

# Epidemiology and Control of Malaria during Pregnancy

# Objectives of talk

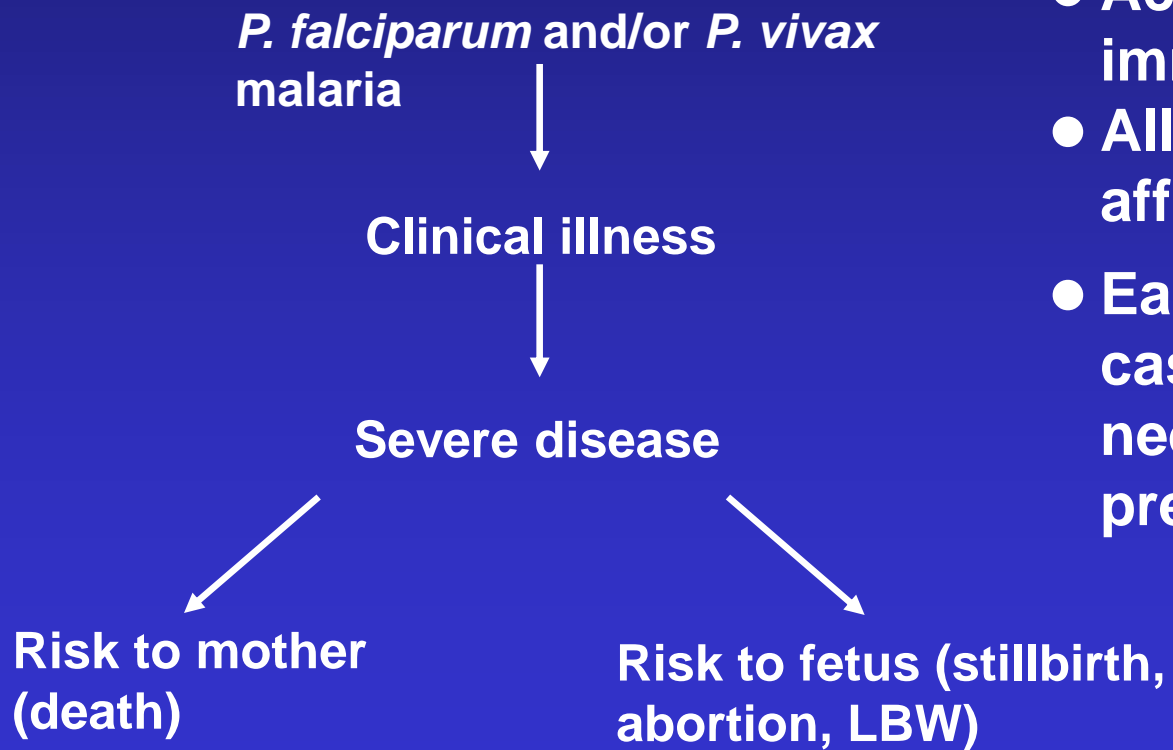
- Discuss the epidemiology of malaria during pregnancy
- Present evidence for current intervention strategies
- Mention gaps in our knowledge

