Assessing the association between malaria prevention in pregnancy and risk of low birth weight and neonatal mortality from national survey datasets

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Malaria in Pregnancy: A Solvable Problem
Bringing the Maternal Health and Malaria Communities Together

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Background / rationale

- Meta-analysis showed IPTp with 2 doses SP to have 29% (protective efficacy) PE against low birth weight (LBW) in 1st 2 pregnancies (ter Kuile et al., 2007)

- Meta-analysis showed ITNs to have 23% PE against LBW in 1st 2 pregnancies (Gamble et al., 2009)

- Meta-analysis of malaria prevention in pregnancy (ITNs and/or IPTp) showed a PE of 35% against LBW in 1st 2 pregnancies (Eisele et al., 2011)

- Recent randomized controlled trial showed IPTp to reduce neonatal mortality by 61% (95% CI 7-84%) across all pregnancies (Menendez et al., 2010)

Background / rationale

How well are efficacy estimates from trials translating into effectiveness under routine program conditions?

- E.g. Lim *et al.* (PLoS Med 2011) analysis of association of ITNs with *P. falciparum* parasite prevalence and all-cause 1-59 m mortality from national surveys

Objective

To assess the association of malaria prevention in pregnancy (ITNs and IPTp) with low birth weight (LBW) and neonatal mortality across national survey datasets in Africa since 2000

Study design

- Modified cross-sectional study design used to assess association of exposure to malaria prevention in pregnancy of IPTp and ITNs on birth outcomes from nationally representative household surveys in Africa

- Important innovation in this research is substantial effort made to limit potential confounding bias through exact matching on confounding factors associated with both exposure to malaria prevention in pregnancy and birth outcomes
  - Poisson and logistic regression models then used to account for additional confounding factors
  - Evaluation literature regards a matched cross-section design as quasi-experimental

Data

- Nationally-representative surveys conducted in sub-Saharan Africa after the year 2000
  - Surveys must contain birth history and net roster
  - Surveys were publicly available in 2011

- Birth histories were used to create a retrospective birth cohort for last live birth within 2 years from survey date for each woman surveyed
  - Net roster records information on nets up to 3 years prior to survey date

Definitions of outcomes

LBW among last pregnancy that resulting in a live birth in past 2 years

- LBW derived from weight of child at birth
  - LBW categorized as < 2,500 grams
  - Majority of births born outside health system and not weighed

- Mother's perception of size of child used for children not weighed at birth to limit bias where children born outside health system (not weighed) very different than those that were (weighed)
  - Categorized as "smaller than average" or "very small"
  - Good agreement between measures when both present in the datasets (kappa coefficient = 0·4286, p-value = 0·005)

Definitions of outcomes

Neonatal mortality among last pregnancy that resulting in a live birth in past 2 years

- Birth histories used to determine age of the child in days at the time of death
- Log of person-days used as offset in Poisson models
- Neonatal deaths were those that occurred at 0 months (within 30 days)
  - Did not use 28 days because of threat of date heaping at 1 month
  - Have done sensitivity analyses around this

Exposure to malaria prevention in pregnancy

Primary exposure

- Full malaria prevention in pregnancy defined as:
  - ≥2 doses of SP during pregnancy (IPTp) or
  - ITN household ownership during 6 consecutive months preceding birth
  - Or both

Secondary exposure

- Any malaria prevention during pregnancy defined as ≥1 dose of SP or any possession of ITN during least some of 6 months of pregnancy or both

Comparison group

- No reported malaria prevention in pregnancy at anytime during pregnancy

Exposure to malaria prevention in pregnancy

- Doses of SP derived from mother's self report in ANC questions in women's questionnaire
  - Mothers reporting SP during pregnancy before it was national policy were excluded from the analysis
- ITN household possession and dates of possession derived from net roster (allows going back 3 years prior to survey date)
  - ITN use by pregnant women not measured other than the night before the survey

Analysis

- **Confounding bias** largest threat to validity of this analysis
  - *Women exposed to malaria prevention in pregnancy predisposed to have better birth outcomes*

