Malaria in pregnancy in low transmission settings

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Pregnant women: a special population

- Increased susceptibility of pregnant women to malaria (Pf, Pv)
- Malaria in pregnancy (MiP) an important driver of maternal and infant health
  - 10,000 pregnant women and 200,000 infants die every year
- Susceptibility is modulated by:
  - Age
  - Parity
  - Gestational age
  - Level of acquired immunity to *P. falciparum*
  - HIV infection

**Primigravid:** lower levels of acquired pregnancy-specific immunity

**Multigravid:** Adequate immunity through previous pregnancies exposure. Ab that inhibit adherence of parasites to CSA in the placenta

(Adapted from Salanti, 2003)
The cycle of *P. falciparum* in the pregnant woman
Factors involved in malaria risk

Estimated number of pregnancies at risk

125.2 million pregnancies annually in malaria endemic areas worldwide

- Largest burden in sub-Saharan Africa
  - 32 mill pregnancies at risk annually
  - Mostly *P. falciparum*
  - More SEVERE
  - WHO malaria in pregnancy control recommendations

- Outside Africa
  - 94 mill pregnancies at risk annually
  - Mostly LOW TRANSMISSION
  - Pf coexists with *P. vivax*
  - Less severe
  - No clear control measures

Figure 1: Malaria risk map for *P. falciparum* and corresponding number of pregnancies in each continent in 2007. doi:10.1371/journal.pmed.1000211001

Figure 2: Malaria risk map for *P. vivax* and corresponding number of pregnancies in each continent in 2007. doi:10.1371/journal.pmed.1000211002

Dellicour et al., PLoS Medicine, 2010
**P. vivax infection in pregnancy**

- Burden and impact of *P.falciparum* well documented
- Much less known about *P.vivax* in pregnancy and its impact on maternal and infant health
- Some evidence on:
  - increased susceptibility to *P.vivax* in pregnancy
  - association with maternal anaemia, preterm birth, miscarriage and severe disease
- Most data from Asia, based on limited numbers or case reports. Few prospective studies:
  - Incomplete picture of real burden. Particularly, in the Americas
Asia-Pacific Region

Figure 1. Malaria risk map for *P. falciparum* and corresponding number of pregnancies in each continent in 2007. doi:10.1371/journal.pmed.1000271.g001

Figure 2. Malaria risk map for *P. vivax* and corresponding number of pregnancies in each continent in 2007. doi:10.1371/journal.pmed.1000272.g002
MiP in the Asia-Pacific region

- **Thailand** (Thai-Burmese border):
  - 6.4% of pregnant women had *P. vivax* (N=9956) (Nosten 1999)
  - Primigravidae at higher risk (OR 1.63)
  - Increased risk of anaemia (OR 1.91) and LBW (OR 1.64)
  - Increased risk of miscarriage and 1st trimester infection (OR 2.70 in asymptomatic, OR 3.99 in symptomatic) (McGready 2012)

- **India.** Multiple studies, heterogeneity in study design:
  - Prevalence varied between 0.8-5.7% (Singh 2003, Prasad 1990)
  - Association with increased risk of anaemia (Singh 1999)
  - Clinical illness higher in pregnant vs non-pregnant women (Scholapurkar 1988)
  - Association with severe disease (Kochar 2005)

- **Papua (Indonesia):**
  - Prevalence at delivery 16.8%. Ratio Pf:Pv 57:43 (Poespoprodjo 2008)
  - Higher risk of anaemia (OR 1.8) and LBW (OR 1.5)
  - Primigravidae at higher risk (OR 1.3)
Malaria in pregnancy in the Asia-Pacific region

Marcus J Rijken, Rose McGready, Machteld E Boel, Rini Poepoprodjo, Neeru Singh, Din Syafruddin, Stephen Rogerson, François Nosten

Most pregnant women at risk of for infection with *Plasmodium vivax* live in the Asia-Pacific region. However, malaria in pregnancy is not recognised as a priority by many governments, policy makers, and donors in this region. Robust data for the true burden of malaria throughout pregnancy are scarce. Nevertheless, when women have little immunity, each infection is potentially fatal to the mother, fetus, or both. WHO recommendations for the control of malaria in pregnancy are largely based on the situation in Africa, but strategies in the Asia-Pacific region are complicated by heterogeneous transmission settings, coexistence of multidrug-resistant *Plasmodium falciparum* and *Plasmodium vivax* parasites, and different vectors. Most knowledge of the epidemiology, effect, treatment, and prevention of malaria in pregnancy in the Asia-Pacific region comes from India, Papua New Guinea, and Thailand. Improved estimates of the morbidity and mortality of malaria in pregnancy are urgently needed. When malaria in pregnancy cannot be prevented, accurate diagnosis and prompt treatment are needed to avert dangerous symptomatic disease and to reduce effects on fetuses.

