malaria management or to presumptive malaria management groups. The follow up of the cohort and collection of data on study endpoints (smear-confirmed malaria, anaemia, overall sick visits and cost-effectiveness) will be completed in June 2012. Study results will be disseminated in the last quarter of 2012.

Childhood Febrile Illness Treatment Study (C-FIT).

***LSHTM Investigators**: Hugh Reyburn & Chris Whitty.*

***External Investigators/Collaborators:** George Mtovu (National Institute for Medical Research, Tanzania).*

***Funding Body:** The Bill & Melinda Gates Foundation through the ACT Consortium.*

In late 2010, WHO guidelines abandoned the policy of presumptive treatment of malaria in favour of treatment guided by a blood slide or malaria Rapid Diagnostic Test (RDT). However, there is limited evidence of the safety of this policy in routine outpatient settings in Africa.

In a malaria endemic area of Tanzania, 965 children with a non-severe febrile illness were enrolled, and treatment for malaria was determined by the results of a clinical examination and RDT result. Blood culture and serum lactate were also collected. RDT-negative children were followed up over 14 days.

Overall, 158 (16.4%) were RDT-positive and treated with artemether-lumefantrine and 807 (83.4%) were RDT-negative and treated with non-anti-malarial medicines. Compared with RDT-positives, RDT-negative children were on average younger with a lower axillary temperature and more likely to have a history of cough or difficulty in breathing. Six (0.6%) children became RDT-positive after enrolment, all of whom were PCR-negative for *Plasmodium falciparum* DNA at enrolment. In addition, 12 (1.2%) children were admitted to hospital, one with possible malaria, none of whom died. A bacterial pathogen was identified in 9/965 (0.9%) children, eight of whom were RDT-negative and one was RDT-positive, but slide-negative. Excluding three children with *Salmonella typhi,* all of the children with bacteraemia were ≤12 months of age. Compared to double-read research slide results RDTs had a sensitivity of 97.8% (95%CI 96.9-98.7) and specificity of 96.3% (95%CI 96.3-98.4).

Use of RDTs to direct the use of anti-malarial drugs in young children did not result in any missed diagnoses of malaria although new infections soon after a consultation with a negative RDT result may undermine confidence in results. Invasive bacterial disease is uncommon in children with non-severe illness and most cases occurred in infants with a current fever.

Evaluation of malaria diagnostic strategies in South Central Asian health facilities where vivax is co-endemic with falciparum.

***LSHTM Investigators**: Toby Leslie, Amy Mikhail, Chris Whitty & Mark Rowland.*

***External Investigators/Collaborators:** HealthNet TPO; MERLIN & Health Protection and Research Organisation.*

***Funding Body:** The Bill & Melinda Gates Foundation through the ACT Consortium.*

Malaria in many areas outside Africa is a consequence of two or more species; in Afghanistan and surrounding countries, the less-often fatal or serious *vivax* malaria predominates although *falciparum* is also seen. This situation complicates diagnosis and treatment of malaria and requires that malaria cases are accurately diagnosed and treatment is targeted at the specific species. In health facilities in low-income countries this is a challenge. Our study aims to assess the effectiveness of current strategies to provide accurate diagnosis and treatment for malaria and non-malarial fevers.

Although Rapid Diagnostic Tests (RDTs) appear more accurate than conventional light microscopy, the study shows that around 50% of patients who do not have malaria, based on a laboratory diagnostic result, received an antimalarial regardless of the negative parasite diagnosis.

The situation decreases the cost-effectiveness of RDTs and results in cases of potentially severe non-malarial febrile illness being mistreated as malaria. Improved guidelines which emphasise the importance of treatment according to laboratory diagnostic results will be part of the solution, but ensuring changes in treatment practice that are sustainable will also require additional point of care diagnostics for alternative, non-malarial causes of febrile illness.

Rapid Diagnostic Test being taken in Tanzania

A cluster-randomised trial of health worker and community interventions to improve adherence to national guidelines for the use of ACT in Tanzania: The TACT trial: (Targeting ACT).

***LSHTM Investigators**: Hugh Reyburn, Clare Chandler, Bonnie Cundill, Shunmay Yeung & Chris Whitty.*

***External Investigators/Collaborators:** Florida Muro (Kilimanjaro Christian Medical Centre, Tanzania); George Mtove (National Institute of Medical Research, Tanzania).*

***Funding Body:** The Bill & Melinda Gates Foundation through the ACT Consortium.*

In 2010, WHO abandoned the policy of 'presumptive treatment for malaria' whereby young children with a fever and no obvious cause were treated with an antimalarial drug even if a diagnostic test for malaria was negative.

The TACT trial aims to address one of the most challenging consequences of this policy shift, i.e. how to maximise the use of malaria Rapid Diagnostic Tests (RDTs) in primary care settings and how to ensure that all and only those with a positive test result are treated for malaria.

Following extensive formative research, a 3-arm cluster randomised trial was initiated in February 2011 and will close in March 2012. Health workers in all arms have received the Ministry of Health's standard 3-day training on use of RDTs. In addition, health workers in two arms have received a complex intervention consisting of 3 sessions of interactive small-group training, feedback of prescribing results and motivational SMS messages. In one of these arms, patient-directed messages have also been provided through leaflets and posters. Results from the 36 health facilities in the trial will be reported later in 2012 and we anticipate an important contribution towards maximising the benefit of RDTs throughout Africa.

ACT PRIME Study: evaluating the impact of enhanced health facility-based care for malaria and febrile illnesses in children in Tororo, Uganda.

