

Malaria in pregnancy: priorities for research

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Research on the important topic of malaria in pregnancy has been relatively neglected. The seven technical reviews in this special issue on malaria in pregnancy provide an overview of current knowledge on key aspects of malaria in pregnancy and highlight the gaps where more research is needed. In this paper, we prioritise research needs, focusing on areas of research likely to lead to improvements in maternal and child health in malaria endemic areas in the near or mid term. We have selected the following as the highest priorities for research: identification of new safe and effective drugs to treat malaria in pregnancy; identification of new drugs to replace sulfadoxine-pyrimethamine for intermittent preventive treatment in pregnancy; identification of optimum combinations of control measures in different epidemiological settings; and determination of optimum ways of scaling-up the use of insecticide-treated mosquito nets and intermittent preventive treatment.

Introduction

Although the problem of malaria in pregnancy was first chronicled in the medical literature approximately 70 years ago,¹ it has been a neglected area of research. Early studies defined the epidemiology of malaria in pregnancy in areas with moderate or high levels of transmission and studied methods of treatment and prevention using chemoprophylaxis. Studies done in the past 15 years have focused on prevention of malaria in pregnancy by administration of sulfadoxine-pyrimethamine intermittently during pregnancy and on use of insecticide-treated mosquito nets. This research has led to recommendations by WHO on the control of malaria in pregnancy in areas with moderate to high levels of transmission.²

Research in the past decade has improved our understanding of the biological basis for susceptibility to malaria in pregnancy including the crucial part played by adherence of *Plasmodium falciparum*-infected red blood cells to the glycan chondroitin sulphate A, resulting in the accumulation of parasitised red blood cells in the placental blood space.³ Following the demonstration that antibody responses can block this process and lead to partial protection from the adverse effects of malaria in pregnancy, the possibility of developing a vaccine that prevents cytoadherence is now being explored.⁴ It has also been shown that inflammatory responses to malaria parasites and their products in the placenta, sometimes resulting in accumulation of mononuclear cells in the intervillous blood space, are an important component of the pathology of placental malaria. However, how these inflammatory processes interfere with placental function is not well understood and many questions about the pathogenesis and management of malaria in pregnancy remain unanswered.^{5,6}

Background and rationale for the malaria in pregnancy research reviews

The rate at which evidence on the efficacy of insecticide-treated nets and intermittent preventive treatment in pregnancy (IPTp) in preventing malaria in pregnancy was gathered, and the rate at which the encouraging findings of this research have been translated into policy

and practice has been too slow. Furthermore, the background knowledge on which current policy recommendations for the management of malaria in pregnancy are based is limited.⁷ The advances in the control of malaria in pregnancy that have been made in recent years are now being jeopardised by the spread of antimalarial and insecticide resistance and there has been lack of progress in the development of new drugs for the treatment and prevention of malaria, and a lack of progress in the development of alternative insecticides that could be used for insecticide-treated nets. Lack of coordination between research groups, the private sector, donors, and policymakers responsible for implementation has also hindered the development of improved methods for managing malaria in pregnancy.

For these reasons, a group of interested scientists met on several occasions in 2005 and 2006 to consider ways in which research on malaria in pregnancy, and the translation of important research findings into practice, could be accelerated. This special issue of *The Lancet Infectious Diseases* is one result of the collaboration established during these meetings. Major gaps in knowledge are identified in the seven preceding reviews. This paper highlights some of the key areas for further research identified by the authors of the preceding papers and shows how these could be drawn together to form a rational research strategy.

Research priorities

The authors of this and the other malaria in pregnancy papers in this issue recognise that there is a need for more research on many aspects of malaria in pregnancy, extending across a wide range of disciplines that include basic biology and immunology, epidemiology, economics, and public health.

In this Review, however, priority has been given to research that is likely to lead to improvements in maternal and child health in malaria endemic areas in the near or mid term. For each of the areas covered by the preceding papers, up to five topics have been selected as high research priorities. Some prioritisation of research issues was done during meetings of the wider group of scientists who have contributed to the reviews in this special issue.