# Epidemiology

# Malaria during pregnancy: bad news

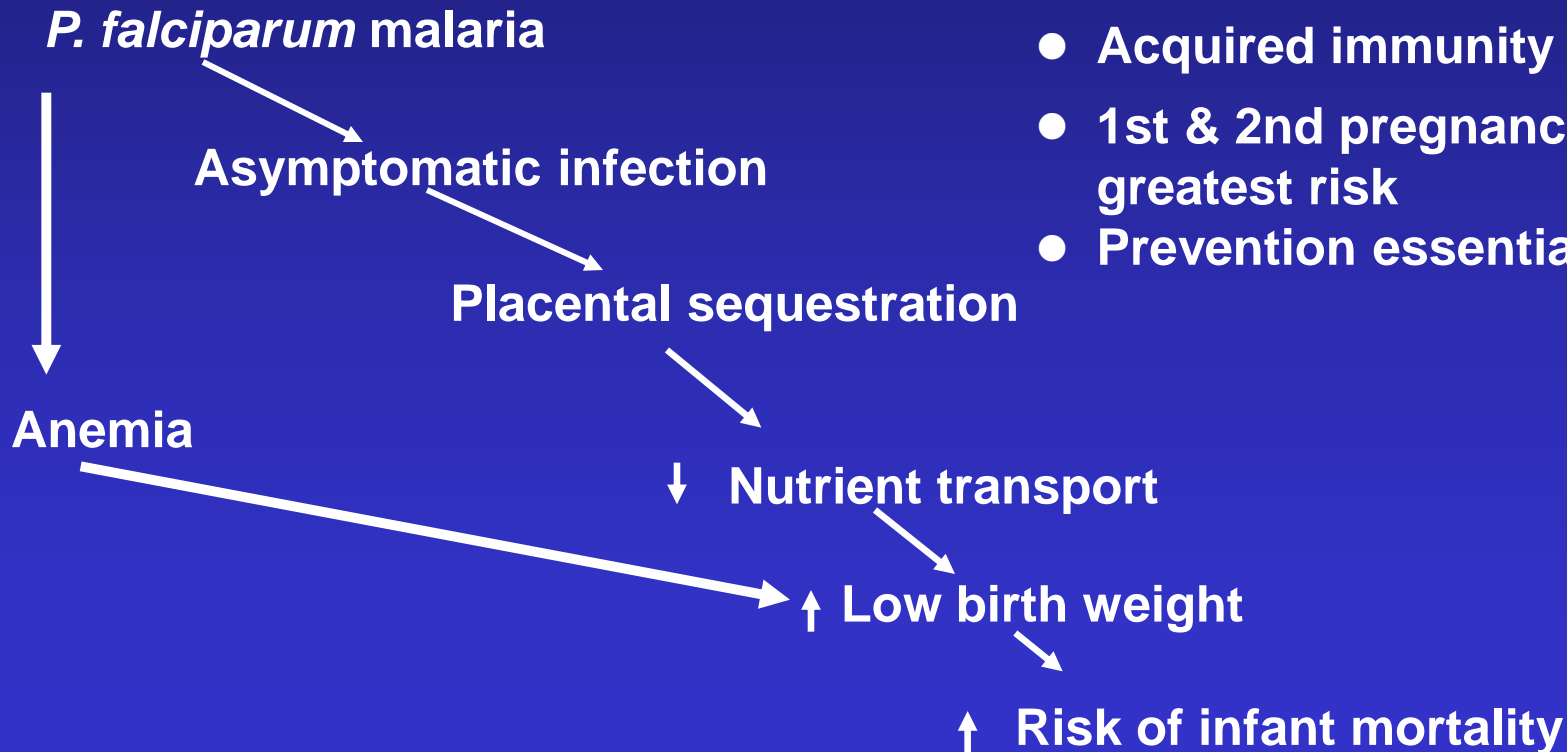
- 50 million women in malaria endemic areas become pregnant each year (UNICEF 2008)
- Malaria during pregnancy most widely evaluated in sub-Saharan Africa and estimated to account for:
  - 400,000 cases of severe anemia in pregnant women (Guyatt 2001)
  - ~ 35% of preventable low birth weight (Steketee 2001, Guyatt 2004)
  - 3-8% of infant mortality (Steketee 2001, Guyatt 2001)
  - 75,000 - 200,000 infant deaths annually (WHO/UNICEF Africa Malaria Report 2003)
- Perinatal effects depend on intensity of transmission: *Plasmodium falciparum* in high transmission areas is most well studied - responsible for most morbidity & mortality

# Malaria during pregnancy: unstable/low transmission areas



- Acquired immunity - low
- All pregnancies affected equally
- Early recognition and case management needed in addition to prevention