***LSHTM Investigators**: Sarah Staedke & Clare Chandler.*

***External Investigators/Collaborators:** Moses Kamya & Fred Wabwire-Mangen (Makerere University, Uganda); Grant Dorsey & Philip Rosenthal (University of California, USA); Ambrose Talisuna (WWARN East Africa Centre); Heidi Hopkins (FIND Diagnostics, Uganda).*

***Funding Body:** The Bill & Melinda Gates Foundation through the ACT Consortium.*

ACT PRIME is designed to evaluate whether enhancing public health facilities by training health workers and supplementing the supply of malaria drugs and diagnostics improves the health of children, as compared to 'standard care' currently available in Tororo, Uganda.

Twenty lower-level health centres were randomly assigned to the Health Facility Intervention (HFI) or to standard care using a cluster-randomised design. The HFI has three components: (1) training in-charges in health centre management, (2) training health workers in fever case management and patient-centred services, and (3) ensuring adequate supplies of artemether-lumefantrine and Rapid Diagnostic Tests (RDTs).

To evaluate the impact of the intervention, a cross-sectional survey was conducted at baseline in randomly selected children from each cluster, and will be repeated annually. A cohort of children was recruited from randomly selected households, and will be followed for 2 years. Health facilities are also assessed using patient exit interviews, health worker knowledge questionnaires, and monthly surveillance. The primary outcome of the study is prevalence of anaemia in children under five. Formative research was completed in September 2010, and the main trial began in December 2010. The intervention was rolled out in May 2011, and the study will continue until May 2013.

Cohort study team.

The role and cost-effectiveness of Rapid Diagnostic Tests (RDTs) in home-based management of malaria: a comparative study in two areas of high and low transmission in rural Uganda.

***LSHTM Investigators**: Sian Clarke, Kristian Hansen, Sham Lal Clare Chandler, Bonnie Cundill & Caroline Lynch.*

***External Investigators/Collaborators:** Richard Ndyomugyenyi (Ministry of Health, Uganda); Pascal Magnussen (DBL Centre for Health Research and Development, Denmark).*

***Funding Body:** The Bill & Melinda Gates Foundation through the ACT Consortium.*

A cluster-randomized controlled trial of use of Rapid Diagnostic Tests (RDTs) for malaria by Community Medicine Distributors (CMDs). The study aims to examine the role and cost-effectiveness of RDTs in home-based management of fever in two contrasting areas of high and low malaria transmission in rural Uganda.

CMDs in the intervention arm received training in use of RDTs, and to only give antimalarial treatment after a positive test result. The training which adopted a participatory approach to build on prior knowledge and experience, also included modules on signs and symptoms of malaria, correct use of ACT, communication, and introduced the use of rectal artesunate pre-referral treatment and referral.

The trial examines the impact and cost-effectiveness of RDT use on the proportion of patients receiving appropriate antimalarial treatment (consistent with their malaria infection status as determined against microscopy of a research slide), compared with CMDs following current practice (presumptive clinical diagnosis and treatment of fever), in each of the two contrasting areas of high and low malaria transmission.

The study also investigates the positive predictive value of RDTs used by CMDs, and perceptions and acceptability of RDTs among malaria patients, CMDs and health staff, in each transmission setting. The impact of improved malaria diagnosis on ACT adherence among patients will also be examined.

Introducing Rapid Diagnostic Tests (RDTs) into the private sector. A cluster-randomised trial among registered drug shops in Mukono district, Uganda.

***LSHTM Investigators**: Sian Clarke, Kristian Hansen, Sham Lal, Clare Chandler, Bonnie Cundill, Caroline Lynch & Harparkash Kaur.*

***External Investigators/Collaborators:** Anthony Mbonye (Ministry of Health, Uganda); Pascal Magnussen (DBL Centre for Health Research and Development, Denmark).*

***Funding Body:** The Bill & Melinda Gates Foundation through the ACT Consortium.*

A cluster-randomized controlled trial of Rapid Diagnostic Tests (RDTs) for malaria in registered drug shops. The study aims to examine the feasibility of introducing RDTs into registered drug shops in Uganda to encourage rational drug use in case management of malaria.

Drug shop vendors in the intervention arm received training in use of RDTs for malaria, and to only recommend antimalarial treatment after a positive test result. The training which adopted a participatory approach to build on prior knowledge and experience, also included modules on signs and symptoms of malaria, correct use of Artemisinin-based Combination Therapy (ACT), patient communication, and introduced the use of rectal artesunate pre-referral treatment and standardised referral forms.

The trial examines the impact and cost-effectiveness of RDT use on the proportion of patients receiving appropriate antimalarial treatment (consistent with their malaria infection status as determined against microscopy of a research slide), compared with prescription practices in control drug shops following current practice (presumptive clinical diagnosis and treatment of fever). The study also investigates perceptions and acceptability of RDTs among malaria patients and private providers, the impact of diagnostic testing on referral and the impact of improved malaria diagnosis on ACT adherence among patients. The socio-economic characteristics of patients seeking treatment for fever from registered drug shops will be described.

Mother and baby in Uganda.

Pharmacokinetics of sulfadoxine-pyrimethamine plus amodiaquine when used for Seasonal Malaria Chemoprevention (SMC) in children.