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We then took these issues and prioritised them under five main areas through a series of one-to-one meetings and electronic exchanges. The ways in which the broader group of topics could be prioritised further to constitute an overall research strategy and how this research programme might be implemented most effectively were then reviewed.

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Malaria in pregnancy as a major cause of mortality and morbidity

In recent years, the burden of malaria in pregnancy in sub-Saharan Africa has been estimated with some degree of confidence as described in the paper by Meghna Desai and colleagues.⁸ However, some questions about the burden of mortality and morbidity attributable to malaria in pregnancy remain unresolved. These unresolved issues are described below.

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The importance of malaria as a cause of maternal mortality in areas of medium or high malaria endemicity

Recent autopsy studies done in Mozambique suggest that malaria may be a more frequent, direct cause of maternal mortality than has previously been appreciated and that it is both under and over-diagnosed as a cause of serious illness or death during pregnancy. Careful clinical studies of serious illnesses in pregnant women resident in areas of varying malaria endemicity, accompanied if possible by post-mortem studies, are needed.

The clinical importance of malaria in pregnancy outside the high-transmission areas of Africa

There are few data on the effect of *P falciparum* infection on pregnancy in areas outside Africa, such as parts of Asia and Latin America where malaria transmission is generally much less intense than in Africa, single infections in pregnancy are common, and women have little immunity to malaria. In many of these areas, both *P falciparum* and *Plasmodium vivax* coexist and little is known about the effect of *P vivax* or combined infections on pregnancy. Further study of the impact of *P vivax* infection on pregnancy is needed to help define health priorities in areas where this infection is prevalent. These studies could also provide valuable information on the pathogenesis of malaria in pregnancy (see below).

The importance of malaria in the first trimester of pregnancy

In most malaria endemic areas, few pregnant women attend an antenatal clinic before the second trimester of pregnancy. Consequently, little is known about the importance of malaria infections in the first trimester of pregnancy and their long-term consequences for the fetus and the infant after delivery. Investigating the effect of malaria during the first trimester of pregnancy is important in determining how aggressively researchers should pursue the development of preventive strategies

that reach women early in their pregnancy. Such studies will not be easy to do and will probably require longitudinal studies of women in the reproductive age-group to detect early pregnancies.

Pathogenesis and immunity

There are many outstanding questions about the pathogenesis of malaria in pregnancy, as set out in the review by Stephen Rogerson and colleagues.⁹ Research in this area is likely to provide important information about the biology of malaria parasites in general as well as elucidating the pathogenesis of malaria in pregnancy. Areas of research likely to contribute to improved management of malaria in pregnancy in the short to medium term include the following:

Study of the pathogenesis of anaemia in pregnant women infected with *P falciparum* or *P vivax*

Severe anaemia is probably the main mechanism by which malaria causes mortality in pregnant women, yet its pathogenesis has not been studied in detail. The relative importance of haemolysis, bone marrow suppression (perhaps cytokine induced), and sequestration of parasites in the placenta as causes of severe anaemia in pregnancy has not been defined. How malaria interacts with other important causes of anaemia in pregnancy, such as HIV and nutritional deficiencies, is also unknown. Careful clinical studies using modern immunological and haematological techniques should allow many of these uncertainties to be resolved.

Study of the pathogenesis of fetal growth restriction and preterm birth

The mechanisms by which malaria parasites cause fetal growth restriction and preterm birth are not well understood. Cytoadherence is likely to be a key factor in the case of *P falciparum* infections but how cytoadherence impairs placental function is not known. Since infection with *P vivax*, which does not cytoadhere, also leads to low birthweight, other factors, perhaps hormonal or nutritional, must be involved. Because HIV also causes preterm births, studies on the role of malaria in the pathogenesis of preterm births should include both HIV-infected and non-infected women. Resolving the complicated and interacting mechanisms involved in the pathogenesis of malaria-induced low birthweight will not be easy. However, new techniques are being developed for the study of malaria-infected placentas obtained at delivery such as perfusion of the placenta or placental lobule, microdissection of the syncytiotrophoblast, and use of cell lines. Nevertheless, study of placental function in vivo is difficult and animal models might be helpful in this area of research.