# Malaria during pregnancy: stable transmission areas



# Vulnerable groups among pregnant women

- In general, pregnancy reduces a woman's immunity to disease, making her more susceptible to malaria. Specific risk factors include:
  - Primigravidae (high transmission areas)
  - 2<sup>nd</sup> trimester
  - Young maternal age (eg, adolescents)
  - HIV-positive women (all pregnancies)
  - Women in rural areas

# Current strategies



# Options for malaria control during pregnancy

- **Drugs**
  - Chemoprophylaxis
  - Intermittent preventive treatment during pregnancy (IPTp)
  - Febrile case management
- **Insecticide-Treated Nets (ITNs)**
- **Prevention and treatment of anemia**
  - Hematinic supplementation
  - Nutritional counseling
- **Vaccines?**

# Chemoprophylaxis: no longer a recommended strategy in high transmission areas

- Most regimens require weekly or more frequent dosing
  - Chloroquine (CQ) is the most commonly used drug
- Usefulness severely limited by:
  - Poor adherence
  - Side effects of CQ
  - Rising levels of *P. falciparum* resistance to CQ

# Intermittent Preventive Treatment for Pregnancy (IPTp)



# Intermittent preventive treatment (IPTp): an alternative strategy

- Most studied regimen: Sulfadoxine-pyrimethamine (SP) 2 curative courses (3 tablets); one second and one third trimester
- Appropriate for settings with CQ-resistant *Pf*
- Inexpensive
- Easily deliverable and may be directly observed
- Generally well-tolerated with few side effects

# Intermittent preventive treatment (IPTp)

- At least 2 doses during pregnancy of SP
- Given at the 1st and 2nd ANC visits after quickening (1<sup>st</sup> noted movement of the fetus)
- In areas where HIV prevalence among pregnant women is >10%, a 3<sup>rd</sup> dose should be given at the last visit
- IPTp should be linked to routinely scheduled ANC visits

# Intermittent preventive treatment (IPTp) with SP: results of clinical trials

Site, Date, Author	Regimens	Anemia	Placental parasitemia	Birth weight
Malawi, 1994 Shultz	(1) CQ trt/weekly (2) SP then CQ weekly (3) SP/SP (IPT)	NE	Decreased	NS
Kenya, 1998 Parise	(1) SP/SP (IPT) (2) Monthly SP (IPT) (3) CM	Decreased	Decreased	LBW – NS; Mean BW increased
Kenya, 1999 Shulman	(1) SP (dose variable) (IPT) (2) Placebo	Decreased	NS	NE
Kenya, 2003 Njagi	(1) SP/SP (IPT) (2) Placebo	Decreased	Decreased*	NS
Mali, 2005, Kayentao	(1) CQ trt/weekly (2) CQ/CQ (IPT) (3) SP/SP (IPT)	Decreased	Decreased	LBW decreased, Mean BW increased

CQ = chloroquine; SP = sulfadoxine-pyrimethamine; CM = case management; LBW Low birth weight

NE = not evaluated; NS = not statistically significant ( $p > 0.05$ )

\* Data in thesis; not included in published manuscript

# Intermittent preventive treatment (IPTp) with SP: program effectiveness evaluations

Site	Study design	Anemia	Placental parasitemia	Birth weight
Malawi, Verhoeff 1998	Observational: Delivering women: comparing 2 or 3 doses of SP vs. 1 dose	Mean Hb increased (multigrav. only)	NS	LBW decreased, Mean BW increased
Malawi, Rogerson, 2000	Observational: Delivering women; number of doses of IPTp/SP vs. outcome measures	Mean Hb increased, anemia decreased (2-dose only)	Reduced (1 and 2 doses)	LBW decreased, Mean BW increased
Kenya, Van Eijk, 2004	Observational: Delivering women; number of doses of IPTp/SP vs. outcome measures	NA	Reduced	LBW decreased, Mean BW increased
Burkina Faso, Sirima 2006	Program evaluation: ANC/DU; number of doses of IPTp/SP vs. outcome measures	NS	Reduced (2 and 3 doses)	LBW decreased (3 doses)