***LSHTM Investigators**: Issaka Zongo, Harparkash Kaur, Neal Alexander, Badara Cisse & Paul Milligan.*

***External Investigators/Collaborators:** Jean Louis NDiaye & Oumar Gaye (Université Cheikh Anta Diop, Senegal).*

Sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) is the most effective regimen for Seasonal Malaria Chemoprevention (SMC), but there is little information about the pharmacokinetics of these drugs in children. This information is important in order to check the bioavailability of the two drugs when used for SMC and to check the adequacy of the currently recommended dosage and to determine the duration of therapeutic levels. To determine the pharmacokinetic profile of sulfadoxine, pyrimethamine, and desethyl amodiaquine, 150 children 3-59 months of age were given one course of treatment with SP+AQs and were followed-up for one month. Finger prick blood samples were taken on four occasions for measurement of drug concentrations by HPLC using photo-diode array detection and samples of the drugs drugs were tested to make sure of their bioavailability.

Dihydroartemisinin-piperaquine for Seasonal Malaria Chemoprevention (SMC) in African children: efficacy, safety, tolerability and pharmacokinetics.

***LSHTM Investigators**: Issaka Zongo, Brian Greenwood, Daniel Chandramohan, Colin Sutherland & Paul Mlligan.*

***External Investigators/Collaborators:** Francois Nosten (Nuffield Department of Clinical Medicine, UK); Jean Bosco Ouedrago (Institut de Recherche en Sciences de la Santé, Burkino Faso), Philip Rosenthal (University of California, USA).*

***Funding Body:** Holley Cotec.*

The aim of this study is to compare the safety, tolerability and efficacy of DHA+PQ with SP+AQ when used for Seasonal Malaria Chemoprevention (SMC). The trial took place in Lena district near Bobo-Dioulasso. 1500 children were randomized to receive SMC with one or other regimen and, outside the trial, a cohort of untreated children was followed to determine malaria incidence without SMC. Four finger prick blood samples were taken each month from a subset of children for measurement of piperaquine concentrations and venous samples were taken from a second subset each month to measure the effect of SMC doses on haematological and biochemical parameters.

Ejisu-Juaben District, Ashanti, Ghana.

The clinical impact of combining Intermittent Preventive Treatment (IPT) with home management of malaria in children aged below 5 years: a cluster randomised trial.

***LSHTM Investigators**: Harry Tagbor, Matt Cairns & Daniel Chandramohan.*

***External Investigators/Collaborators:** Emmanuel Nakwa, Edmund Browne (Kwame Nkrumah University of Science and Technology, Ghana); Badu Sarkodie (District Health Administration, Ghana); Helen Counihan & Sylvia Meek (Malaria Consortium, UK).*

***Funding Body:** Communicable Diseases Research Consortium.*

Seasonal Intermittent Preventive Treatment in children (IPTc) has been shown to provide substantial reductions in malaria morbidity but this has not been investigated where children also have access to prompt treatment of malaria in their communities. We investigated the additional impact of seasonal IPTc in Ghanaian communities using home-management of malaria for presumptive treatment of fevers in a cluster-randomised trial. Bimonthly courses of seasonal IPTc with artesunate-amodiaquine reduced the incidence of fevers, particularly among children who received all three IPTc courses. Using IPTc to reducing the number of fevers that require management in the community could reduce selection pressure for resistance on the first-line treatment drug. However, high coverage will be necessary to maximise the impact of IPTc. Community-based delivery may be one approach to achieving this goal.

Cluster randomized trial of SMC with sulfadoxine-pyrimethamine over 5 months combined with community case management, versus community case management alone, in children under 10 years of age in Southern Senegal.

***LSHTM Investigators**: Paul Milligan, Colin Sutherland & Rachel Hallett.*
***External Investigators/Collaborators:** Jean Louis NDiaye, Youssoupha NDiaye & Oumar Gaye (Université Cheikh Anta Diop, Senegal).*

***Funding Body:** The European and Developing Countries Partnership.*

Although the overall incidence of malaria has recently declined in Senegal as in some other countries, this hides the fact that the burden of malaria remains very high in some parts of the country, such as Saraya district, where 70% of the community lives more than 15km from the nearest health post.

Community case management for malaria is being introduced by volunteers (Distributeurs de soins à domicile or DSDOM) who are trained to recognize the signs and symptoms of uncomplicated and severe malaria, to use Rapid Diagnostic Tests (RDTs) and to treat malaria with Artemisinin-based Combination Therapy. The DSDOM could also deliver Seasonal Malaria Chemoprevention (SMC) to children, SMC is known to be highly effective in preventing malaria illness but the relative advantage of adding SMC in villages which have access to prompt effective treatment from the village health worker has not been evaluated. In this trial, 24 villages were randomized to deliver SMC with community case management, or community case management alone. In SMC villages, the DSDOM gave all children under 10 years old preventive treatment with sulfadoxine-pyrimethmine plus amodiaquine each month from July to November 2011.

Previously SMC has been delivered over three months so this study will also provide new evidence about the feasibility, tolerability and acceptability of delivery over a longer period. The DSDOM were trained to make blood films which were collected by the study team so that malaria cases could be confirmed by microscopy. The impact of SMC on drug resistance is being evaluated by analysis of used RDTs and from blood samples taken from a sample of children at the end of the transmission season.

Safety of Seasonal Malaria Chemoprevention (SMC) with sulfadoxine-pyrimethamine+amodiaquine when delivered on a large sacale by district health staff in Senegal.

***LSHTM Investigators**: Badara Cisse, Colin Sutherland, Rachel Hallett, Matt Cairns, Catherine Pitt, Brian Greenwood & Paul Milligan.*
***External Investigators/Collaborators:** El Hadj Ba, Oumar Gaye, Jean Louis NDiaye, Babacar Faye, Cheikh Sokhna, Jean Francois Trape, Yankouba Dial, Oumar Faye, Ousmane Faye; Lesong Conteh.*

***Funding Body:** The Bill & Melinda Gates Foundation.*

The WHO now recommends Seasonal Malaria Chemoprevention (SMC) for prevention of malaria in children in areas of highly seasonal malaria transmission.