Study of the impact of effective control measures on the development of immunity to malaria in pregnancy

Women infected with malaria during their first pregnancy develop immunity to parasites that sequester in the

placenta. Thus, there is a danger that effective control of malaria in first pregnancies through IPTp, insecticide-treated nets or indoor residual insecticide spraying will impair this process, increasing the risk of malaria acquired during subsequent pregnancies. Whether or not this is the case needs to be established by clinical and epidemiological studies and by studies of cellular and humoral immune responses in women living under different epidemiological situations protected from malaria in various ways. Study of the impact of effective control of malaria in pregnancy on vertical transmission of HIV is also required.

Vaccination

Vaccines provide a potentially important way of preventing malaria in pregnancy. Any highly effective, pre-erythrocytic vaccine that induces protection and is not strain specific should protect against malaria in pregnancy. Thus, once it has been established that a pre-erythrocytic vaccine can induce a substantial and sustained level of protection in non-pregnant adults or children, a trial to determine its ability to protect against malaria in pregnancy would be justified. Vaccination with the product of the *var* gene responsible for binding of *P falciparum* to chondroitin sulphate A is a potential method for preventing malaria-induced damage to the placenta and consequent low birthweight. It is likely, but not proved, that prevention of sequestration would also reduce the incidence of maternal anaemia. Research to develop pregnancy specific, anti-cytoadherence vaccines is, therefore, a priority. Vaccination during pregnancy is unlikely to be the most effective way of deploying a malaria in pregnancy vaccine because it may be important to protect women from malaria during the first trimester of pregnancy before they present at an antenatal clinic. Additionally, there are concerns over the safety of vaccination during pregnancy. Thus, vaccination of women in the child-bearing age before pregnancy, including adolescents, is likely to be a more effective and safer option than vaccination during pregnancy. Research will be needed on the acceptability of this approach and on the optimum way of achieving this goal, perhaps by giving the malaria vaccine with other adolescent vaccines such as the human papilloma virus vaccine.

Case management and pharmacovigilance

Finding alternatives to the failing drugs currently being used for the treatment and prevention of malaria in pregnancy is probably the most urgent task facing the research community, as pointed out by François Nosten and colleagues.¹⁰ It is generally agreed that new drugs or drug combinations that do not already have a clear safety record in pregnant women should be tested first in pregnant women with proven malaria before they are tried for IPTp because the risk–benefit ratio is likely to be more favourable in the former situation. There are several priority areas for research in this area:

Diagnosis

In some epidemiological situations—eg, areas with low levels of transmission—case detection and treatment may be the most effective approach to the management of malaria in pregnancy. However, peripheral blood microscopy is a relatively insensitive method of detecting malaria infection of the placenta and new diagnostic tests are needed that are sensitive enough to detect infection of the placenta, and yet simple and cheap enough to be used in the clinic.

Finding new drugs for the treatment of malaria in pregnancy

In nearly all malaria endemic areas, chloroquine can no longer be used for the treatment of *P falciparum* infections in pregnancy, although it can still be used to treat *P vivax* infections in many places. The efficacy of sulfadoxine-pyrimethamine is also falling. Thus, trials of potential alternatives to these two drugs are needed urgently. The drugs that have the highest priority for testing will vary from area to area depending upon the local pattern of resistance.

Development of a standard method for the evaluation of new treatments for malaria in pregnancy

Evaluation of new treatments in asymptomatic, parasitaemic pregnant women requires a different approach from that used to measure efficacy in symptomatic, highly parasitaemic children and may give different results. Assessment of safety requires demonstration that the drug does not produce adverse effects in the mother or the fetus. Determining the latter requires that the pregnancy should be followed to its conclusion, the newborn baby examined for congenital abnormalities and the baby followed until 6 weeks of age and, whenever possible, to 1 year of age. Thus, evaluation of new treatments for malaria in pregnancy is more complex, demanding, and expensive than treatment trials in children or non-pregnant adults. The development of standard ways of conducting such trials is a priority.