SP = sulfadoxine-pyrimethamine; Hb Hemoglobin; LBW Low birth weight

NS = not statistically significant ( $p > 0.05$ )

# IPTp with SP: summary of evidence and benefits

- 2 doses of IPTp with SP is associated with:
  - Reduction in 3<sup>rd</sup> trimester maternal anemia
  - Reduction in placental malaria parasitemia
  - Reduction in low birth weight
- At least 2 doses required for optimal benefit
- Regimen is safe and well tolerated
- Monthly dosing more beneficial in HIV+ women (but not recommended if pregnant woman is taking cotrimoxazole)



# Insecticide treated bed nets (ITNs)



# ITNs-efficacy in pregnancy: design

<b>Study</b>	<b>Trans- mission</b>	<b>Group vs individual randomization</b>	<b>Trim ester</b>	<b>Comments</b>	<b>ANC</b>	<b>Mass Effect</b>
Dolan Thailand	Low Seasonal	Individual	2-3	G-ALL	Yes	Yes
D'Alessandro Gambia	Low Seasonal	Village	ALL	G1	No	Yes
Shulman Kenya	Intermed. Seasonal	Village	ALL	G1	Both	Yes
Brown Ghana	High Seasonal	Village	P:2-3 M:ALL	G-ALL	No	Yes
Marchant Tanzania	High Perennial	Not random	ALL	G-ALL	NO	+/-
ter Kuile Kenya	High Perennial	Village	ALL	G-ALL	No	Yes
Njagi Kenya	High Perennial	Individual	2-3	G1+2	Yes	No

# ITNs during pregnancy

- Meta analyses of 5 random control trials (4 from Africa, 1 from Thailand)
- In Africa, ITNs reduced
  - Placental parasitemia in all pregnancies (RR=0.79 [0.63-0.98])
  - LBW (RR=0.77 [0.61-0.98]) and stillbirths/abortions in G1-4 (RR=0.67 [0.47-0.97])\*
- In Thailand, ITNs reduced anemia and stillbirth/abortions in all pregnancies

# ITNS (current programmatic issues)

- Supply of ITNs in sub-Saharan Africa increasing, but disparity exists between urban and rural sites
- Need to increase access to ITNs for pregnant women by using multiple outlets
- Encourage pregnant women to sleep under ITNs

# Case management of malaria and anemia



# Case management of malaria in pregnancy

## Safe drugs

- Chloroquine
- Quinine / quinidine
- Proguanil, chlorproguanil
- Pyrimethamine
- Sulfonamides
- Dapsone (+pyrimethamine= Maloprim)
- Mefloquine (prophylaxis)
- Clindamycin (300 mg qid, 5-7 days)
- Artemisinin??

## Drugs with questionable safety or insufficient data

- Mefloquine (treatment dose)
- Artemisinins??
- Amodiaquine
- Azithromycin
- Lumefantrine (component of coartem/Riamet)
- Combination therapy
  - Artemisinin derivative with other drugs
  - Lapdap (chlorproguanil-dapsone)
  - Atovaquone-proguanil (Malarone)
  - Amodiaquine-SP

# Antimalarials contra-indicated in pregnancy

- Tetracycline
- Doxycycline
- Halofantrine
- Primaquine
- Tafenoquine

Note: if serious illness, and where limited number of drugs are available, it is necessary to balance the risk of maternal death with the hypothetical risks to the infant

# Interventions depend on level of transmission

- High transmission areas
  - Women don't feel sick - need prevention of adverse effects
  - Prevention by IPTp and ITNs
- Low transmission areas
  - IPTp will not necessarily keep the woman well
  - Prevention by ITNs
  - Any role for chemoprophylaxis or IPTp in select areas?
- Both areas need prompt appropriate febrile case management