This study provided key evidence establishing the safety of the intervention and feasibility of delivery. In three rural districts SMC with sulfadoxine-pyrimethamine (SP) plus amodiaquine (AQ) was delivered to children aged 3 months to 10 years by community health workers supervised by heath post nurses. A surveillance system was established to record all deaths, malaria cases diagnosed at health facilities and to detect adverse drug reactions. Community health workers visited each child one month after the first and second round of treatment to check that there had been no severe reactions to the previous treatment and to give the next round of treatment and surveillance for adverse events was maintained at 54 health posts and 6 hospitals serving the population.

Training workshops were held to explain how to recognize, manage and document adverse drug reactions, leaflets illustrating the most common features of adverse reactions to SP or AQ were distributed and a reminder system was implemented using text messages sent to nurses just before the start of SMC delivery and sending them a phone credit as an incentive.

Coverage was independently assessed after each transmission season using cluster sample surveys. Nearly 800,000 documented courses of SMC were administered, high coverage was achieved and though a number of cases of liver failure and Steven Johnson syndrome were detected in study hospitals none had received SMC medication and no serious adverse events attributable to the intervention were detected despite a high level of surveillance.

Intermittent parasite clearance in schools: a randomised double-blind placebo-controlled trial of the impact of IPC on malaria, anaemia and cognition amongst schoolchildren in Kedougou, Senegal.

***LSHTM Investigators**: Sian Clarke, Daniel Chandramohan, Badara Cisse, Paul Milligan & Simon Brooker.*

***External Investigators/Collaborators:** Jean-Francois Trape, Cheikh Sokhna & Alioune Badara Ly (Institut de Recherché pour le Developpement, Senegal); Oumar Gaye & Jean-Louis Ndiaye (Université Cheikh Anta Diop, Senegal); Malick Sembene, Aliou Dia, Khady Diallo & AlHousseynou Sy (Ministry of Education, Senegal); Fatou Ba Fall (National Malaria Control Programme, Senegal); Matthew Jukes (Harvard Graduate School of Education, USA).*

***Funding Body:** Wellcome Trust.*

Although the risk of malaria is greatest in early childhood, significant numbers of school-aged children remain at risk from malaria. Previous research, in an area of intense perennial transmission, showed that Intermittent Preventive Treatment, given once each term, can reduce malaria-related anaemia and increase sustained attention in class – suggesting that malaria control in schoolchildren could yield educational, as well as health, benefits.

This study investigates the impact of malaria control in schools in a different epidemiological setting - highly seasonal transmission - in Senegal, West Africa. Here, despite a new policy of universal coverage of ITNs with mass distribution of long-lasting nets to all age groups and almost 100% reported utilisation of ITNs, over a third of schoolchildren were found, at the end of the transmission season, to harbour asymptomatic malaria infections.

The study thus examines whether a single round of curative treatment, using sulphadoxine-pyrimethamine and amodiaquine, to clear asymptomatic parasitaemia at the end of the rains would confer any additional benefit in schoolchildren sleeping under insecticide-treated nets. Study design: An individually-randomized placebo-controlled trial of intermittent parasite clearance given in primary schools, with 845 children recruited into the study in Oct 2011. Trial outcomes include malaria, anaemia, cognitive function and school performance.

School staff are also providing scientific advice on intervention design and analysis for a similar cluster-randomised trial being conducted in Sikasso, Mali by Save the Children.

A randomised trial to compare the safety, tolerability and efficacy of artesunate plus mefloquine, amodiaquine plus sulfadoxine-pyrimethamine and proguanil in prevention of malaria and related complications in patients with sickle cell anaemia.

***LSHTM Investigators**: Paul Milligan & Brian Greenwood.*

***External Investigators/Collaborators:** Rasaq Olaosebikan, Ernest Kolade, Kalifa Bojang & Olugbenga Mokuolu.*

***Funding Body:** Wellcome Trust.*

Effective prophylaxis should be provided for people with sickle cell disease in malaria endemic areas. In Nigeria daily proguanil or weekly pyrimethamine are the most commonly prescribed regimens, but the effectiveness of this policy is limited by poor compliance and drug resistance. Sickle-cell patients who are stable are recommended to visit the clinic once every two months. A long-acting drug regimen that could provide prophylaxis for two months could be administered under supervision at each clinic visit, this might be more effective than the current practice that relies on patients remembering to take their prophylaxis regularly.

The aim of this trial is to compare the tolerability and acceptability of supervised bimonthly treatment with either sulfadoxine-pyrimethamine plus amodiaquine or mefloquine plus artesunate, with unsupervised daily proguanil. Two hundred and seventy patients with sickle cell disease attending the paediatric sickle cell disease clinic in Ilorin hospital were randomized to one of the three prophylactic regimens and were asked to return to clinic every two months and whenever they are sick. Participants will be followed for one year. If the bimonthly regimens are well tolerated and the preliminary data from this study are promising, a larger multicentre trial will be required to determine efficacy.

A Phase II/III randomised clinical trial of the efficacy & safety of artesunate + suplhadoxine-pyrimethamine and artesunate + mefloquine to treat uncomplicated falciparum malaria in pregnancy .