- Prevalence of infected women with malaria 15.3% (range 1.2-40.8) at ANC and 8.1% (range 1.6-18.5) at delivery
- Most malaria infections caused by *P. vivax*. Mixed infections uncommon
- Differences in transmission intensities. Discrepancies in methods
- Most pregnant women at risk of *P. vivax* live in the Asia-Pacific region
Region of the Americas
Burden of malaria in the Americas

- 112 million people in 21 countries at risk for malaria
- Malaria cases decreased from 1.2 million in 2000 to 390,000 in 2014 (70% reduction)
Prevalence of malaria

- Community-based studies: 4.3%
- Hospital-based (ANC, delivery):
  - 0.2-13% in peripheral blood
  - 0.6-11.7% in placental blood
  - 2% in cord blood
  - More than 3-fold increase detection of infection with PCR
- Heterogeneity in study design, and in malaria detection methods
- Few prospective and cohort studies

Burden in pregnancy in the Americas:
commissioned paper by RBM MiP WG

Proportion of malaria cases by species, Manaus area*, Brazil

Reported malaria cases in pregnant women through SIVEP, Brazil

Martínez-Espinosa, personal communication

SIVEP. Brazil National Surveillance System
Burden in pregnancy in the Americas: commissioned paper by RBM MiP WG

• Epidemiology of malaria during pregnancy in the region mirrors global trends in the region over the last decade:
  - Decrease in incidence of confirmed cases
  - Decrease in prevalence of infection
  - Increase in the proportion of *P. vivax* compared to *P. falciparum*. *P. vivax* is the predominant species

• High proportion of submicroscopic infections, not detected by routine methods (microscopy):
  - High proportion of asymptomatic carriers
  - Though not clear impact on maternal anaemia and LBW

• Risk of malaria in pregnancy associated with age, parity and gestational age
**Plasmodium vivax infection in pregnancy**

- **Multicentre cohort observational study**: enrolment at ANC, follow up until delivery
- **Evaluation of pregnancy outcomes**: Maternal anaemia, LBW, prematurity, congenital malaria
- **Active detection of infection (ADI)**: LM, RT-PCR, placental histology. Passive surveillance (PCD) at each site

Total pregnant women recruited: 4953 (2009 in GT, 2043 in CO, 1657 in BR, 1982 in IN, 1796 in PNG)
Prevalence of *P. vivax* infection

At enrolment. **Prevalence** *P. vivax* by microscopy 0.8% (73/9299), PCR 8.5% (124/145)

At delivery. **Prevalence** *P. vivax* by microscopy 0.4% (20/4461), PCR 6.9% (104/1488)
Prevalence of *P. falciparum* infection

**Enrolment.** Prevalence *P. falciparum* microscopy 1.3% (124/9305), PCR 6.9% (80/1157)

**Delivery.** Prevalence *P. falciparum* microscopy 0.5% (22/4463), PCR 2% (24/1191)
### Malaria infection in the placenta

**P. vivax** infection 0.4% by microscopy, 3.7% by PCR

Histological evaluation: **12.4% of placentas infected** (parasites or pigment)
Incidence of malaria

- Incidence of P. vivax infection 0.072 cases PYAR (passive and active detection)
- The risk of P. vivax infection not associated by parity (p=0.619).
- Unlike with P. falciparum (p<0.005) (IRR ≥ 4 pregnancies, 0.39, [95% CI 0.25–0.62])
Impact of *P. vivax* and *P. falciparum* malaria

- *P. vivax* clinical malaria associated with 5-fold increased risk of anaemia (OR, 5.48) No association with an increased risk of LBW
- No association for *P. vivax* asymptomatic (submicroscopic or microscopic) infection and maternal anaemia or LBW
Study conclusions

• Burden of \textit{P. vivax} malaria is overall low (<2%) across study sites

• Clinical illness due to \textit{P. vivax} was associated with maternal anaemia

• Microscopy, not a sensitive method for routine screening in \textit{P. vivax} endemic areas (generally low densities):
  - PCR methods detected significantly more infections than microscopy. Most infections were submicroscopic
  - Implication for malaria elimination activities

• Results useful for guiding malaria control policies in pregnancy in settings where vivax malaria predominates
In the context of:

• **DECREASING TRANSMISSION** (most recent data prevalence Pv 0.4%, Pf 1.3%)

• Low SENSITIVITY of routine screening methods (microscopy)
  Mostly, submicroscopic

• **MALARIA ELIMINATION** context

Need to **EVALUATE** if current strategies for **MALARIA CONTROL** in pregnant women in low resource settings are **ADEQUATE**

In order to **ESTABLISH**:

• **Clinical and Epidemiological SURVEILLANCE SYSTEMS (M&E)**

• **Tailor INFORMED-BASED RECOMMENDATIONS** according to most recent evidence on malaria risk
Pregnant women as SENTINEL group for MALARIA surveillance

How useful is malaria prevalence (or serology) among pregnant women to track malaria transmission in an area?

Impact of malaria infection

<table>
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<tr>
<th>Year</th>
<th>Maternal Hb</th>
<th>Newborn weight</th>
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<tbody>
<tr>
<td>2003-5</td>
<td>-0.12 g/dL</td>
<td>-44.8 g</td>
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<tr>
<td></td>
<td>95%CI [-0.67; 0.43]</td>
<td>95%CI [-139.1; 49.5]</td>
</tr>
<tr>
<td>2010-12</td>
<td>-0.82 g/dL</td>
<td>-164.5 g</td>
</tr>
<tr>
<td></td>
<td>95%CI[-1.39; -0.25]</td>
<td>95%CI[-289.7;9.4]</td>
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Multivariate analysis adjusted for HIV, parity and age
Thank you!

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