# Roll Back Malaria Targets

- 80% of malaria patients are diagnosed and treated with effective antimalarial treatments
- In areas of high transmission, 100% of pregnant women receive intermittent preventive treatment (IPTp)
- 80% of people at risk from malaria are using locally appropriate vector control methods such as long-lasting insecticidal nets, indoor residual spraying and, in some settings, other environmental and biological measures;

# Malaria during pregnancy: Research to program - a continuous cycle

Monitoring &  
evaluation



Programmatically  
relevant research



Policy change



Program  
implementation



# Timeline for IPTp policy change

- 1998: WHO recommended IPTp-SP
- 2003: Of 36 African countries with the right epidemiologic conditions for IPTp, only 9 had adopted it as policy
- 2008: 36/36 (100%) have adopted it as policy

# Rapid assessment of burden of malaria during pregnancy

- Survey at antenatal care
  - peripheral malaria parasitemia and anemia
- Survey at delivery units
  - Peripheral and placental parasitemia, birth weight, and gestational age
- Other modules: severe disease, health facility assessment, rapid ethnographic evaluation

# Malaria during pregnancy: gaps in knowledge and future directions

# Malaria in Pregnancy (MiP) Consortium

- Focused on addressing gaps in knowledge regarding all aspects of MiP
- Initial funding for meetings and development of review papers from Bill & Melinda Gates Foundation
- Full research agenda to be finalized in 2006
- Comprehensive reviews (7) to be published as part of an LID supplement by end of 2006

# Technical Reviews

1. **Epidemiology and Burden of disease:** M Desai, F ter Kuile, F Nosten, R McGready, K Asamo, B Brabin, R Newman
2. **Pathophysiology and immunology:** S Rogerson, R Leke, et al
3. **Drug safety and kinetics:** S Ward, E Sevine et al
4. **Case management:** F Nosten, R McGready, TK Mutabingwa
5. **Prevention:** C Menendez, F ter Kuile
6. **Implementation and Policy:** J Crawley, A Palmer, K Asamo, R Steketee, et al
7. **Economics of malaria in pregnancy:** E Worrall, A Mills
8. **Summary concept paper:** B Greenwood, R Steketee and P Alonso

# Priorities: Epidemiology and Burden

- What is the importance of MiP in low transmission areas including areas where *P. vivax* is the dominant parasite ?
- What is the impact of malaria in the first trimester ?
- Is malaria an important cause of maternal mortality in medium to high transmission areas?



# Priorities: Pathogenesis and immunity

- How does malaria cause severe anemia in pregnancy ?
- How does malaria cause low birth weight ?
- What impact will the introduction of effective control measures have on naturally acquired immunity to malaria ?
- Can malaria in pregnancy be prevented by:
  - partially effective pre-erythrocytic vaccines
  - a 'malaria in pregnancy' vaccine

# Priorities: Case Management

- Can the diagnosis of malaria be improved ?
- Which drugs can be used to replace CQ and SP for the treatment of malaria in pregnancy and how can the efficacy of new drugs best be measured ?
- How are the pharmacokinetics of antimalarial drugs (old and new) influenced by pregnancy ?  
Are there pharmacokinetic interactions between antimalarials and ARVs ?
- Are antimalarials safe in pregnancy (pharmacovigilance) ?

# Priorities: Prevention of MiP

- How can preventive strategies (ITNs, indoor residual spraying [IRS], IPTp, repellents) be used together most effectively in different epidemiologic situations:
  - low or high transmission
  - areas with *P. vivax* infection
  - low or high HIV prevalence
- What drug(s) can be used to replace SP for IPTp?  
Do they need to be long acting ?
- Are existing insecticides and new ones under development safe in pregnancy when used for ITNs or IRS ?
- Pharmacovigilance

# Priorities: Economic aspects of MiP

- What is the overall economic burden of malaria in pregnancy ?
- What are the comparative cost efficacies of different control measures in different circumstances ?

# Priorities: Health systems research

- How can usage of ITNs and IPTp be scaled up most effectively and equitably in different situations ?
- How can malaria control in pregnancy be integrated into reproductive health and HIV management programmes more effectively ?
- Will new interventions be accessible, affordable and acceptable?