***LSHTM Investigators**: Daniel Chandramohan, Irene Kuepfer, Jane Bruce, Jayne Webster & Brian Greenwood.*

***External Investigators/Collaborators:** Neena Valecha, Anupkumar Anvikar & Bhartendu Shahi (National Malaria Research Institute, India); Feiko ter Kuile (Liverpool School of Tropical Medicine, UK).*

***Funding Body:** The Bill & Melinda Gates Foundation through the MiP Consortium.*

Investigators meeting, Delhi February 2012.

The current first line treatment for Malaria in Pegnancy (MiP) during second and third trimester in India is artesunate + sulphadoxine-pyremethamine (AS+SP). The emergence of malaria parasites resistant to SP from some parts of India is a concern. The primary objective of this study is to assess the efficacy and safety of artesunate +mefloquine (AS+MQ) as an alternative to AS+SP for treatment of MiP. This is an open label randomised superiority trial the required sample size is 500 women. The primary endpoint is adequate clinical and parasitological response by day 63. The secondary endpoints include adverse events (clinical, haematological & biochemical), re-infection rates by day 63, birth outcomes, and pharmacokinetic profile of AS+MQ. By January 2012, 4341 pregnant women had been screened for malaria, 158 women were found to have either symptomatic or asymptomatic malaria and 136 women have been enrolled in the study. The study is expected to be completed in 2013.

Comparison of three interventions to prevent malaria in pregnancy in a highland area of low transmission in Southwest Uganda.

***LSHTM Investigators**: Sian Clarke, Kristian Hansen & Daniel Chandramohan.*

***External Investigators/Collaborators:** Richard Ndyomugyenyi (Ministry of Health, Uganda); Pascal Magnussen (DBL Centre for Health Research and Development, Denmark).*

***Funding Body:** The Bill & Melinda Gate Foundation through the Gates Malaria Partnership.*

Pregnant women and their unborn children are vulnerable to malaria, increasing the risk of maternal anaemia, low birthweight, abortion and stillbirth. Intermittent Preventive Treatment in pregnancy (IPTp) and Insecticide-Treated Nets (ITNs) have proven benefits, yet the impact and cost-effectiveness of these approaches in areas of low and unstable transmission remains unknown.

An individually-randomised placebo-controlled trial was undertaken in the highlands of Uganda to compare the impact and cost-effectiveness of IPTp using sulfadoxine-pyrimethamine given in combination with ITNs, IPTp-SP alone and ITNs alone on maternal anaemia and low birthweight. Data was recorded on stillbirth, abortion, neonatal and maternal mortality. No differences were observed between the three alternative interventions in any of the maternal and infant health outcomes examined. The cost-effectiveness and sensitivity analyses performed did not provide convincing evidence for replacing IPTp-SP (current policy) by ITNs alone or the combined intervention, on economic grounds.

Other factors may be of greater relevance for policy setting in areas of low transmission, including risks of each approach and extended benefits beyond the period of pregnancy. The relative cost-effectiveness of antenatal distribution of ITNs might improve if the cost savings accruing from continued use of a long-lasting insecticidal net after pregnancy and other positive externalities are also taken into account.

Intermittent Preventive Treatment (IPT) with sulfadoxine-pyrimethamine versus intermittent screening and treatment of malaria in pregnancy.

***LSHTM Investigators**: Harry Tagbor, Paul Milligan, Daniel Chandramohan & Brian Greenwood.*

***External Investigators/Collaborators:** Sheick Oumar Coulibaly (Université de Ouagadougou, Burkino Faso); John Williams & Abraham Hodgson (Ghana Health Research Centre, Ghana); Kalifa Bojang (Medical Research Council, UK); Kassoum Kayentao (Medical Research and Training Centre, Mali); Feiko Ter Kuile (Liverpool School of Tropical Medicine, UK); Pascal Magnussen (DBL Centre for Health Research and Development, Denmark).*

***Funding Body:** The Bill & Melinda Gates Foundation through the MiP Consortium & European Union.*

The incidence of malaria, including the incidence in pregnant women is declining in many African countries. Thus, there is a need to re-examine the efficacy and cost effectiveness of giving Intermittent Preventive Treatment in pregnancy (IPTp) on several occasions during pregnancy.

A randomised, multi-centre controlled trial in 5000 pregnant women who sleep under an insecticide treated bed net to compare the standard SP - IPTp regimen (3 doses of SP in second and third trimester) and intermittent screening using a Rapid Diagnostic Test and treatment of parasitaemia at scheduled antenatal clinic visits in the second and third trimester undertaken in four west African countries. The primary end points of the trial are birth weight; anaemia at 36 – 38 weeks of gestation and at the time of delivery or shortly afterwards and placenta malaria. Mothers and infants are seen again six weeks after delivery. The study was powered to show that intermittent screening and treatment of parasitaemia is not inferior to standard SP - IPTp regimen. The costs and cost effectiveness of each intervention will be evaluated.

Recruitment of study participants is over now. Progress is currently being monitored closely to ensure that follow up is completed successfully. We anticipate study completion and final reporting in the fourth quarter of 2013.

Effective and save interventions for prevention of malaria in pregnancy in India: an assessment of burden of malaria in pregnancy, implementability of a screening strategy and barriers to scaling up interventions.