Pharmacokinetics

There are few data on the pharmacokinetics of antimalarial drugs in pregnancy and several antimalarials, including sulfadoxine-pyrimethamine, have been used extensively in pregnancy in the absence of the information needed to determine the correct dose. Pharmacokinetic studies in pregnant women are urgently required for some of the antimalarials currently in use for the treatment and prevention of malaria in pregnancy. Pharmacokinetic studies are also an essential, early requirement in the evaluation of new antimalarials being considered for this purpose. Such studies are likely to require the collection of detailed measurements in a small number of women together with smaller numbers of samples from a larger number of treated women with modelling of the findings (population pharmacokinetics).

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Important areas of research that have attracted little attention from the research community are the potential for adverse pharmacokinetic interactions between antimalarials and antiretrovirals and the effect of malaria on the pharmacokinetics of antiretrovirals.

Pharmacovigilance

Conventional trials of new treatments are likely to involve only a few hundred women and are too small to detect rare but important adverse events. Thus, the establishment of pharmacovigilance systems able to detect rare adverse events following treatment with new antimalarial drugs is a priority. Because artemisinin-based combination therapies, now being used increasingly widely, can cause fetal loss in monkeys as well as rodents when exposure takes place early in pregnancy, establishing effective pharmacovigilance systems at selected sites where these drugs are being used has become urgent. Ways in which this might be done are discussed by Stephen Ward and colleagues.¹¹

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Prevention of malaria in pregnancy

Detecting malaria infections in pregnancy can be difficult in highly endemic areas since most infections are asymptomatic. Thus, in such communities, prevention of malaria in pregnancy is a major public-health priority. Two tools are currently being used to do this—IPTp and insecticide-treated nets—as discussed by Clara Menendez and colleagues.¹² The research priorities related to increasing use of these interventions are discussed subsequently by Jane Crawley and colleagues.¹³ Additional research issues include the following:

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New drugs for IPTp

Sulfadoxine-pyrimethamine is currently the only drug recognised for IPTp and, although it may remain effective for IPT, even when its efficacy in treating symptomatic malaria has waned, alternatives are needed urgently. It is not known whether IPT requires a long-acting drug and therefore trials of effective short and long-acting drugs are needed to resolve this issue. Whether IPTp with sulfadoxine-pyrimethamine is of benefit and safe in HIV-infected women who are receiving co-trimoxazole prophylaxis for opportunistic infections needs to be resolved.

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Combinations of interventions

There is an urgent need to determine the best possible combination of drug-based and vector control strategies needed in different epidemiological settings.

Moderate to high transmission areas

It is uncertain whether IPTp with sulfadoxine-pyrimethamine provides added benefit to insecticide-treated nets in all circumstances. It is possible that in some situations, use of a long-lasting insecticidal net and case detection may be as effective as an insecticide-treated

net plus IPT, or that the frequency of dosing with existing and future drugs used for IPT can be reduced when an insecticide-treated net is used. Similarly, it needs to be established whether IPT adds to the protection provided by indoor residual spraying.

Low transmission areas including those outside Africa

Remarkably little is known about how malaria in pregnancy can be prevented most effectively in Asia and Latin America. Studies comparing case management alone against preventive approaches plus case management are needed. More information is needed on the value of insecticide-treated nets in Asia and Latin America where the diversity and complexity of the main vectors are much greater than in Africa. In some areas outside Africa, where vectors bite predominantly during the day or early evening, repellents may have a role in preventing malaria in pregnancy and this needs to be investigated.

Safety of insecticides in pregnancy

Research to develop alternative insecticides that could be used for treatment of nets or for indoor residual spraying in areas where there is resistance to insecticides currently used for public health is underway. It will be necessary to demonstrate as far as possible that exposure of pregnant women to such insecticides is not harmful to them or to their fetuses. Information on the safety in pregnancy of the insecticides currently being used for treating nets or for indoor residual spraying, mainly pyrethroids and DDT, is limited and may also need further evaluation.