# Overall priorities identified from technical reviews

- New drugs for treatment
- New drugs for prevention
- Clarity on optimal methods of deploying combinations of interventions in different epidemiological settings
- Improved delivery of existing recommendations to achieve high coverage

# Malaria in Pregnancy

## Conclusions

- A significant public health problem, associated with anemia, LBW and increased infant mortality
- Effective intervention strategies exist, and need to be implemented
  - ITNs, IPTp, CM, anemia prevention
- Combating MiP will require
  - Better coordination and harmony among various groups invested in this subject (research + program)
  - Stronger advocacy

# Resources

## ■ MiP

- Strategic framework for malaria prevention and control during pregnancy in the African Region (WHO/2005)
  - ◆ English, French, Portuguese
- Malaria during Pregnancy Resource Package (JHPIEGO/2003)
  - ◆ English, French, Portuguese: all soon to be updated
  - ◆ [Orders@jhpiego.net](mailto:Orders@jhpiego.net)
- Malaria in Pregnancy: Guidelines for Measuring Key Monitoring and Evaluation Indicators (WHO/Draft): available from CDC

## ■ IPTi

- IPTi Consortium website: [www.ipti-malaria.org](http://www.ipti-malaria.org)



**EXTRA INFORMATION**

# Malaria in Low Transmission Areas

- Countries may have range of transmission intensities (e.g. Madagascar or Brazil)
- Burden may differ by transmission zone:
  - High transmission, stable malaria
  - Moderate transmission, stable malaria
  - Seasonal transmission, stable and unstable malaria
  - Epidemics, unstable malaria

# Malaria in Low Transmission Areas: Differences in Burden

- Effect of different species
  - More *P. malariae* and *P. ovale*? As far as known, no clear adverse events for malaria in pregnancy
  - *P. vivax* may also be associated with maternal anemia and LBW
- Wider spectrum of effects:
  - LBW (primarily due to preterm delivery)
  - Anemia
  - Maternal morbidity / mortality
  - Epidemics

# Treatment of malaria in low transmission areas

- Treatment of severe malaria is more complicated in pregnancy
  - More complications:
    - ◆ Hypoglycemia (malaria, quinine)
    - ◆ Pulmonary edema
  - Treatment options different (in particular 1<sup>st</sup> trimester)
- Higher risk of maternal death

# Malaria during Pregnancy in Low Transmission Areas

## Differences in Potential to Intervene

- Drug resistance pattern of *P. falciparum* to chloroquine
- Treatment options for other species
  - Primaquine contraindicated in pregnancy
- Delivery of prevention/intervention methods: Use of ANCs or other care sources?
  - ANC attendance may be low, and influenced by household wealth

# Program Implementation I (Strategic Framework, African Region, 2004)

1. Establish a technical advisory group with national and partner stakeholders to advise on policy and national implementation planning
2. **Conduct needs assessment and situation analysis to define the epidemiology of malaria during pregnancy and the capability of the reproductive health and antenatal program**
3. Develop or review the national malaria control policy and guidelines for malaria prevention and control during pregnancy
4. Develop or update a comprehensive strategy and implementation plan for malaria prevention and control during pregnancy

# Program Implementation II (Strategic Framework, African Region, 2004)

5. Develop advocacy and communication strategies for malaria prevention and control during pregnancy
6. Assist to strengthen support systems for ANC services, including interventions for malaria prevention and control during pregnancy
7. Build personnel capacity for malaria prevention and control during pregnancy
8. Define a research agenda for malaria prevention and control during pregnancy

# Objective of this Assessment

- Know more about what you need to know about the burden of malaria during pregnancy
- Assess how to address or better address the problem





# Rapid Assessment

- Manual
  - The problem
  - Planning and conducting the assessment
  - Data processing
- Modules
  - Specific information about different assessment “tools” (surveys) to gather needed information
- Tools
  - Questionnaires ready to adapt and use