***LSHTM Investigators**: Daniel Chandramohan, Jayne Webster, Irene Kuepfer, Jane Bruce, Chris Drakeley & Brian Greenwood.*

***Funding Body:** The Bill & Melinda Gates Foundation through the MiP Consortium.*

The current strategy for control of Malaria in Pregnancy (MiP) in India is to test for malaria during antenatal care (ANC) visits only in a woman has any sign or symptom suggestive for malaria. This strategy is probably inadequate to reduce the burden of MiP because a substantial proportion of MiP cases remain asymptomatic. The aim of this study is to evaluate Intermittent Screening and Treatment (IST) as a new control strategy delivered through routine ANC. In the phase one of this study starting in April 2012, a total of 8000 pregnant women will be enrolled into a cluster randomized controlled trial with two arms. Women in the IST arm will be screened for malaria using a Rapid Diagnostic Test (RDT) at each routine ANC visit. If positive, they will be treated according to the national policy (AS+SP). The women in the control will be tested for malaria only if they have any sign or symptom of malaria. The primary outcome is placental malaria. In the second phase of the study starting in September 2012, RDT based IST will be implemented at pilot scale in a sub-district. A series of studies (household & health facility surveys, structured observations, focus group discussions) will be conducted to assess the implementability of IST, including costs for provider and users.

Child from the primaquine study, Uganda.

Evaluation of the efficacy and safety of primaquine for clearance of gametocytes in uncomplicated falciparum malaria in Uganda.

***LSHTM Investigators**: Chi Eziefula, Chris Drakeley, Shunmay Yeung & Sarah Staedke.*

***External Investigators/Collaborators:** Infectious Diseases Research Collaboration, Uganda; Mahidol Oxford Research Unit, Thailand.*

***Funding Body:** Wellcome Trust.*

The study is a randomized placebo-controlled trial of the anti-malarial drug primaquine. For *Plasmodium falciparum* primaquine has specific gametocytocidal properties, meaning it destroys the form of the parasite in human blood that is infectious to mosquitoes. It is recommended for reduction of malaria transmission by the WHO. However, treatment with primaquine is associated with haemolysis in individuals with G6PD deficiency. This effect is dose-related. This study aims to evaluate whether lower doses of primaquine have equally potent gametocytocidal effects but result in reduced levels of haemolysis. This would potentially allow more widespread use of the drug as part of malaria control and elimination strategies.

The study is conducted at Walukuba Health Centre, Jinja, Uganda in children with uncomplicated (mild) malaria. Children with G6PD deficiency are excluded. Participants receive the local standard malaria treatment artemether-lumefantrine on days 0-2 and are randomized to one of four treatment arms (placebo and three different doses of primaquine) on day 2. They are followed up for 28 days.

The general objective is to evaluate the efficacy and safety of different doses of primaquine administered with AL for the purpose of reducing *Plasmodium falciparum* gametocytes in the infected human host to prevent transmission of *falciparum* malaria to the *anopheles* mosquito vector. Efficacy endpoints are assessed by measuring gametocyte prevalence and density on days 3, 7 and 14 after treatment. Safety is evaluated by measuring haemoglobin, prevalence of severe anaemia and active detection of serious adverse events on days 3, 7, 10, 14, 21 and 28 and passively throughout the trial.

Street scene in Senegal.

Randomized trial of spatially targeted malaria control to virtually eliminate malaria in areas of low and patchy transmission in Senegal.

***LSHTM Investigators**: Badara Cisse, Catherine Pitt, Mark Rowland, Immo Kleinschmidt, Matt Cairns, Colin Sutherland, Chris Drakeley & Paul Milligan.*

***External Investigators/Collaborators:** Oumar Gaye, Ousmane Faye, El Hadj Ba, Babacar Faye, Yemou Dieng, Fatou Ba Fall, Bakary Sambou, Cheikh Sokhna, Jean Francois Trape & Jean Louis NDiaye.*

***Funding Body:** Medical Research Council, UK, Wellcome Trust & UK Department for International Development,.*

In Senegal, as in some other parts of Africa, there has recently been a sharp decline in the incidence of malaria, coinciding with increased control efforts, primarily the large-scale distribution of free and highly subsidized insecticide-treated nets. This raises the prospect that malaria could be eliminated, but despite scaling up of control methods, transmission persists in foci which provide a continuing source of infection. Additional strategies are needed to eliminate these foci. Strategies to target communities with high incidence of malaria in order to achieve community-wide malaria control have a sound basis in population theory but have not been evaluated in randomized trials. Such strategies become increasingly relevant as malaria incidence declines and the geographical distribution becomes very patchy. The purpose of this trial is to evaluate the extent to which a targeted malaria control strategy combining vector control with Indoor Residual Spraying and chemotherapy, delivered by district health staff to villages reporting clinical cases, can virtually eliminate malaria, in an area in central Senegal where malaria incidence is very low and patchy. Secondly we will determine whether, as part of this strategy, chemotherapy should be delivered to all members of targeted communities or only those who have been tested and are known to be infected.

A phase 2b double blind, randomized, controlled trial to evaluate the safety, immunogenicity and protective efficacy of merozoite surface protein-3 (MSP3-LSP) vaccine candidate adjuvanted in aluminium hydroxide against Plasmodium falciparum clinical malaria in healthy children aged 12-36 months in Mali.