Economics

The economic aspects of malaria in pregnancy have been neglected. The limited information available is summarised in the review by Eve Worrall and colleagues,¹⁴ which identifies gaps requiring further research.

An analysis of the overall economic burden of malaria in pregnancy

An analysis of the overall economic burden of malaria in pregnancy that considers both direct and indirect effects—eg, the long-term consequences of low birthweight on child development—would be helpful in defining the importance of malaria in pregnancy as a global public-health priority. More information on the burden of malaria in low transmission areas (see above) will be needed to guide this review.

Cost-effectiveness of insecticide-treated nets and IPT in pregnancy

Previous studies have demonstrated that, overall, both insecticide-treated nets and IPT are highly cost-effective interventions when used in pregnancy. However, more refined studies are needed to establish the cost-effectiveness of insecticide-treated nets, indoor residual spraying, and IPT in different epidemiological situations and when delivered through alternative systems. For

Panel: The top priorities for research on malaria in pregnancy.

- 1 Finding safe and effective new drugs or drug combinations for the treatment of malaria in pregnancy
- 2 Finding safe and effective alternatives to sulfadoxine-pyrimethamine for IPTp
- 3 Defining the optimum combination of control measures in different epidemiological situations
- 4 Finding optimum ways for scaling-up use of insecticide-treated nets and IPTp

example, it is not known at what level of malaria transmission use of insecticide-treated nets or IPT become cost-effective interventions nor what level of resistance to sulfadoxine-pyrimethamine would negate the cost-effectiveness of IPT.

Implementation and health policy research

New tools for the control of malaria in pregnancy have become available during the past decade but coverage with these interventions is still unacceptably low. Jane Crawley and colleagues¹³ point out that research on defining the obstacles to progress has been neglected and they identify a number of areas where research is needed. These topics are listed below.

Identification of optimum delivery strategies for scaling-up the use of insecticide-treated nets and IPT

Research is needed to identify the most effective and most cost-effective ways of delivering insecticide-treated nets and IPT in different epidemiological and social circumstances in a sustainable way. Universal coverage with insecticide-treated nets is the ultimate goal for high risk areas but, in the meantime, some more restricted strategies may be required—eg, distribution of free or subsidised nets at antenatal and immunisation clinics. Alternative approaches to delivery need to be explored.

Integration of malaria control with reproductive health programmes

An important area of operational research that needs to be addressed is how malaria control can be integrated more effectively than in the past with reproductive health and other programmes directed at women of childbearing age. For example, schedules for IPTp may need to be adapted to meet the new WHO four-visit recommendations for antenatal care. Could the skills of traditional birth attendants be used to facilitate malaria control? Collaboration with adolescent health programmes may provide access to women during (or before) their first pregnancy and a possible route for the distribution of preventive measures such as insecticide-treated nets or vaccines. Ways need to be found of improving collaboration between malaria control and HIV treatment programmes.

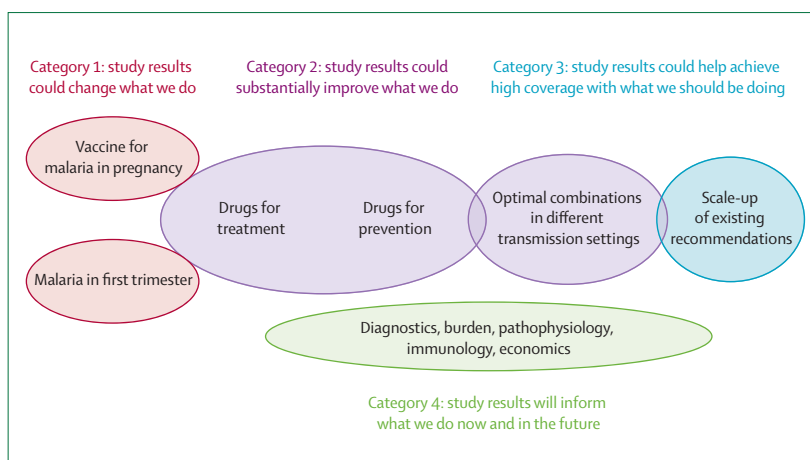


Figure: A conceptual framework and strategy for a programme of research on malaria in pregnancy

