Passive case detection in the control of malaria in pregnancy in low transmission areas in Africa; an meta-analysis of observational studies of the association between fever and malaria infection

A.M. van Eijk, J. Hill, F. ter Kuile

Liverpool School of Tropical Medicine, Liverpool, UK
Malaria in pregnancy

• Predominantly asymptomatic in Africa
  – The presence of symptoms depends on
    • acquired immunity
    • malaria transmission intensity

• Prevention strategies
  – Stable, moderate to high transmission areas
    • Intermittent preventive treatment with sulfadoxine-pyrimethamine
    • ITNs
  – Low transmission areas
    • Passive case detection (case-management of symptomatic women)
    • ITNs
Background

• Passive case detection
  – Assumes IPTp not cost-effective
  – Assumes
    • Most women with malaria develop symptoms
    • Asymptomatic infections represent a small proportions of infections
    • Asymptomatic infections not harmful?

• Recent data from Asia shows
  – Asymptomatic infections are more common than anticipated
  – Asymptomatic infections are harmful
    • Associated with maternal anaemia and LBW (although less strongly than with symptomatic infections)
Research questions

Meta-analysis to assess the relationship between fever in pregnant women and malaria transmission intensity

- Are pregnant women with malaria in low prevalence areas more likely to have fever than pregnant women in areas with higher malaria transmission?
- If pregnant women with malaria in low prevalence areas are more likely to present with fever, does this justify passive case detection?
Methods I

• Studies with useful information in Africa identified through the malaria in pregnancy library
  – http://www.update-software.com/Publications/Malaria/
  – Minimal sample size of 10

• Data extracted
  – Limited to pregnancy, not delivery
  – Prevalence of fever (history of fever, documented fever)
  – Prevalence of malaria (by blood smear)
  – Crosstab fever-malaria if available
Methods II

- Studies matched with malaria transmission intensity indicator for location obtained from the Malaria Atlas Project (MAP: Wellcome Trust/KEMRI, Nairobi, Kenya)
  - Models from surveys in children aged 2-10 years
  - Locations divided into:
    - Low malaria intensity: Mean *Plasmodium falciparum* prevalence (*Pfpr*) among children 2-10 years of age < 5%
    - Medium intensity: *Pfpr* 5-39%
    - High intensity: *Pfpr >39%*

- Data evaluated using SPSS and random effects model (Comprehensive meta-analysis: [http://www.meta-analysis.com/](http://www.meta-analysis.com/))
Studies with information on fever in pregnancy

• Largest “sample size” for documented fever:
  – 45 entries from 25 studies with indicator of transmission intensity
  – Countries: 16
    • (Benin, Burkina Faso, CAR, Ghana, Kenya, Madagascar, Malawi, Mali, Mauritania, Mozambique, Nigeria, Senegal, Somalia, Sudan, Tanzania, Zambia)

– Recruitment
  • ANC 22
  • Community 22
  • Other 1 (study clinic after identification in community)

– Documented fever definition:
  • 40 used 37.4 or 37.5 degrees Celsius or more
Meta-analysis prevalence documented fever, fever in the past week and parasitemia by malaria transmission intensity

Fever and MIP

- Documented fever: 5.3, 2.2, 3.3
- History of fever (past week): 7.9, 24.9
- Parasitemia: 3.5, 19.1, 38.8

No of studies: 14, 16, 15

P = 0.183  
P = 0.04  
P < 0.001
Risk ratio documented fever in parasitemic vs. non-parasitemic women

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<tr>
<th>Study name</th>
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<th>No malaria</th>
<th>Risk ratio</th>
<th>Risk ratio and 95% CI</th>
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</table>

Medium malaria transmission

Summary RR 2.14 (1.68-2.71)

High malaria transmission

Summary RR 0.99 (0.44-1.19)

Overall model:

\[ P = 0.07, \; I^2 = 78\% \]
RR history of fever in past 1 to 2 weeks in parasitemic vs. non-parasitemic women

<table>
<thead>
<tr>
<th>Study name</th>
<th>Fever / Total Malaria</th>
<th>No malaria</th>
<th>Risk ratio</th>
<th>Risk ratio and 95% CI</th>
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\( P < 0.001, I^2 = 79\% \)
So in Africa.....

• Pregnant women in low transmission areas were ≈5 times more likely to report a history of fever when parasitaemic than women in medium and high transmission areas

• Is screening febrile women for malaria a useful strategy to identify women with malaria in low malaria transmission areas?

• Depends on the fraction of infected women that develop fever
Using history of fever between 1 and 2 weeks for case management

• Summary estimates by transmission area for:
  – Prevalence of history of fever (1 – 2 weeks)
  – Malaria among women with fever (1 – 2 weeks)
  – Malaria among women without fever (1 – 2 weeks)

• Applied to a model with 100 pregnant women
Case management for a history of fever (1 – 2 weeks)

Malaria transmission

Low ($Pfpr <5$) (summary estimates based on 3 studies)

- 100 pregnant women
- 7 fever
- 93 no fever
- 16% malaria = 1
- 5% malaria = 4
- Case management detects 20% (1/5)

Medium ($Pfpr 5-39$) (summary estimates based on 6 studies)

- 100 pregnant women
- 23 fever
- 77 no fever
- 22% malaria = 5
- 15% malaria = 12
- Case management detects 29% (5/17)

High ($Pfpr >39$) (summary estimates based on 7 studies)

- 100 pregnant women
- 30 fever
- 70 no fever
- 41% malaria = 12
- 40% malaria = 28
- Case management detects 30% (12/40)

(Assuming microscopy detects 100%)
Comments

- Limited number of studies
- Assuming that malaria test had 100% sensitivity
- Assuming that malaria indicators among children are reliable in categorization of malaria transmission areas
  - Using Newman 2003 a only: 50% cases detected
- Studies in low prevalence areas may be less likely to have workable malaria or fever prevalence (large sample sizes needed)
- Combinations of complaints may be better in detecting malaria in low prevalence areas
  - Documented and history of fever
  - Other complaints such as headache etc
Conclusion

• In low transmission areas pregnant women were 5 times more likely to have a history of fever when parasitaemic compared to other areas

• Passive case detection may only detect ≈ 20-50% of women with active infections in low transmission areas

• Cost-effectiveness of alternative strategies could be considered
  – Intermittent screening of all pregnant women?
  – Intermittent preventive therapy?
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  – Bob Snow
  - Margaret Nagasa, Family-tenderly together, 2003

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  - Margaret Nagasa, Family-tenderly together, 2003