***LSHTM Investigators**: Paul Milligan*

***External Investigators/Collaborators:** Pierre Druihle, Mahamadou Sissoko, Issaka Sagara, Zarifah Reed & Ogobara Doumbo.*

MSP3-LSP is a synthetic peptide of 95 amino acids, derived from the highly conserved MSP3 C-terminal region of Merozoite Surface Protein 3. The vaccine is based on an immune mechanism associated with reduction in parasite density observed when antibodies were transferred from immune subjects to non-immunes infected with *Plasmodium falciparum.* Phase 1 trials have shown the vaccine is safe and immunogenic in adults and children and provided preliminary evidence of efficacy. This phase2b efficacy trial is being conducted in two sites in Mali, Doneguebougou, which has a short transmission season, and Bougoula, with a longer season with rainfall from May to October. In 2011 400 children aged 12-48 months were enrolled in each site and randomized to receive three doses one month apart of 30 µg of MSP3-LSP adjuvanted in Aluminium hydroxide, or rabies vaccine, followed by a fourth dose three months after the third dose. Follow-up will be for 2 years from dose 1. Dispensaries were set up so that all children are within 1km of a study nurse, and each household is visited weekly to ask if the child is well and to remind the family to take the child to the nearest clinic if they are unwell. The primary endpoint of the trial is the number of malaria episodes with an auxiliary temperature of at least 37.5oC and parasite density ≥5000/µL, assessed initially after three months and the trial is designed to have at least 90% power to detect a vaccine efficacy of 30% over this period.

A Phase II, randomized, controlled, double-blind, multi-centre study to evaluate the efficacy, safety, and immunogenicity of the GMZ2 candidate malaria vaccine in Ugandan, Ghanaian, Burkinabe and Gabonese children aged 12 – 60 Months.

***LSHTM Investigators**: Samuel Bosomprah & Paul Milligan.*

***External Investigators/Collaborators:** Sodiomon Sirima, Saadou Issifou, Kalifa Bojang, Fred Kironde, Tiono Alfred, Ateba Ngoa, Kaddu Mukasa, Frank Atuguba, Roma Chilengi, Brenda Okech, Dawit Ejigu, Michael Thiesen, Benjamin Mordmuller, Soren Jepsen, Ismaela Abubakar.*

***Funding Body:** The European and Developing Countries Partnership.*

The aim of this phase 2b trial is to determine whether the GMZ2 vaccine, a recombinant fusion protein of *Plasmodium falciparum* Glutamate Rich Protein and Merozoite Surface Protein 3, adjuvanted with aluminium hydroxide, can protect against clinical attacks of malaria in children aged 1-5yrs.

Baseline studies were conducted to determine the incidence of malaria in potential trial sites. 1840 children have been enrolled in five sites, in Uganda, Burkina Faso, Ghana and Gabon. The primary endpoint is the incidence of clinical malaria defined as fever or history of fever in the previous 24 hours with parasite density of 5000 asexual parasites per ul or more, detected by passive surveillance over a 6 month period from the third vaccination. Immune responses to the vaccine antigens GMZ2, GLURP and MSP3 will be assessed by measuring antigen specific IgG by ELISA, and antigen specific memory B-cell responses by ELISA spot.

Functionality of the immune response will be assessed by growth inhibition of *Plasmodium falciparum* in the presence or absence of monocytes. Cell mediated immunogenicity will be assessed by cytokine profiling and intracellular cell staining following stimulation with the vaccine antigen, and the quality of the antibody response by type and subclass-specific ELISA. Children will be followed for a total of 22 months from the third vaccination.

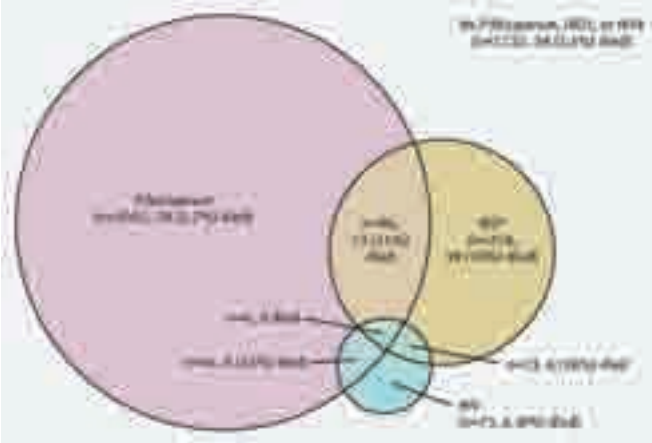
In Focus: Intermittent Preventive Treatment for malaria.

In the late 1990's and early 2000's a set of new strategies were evaluated – the Intermittent Preventive Treatments (IPT). IPT is the delivery of a treatment dose of an anti-malarial drug at pre-specified times, regardless of the presence of malaria parasites at the time of treatment. IPT in pregnancy (IPTp), IPT in infants (IPTi) and IPT in children (IPTc) are now all recommended by WHO for malaria control in parts of Africa. LSHTM staff led the first major randomised controlled trials of each of the three IPT strategies and have generated additional evidence to inform policy and implementation.

In 2010, IPTp was part of the malaria control strategy for 33 of the 43 malaria-endemic countries in Africa. Good coverage data is illusive but surveys in 8 countries (total population 270 million) have shown that 2.4-62% of women in pregnancy received at least 2 doses of IPTp in pregnancy.

WHO recommended IPTi as a malaria control tool for implementation in areas of moderate to high transmission in 2010. Although IPTi has not yet been adopted by any national malaria control programmes, if it were rolled out in those countries where studies have been conducted, unpublished estimates suggest that up to 1 million clinical episodes could be prevented every year.

The WHO Technical Expert Group recommended IPTc (Seasonal Malaria Chemoprevention) for malaria control in May 2011. SMC has now been recommended by WHO for areas of the Sahel and sub-Sahel where malaria transmission is highly seasonal. Geospatial models show that SMC has the potential to prevent about 100,000 deaths per year.