The figure depicts four categories of research. Category 1: studies in this category include those which could change how malaria in pregnancy is managed. They include development of a safe and effective vaccine and demonstration that prevention of malaria in the first trimester is crucial to maternal, fetal, and newborn health. Category 2: the results of studies in this group could substantially improve existing tools and control strategies. Examples include the development of new safe and effective drugs for treatment and for IPTp and the development of strategies for the prevention of malaria in pregnancy. Category 3: the results of studies in this category could help to achieve higher levels of coverage with existing, proven interventions. Research findings could be available in the near term and rapidly influence control strategies. Category 4: research in this category includes a broad range of studies in which important information can be obtained in association with other investigations, for example acquiring knowledge on the immunology of malaria in pregnancy during treatment or vaccine trials or combining studies of new diagnostics with intervention studies.

Access, affordability, and acceptability

More research is needed on the accessibility, affordability, and acceptability of current and new interventions. Physical access to services does not guarantee their use because of factors such as quality of care or waiting time. Assessment of the acceptability of a new intervention, both by pregnant women and by the health-care workers asked to deliver it, must be an integral component of the evaluation of any new method for the prevention of malaria in pregnancy and requires the participation of social scientists.

The top research priorities and a strategy for future research

Four areas have been selected from among the topics considered above as being the most urgent research priorities (panel). Identification of new drugs and new drug combinations that can be used safely and effectively in pregnancy heads the list. We have also categorised future research needs into four main areas (figure). New studies will vary in their feasibility, ease of conduct and timeframe. For example, the timeframe for the development of a vaccine that is safe and effective in pregnancy is likely to be long, but success could greatly change the way in which malaria in pregnancy is managed. The second category of research focuses on crucial studies that are required to give early results and which need to be coordinated effectively to achieve this goal. Their feasibility is higher than studies in the first category and they are likely to give early, practical benefits. The third category of

Search strategy and selection criteria

This paper is based on a review of the preceding papers in this issue and of relevant supporting articles.

research—eg, studies on the pathogenesis of malaria in pregnancy, informs the future but may not immediately change or modify existing interventions. Finally, studies in category four tend to be less about research and more about acquiring the knowledge needed to make good decisions on service delivery and to increase coverage.

Each of these sets of research questions needs to be approached systematically by groups that have the necessary technical knowledge to address them; this may require a new and larger set of scientific and programmatic relationships than currently exist. Study of new treatments will require the creation of clinical trials networks with experience of treatment of malaria in pregnancy, and groups with experience in large-scale field studies and demographic surveillance will be needed for epidemiological studies and prevention trials. With skill, it should be possible to integrate into these major work programmes studies of cross-cutting issues such as those on burden of malaria in pregnancy, pathogenesis, immunology, pharmacokinetics, pharmacovigilance, and the economic consequences of malaria in pregnancy in a cost-effective way.

Finally, we suggest that the most effective way of accelerating research on malaria in pregnancy is the creation of a consortium of interested scientists, funding agencies, policymakers, industrial partners, and implementers who will work together in a coordinated way on an agreed overall programme of research. The consortium could act as an advocate for the need for research on malaria in pregnancy, help to reduce unnecessary duplication between research groups, facilitate standardisation of methods across studies and reinforce the communication network that has been so productive for current research groups to date. However, the consortium must not be allowed to become an exclusive organisation that imposes conformity and hinders the emergence of original but unconventional approaches to malaria in pregnancy research. Involving policymakers and funding agencies early in the research process should help in the rapid translation of promising

research findings into policy and practice and the implementation of effective new ways of containing malaria in pregnancy as speedily and cost effectively as possible.

Conflicts of interest

We declare that we have no conflicts of interest.

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