*Numbers and deaths of children infected with Plasmodium falciparum by blood slide, invasive bacterial disease (IBD), or HIV. Areas in Venn diagram approximately to scale. *IBD consisted of 336 children with a positive blood culture, of whom 20 also had a positive cerebrospinal fluid (CSF) culture, and an additional five with a pathogenic organism isolated from CSF and a negative or contaminated blood culture. †Blood cultures classified as negative included 251 (6.9%) from which contaminant organisms were cultured. ‡Three negative HIV results were based in Capillus testing only (negative predictive value 99.5%, details not shown); all other HIV results were based on at least two concordant test results.*

The severe febrile illness study.

***LSHTM Investigators**: Behzad Nadjm, Christopher Whitty & Hugh Reyburn.*

***External Investigators/Collaborators:** George Mtove (National Institute of Medical Research, Tanzania).*

***Funding Body:** European Commission.*

The aims of the study were to establish the treatable causes of febrile illness among children admitted to hospital in a high malaria transmission region of Tanzania and the clinical features that accompanied them. Children were enrolled at admission. Over 1 year 3,708 children were enrolled and results were available for 3,639. Blood slides for malaria were positive in 2195 (60.3%), 341 (9.4%) had invasive bacterial disease and 142 (3.4%) were seropositive for HIV. Non-typhi Salmonella were the most common bacterial isolate (160/341, 46.9%). Mortality in children with invasive bacterial disease was significantly higher (58/341, 17%) than in those without (126/3298, 3.8%, p<0.001) and this was true regardless of the presence of *Plasmodium falciparum* parasitaemia.

The sensitivity and specificity of WHO criteria in identifying invasive bacterial disease in slide positive children were 60.0% (95% confidence interval 58.0% to 62.1%) and 53.5% (51.4% to 55.6%), compared with 70.5% (68.2% to 72.9%) and 48.1% (45.6% to 50.7%) in slide negative children. In children with WHO criteria for invasive bacterial disease, only 99/211(47%) of isolated organisms were susceptible to the first recommended antimicrobial agent. The site went on to be involved in 2 large randomised controlled trials (AQUAMAT & FEAST) and typhoid surveillance studies.

Point-of-care measurement of blood lactate in children admitted with febrile illness to an African district hospital.

***LSHTM Investigators**: Behzad Nadjm & Hugh Reyburn.*

***External Investigators/Collaborators:** George Mtove (National Institute for Medical Research, Tanzania).*

***Funding Body:** European Commission.*

Lactic acidosis is a consistent predictor of mortality due to severe infectious disease but its detection in low-income settings is limited to the clinical sign of 'deep breathing' due to lack of accessible technology for its measurement. We evaluated the use of a point-of-care diagnostic device for blood lactate to assess the severity of illness in children admitted to a district hospital in Tanzania.

Children between the age of 2 months and 13 years with a history of fever were enrolled in the study over 1 year. A full clinical history and examination were undertaken and blood drawn for culture, microscopy, complete blood count and POC measurement of blood lactate and sugar.

3,248 children were included in the study of whom 164 (5.0%) died; 45 (27.4%) of these had raised blood lactate (>5mmol/L) but no deep breathing. Compared to mortality in children with lactate of >=3mmol/L, the unadjusted odds of dying were 1.6 (95%CI 0.8-3.0), 3.4 (95%CI 1.5-7.5) and 8.9 (95%CI 4.7-16.8) in children with blood lactates of 3.1-5.0mmol/L, 5.1-8.0 mmol/L and >8.0mmol/L respectively. The prevalence of raised lactate (>5mmol/L) was greater in children with malaria than in children with non malarial febrile illness (P<0.001) although the associated mortality was greater in slide-negative children.

POC lactate measurement can contribute to the assessment of children admitted to hospital with febrile illness and can also create an opportunity for more hospitals in resource-poor settings to participate in clinical trials of interventions to reduce mortality associated with hyperlactataemia.

The use of a HRP2 based Rapid Diagnostic Test (RDT) to guide treatment of children admitted to hospital in a malaria endemic area of Northeast Tanzania.

***LSHTM Investigators**: Behzad Nadjm & Hugh Reyburn.*

***External Investigators/Collaborators:** George Mtove (National Institute for Medical Research, Tanzania); Ilse Hendriksen (The Mahidol Oxford Tropical Medicine Research Unit, Thailand).*

***Funding Body:** European Commission.*

In a busy paediatric ward in Tanzania children with a febrile illness were enrolled over 1 year. A standard clinical history and examination were recorded and blood drawn for culture, complete blood count, Paracheck RDT and double-read blood slide.

Of 3,639 children in the study 2,195 (60.3%) were slide-positive. The sensitivity and specificity of Paracheck results were 97.5% (95% CI 96.9-98.0) and 65.3% (95% CI 63.8-66.9) respectively. There was an inverse relationship between age-specific prevalence of parasitaemia and the specificity of Paracheck. In a logistic regression model, false-positive Paracheck results were significantly associated with pre-admission use of an antimalarial drug (OR 1.44, 95% CI 1.16-1.78), absence of current fever (OR 0.64, 95% CI 0.52-0.79) and a positive blood culture for non-typhi Salmonella (OR 3.89. 95% CI 2.27-6.63). In spite of high sensitivity, only 56/2,195 (2.6%) of true infections were Paracheck-negative and 8(14.3%) of these were in patients with >50,000 parasites/µl.

Paracheck had poor specificity in diagnosing malaria in severely ill children and this was likely to be due to persistence of HRP2 following recent clearance of parasites. The combination of a positive Paracheck and negative blood slide result identified a group of children at high risk of non-typhi Salmonella infection. While Paracheck was highly sensitive, some high-density infections were missed. For children with severe febrile illness at least 2 reliable negative parasitological test results should be available to justify withholding antimalarial treatment.