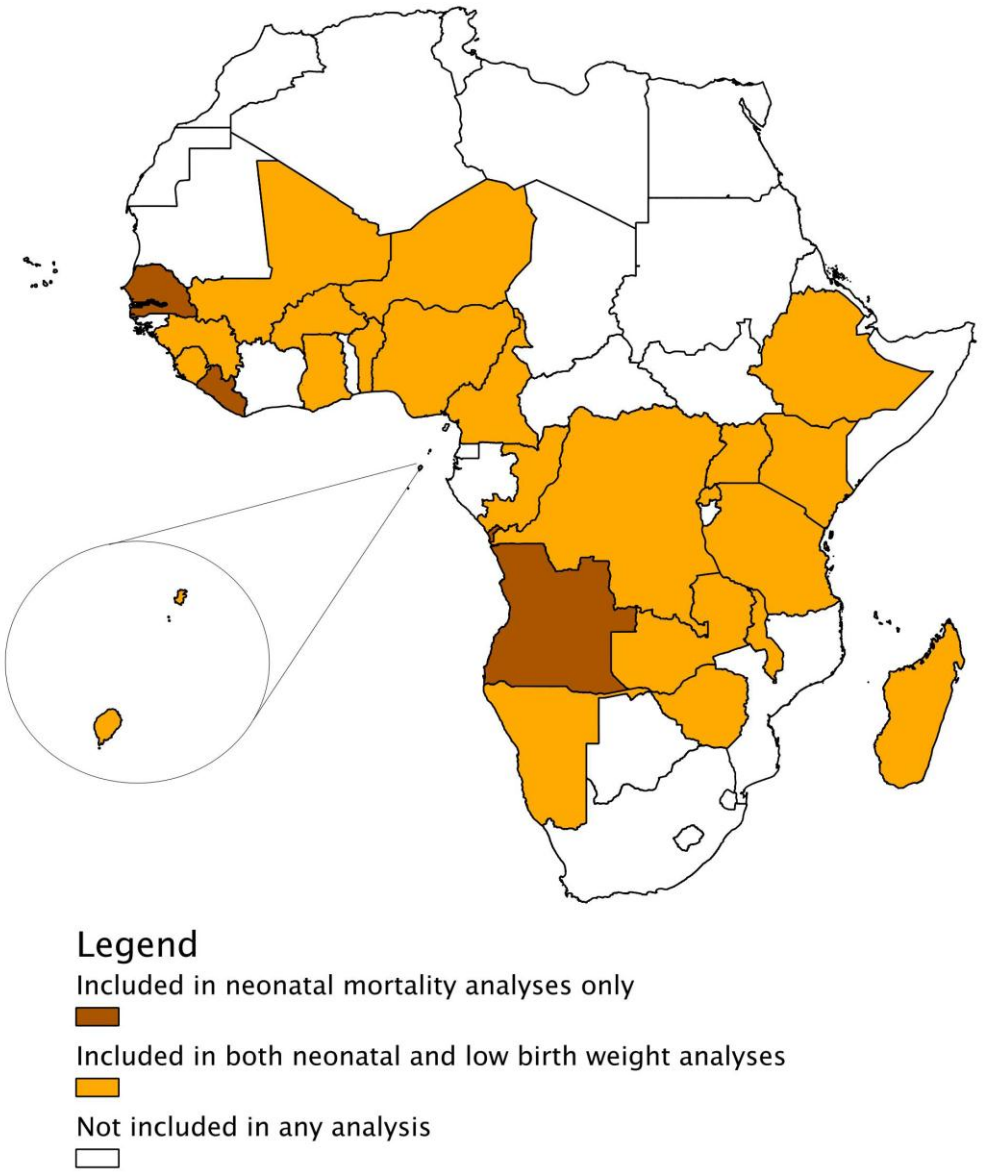
- To help mitigate this-
  - Exact matching used to account for confounding bias (MatchIt package in R)
  - Births matched by covariates through to be associated with exposure to malaria prevention in pregnancy and birth outcomes:
    - Country dataset
    - Wealth quintile (high – low)
    - Mother's education (none – any)
    - 2+ doses of prenatal tetanus vaccine (DHS) or ANC visit (MIS and AIS)]
    - Iron supplementation (DHS) or ANC visit (MIS and AIS)]
    - Urban/rural
    - Malaria transmission (<25% *Pf*PR_{2-10} or ≥25%)

Analysis

- Individual logistic regression model used for LBW
- Individual Poisson regression model used for neonatal mortality
- Matching strata included as random effect in both
- Models also included following covariates
  - Mother's age (<18, 18-35, >35)
  - Birth spacing (firstborn, <24 months, ≥24)
  - Season (quarter)
  - Malaria transmission intensity at PSU level – continuous (*Pf*PR_{2-10} 2007 from MAP)
  - Sex of the child
  - Child twin or triplet
  - Skilled birth attendant present at delivery
- Analyses stratified by first 2 parities (where consequences of malaria in pregnancy concentrated), 3 or more parities, and all parities

Analysis

- 26 survey datasets identified that measured LBW (2003-2010 across 20 countries)- all DHS
  - 114,047 live births after matching
- 32 survey datasets across 23 countries 2003-2010 identified for analysis of neonatal mortality
  - 27 DHS, 4 MIS and 1 AIS
  - 135,266 live births after matchng



Results- LBW

Matched random effects logistic regression for assessing association of full malaria prevention (ITNs and/or IPTp) with measured and perceived small birth size

n=26 datasets; 113,911 live births	AOR (95% CI)	AOR (95% CI)
	Measured LBW	Perceived small birth size
None	Reference	Reference
1st 2 parities	0·824*** (0·739 – 0·917)	0·845*** (0·785 – 0·910)
≥3 parities	0·921 (0·827 - 1·026)	0·843*** (0·791 - 0·897)

*p < 0.05; **p<0.01; ***p<0.001

Results- LBW

Matched random effects logistic regression assessing association of malaria prevention in pregnancy and LBW (composite of measured and perceived small birth size)

n = 26 survey datasets, 114,047 live births	AOR (95% CI) 1st 2 parities	AOR (95% CI) 3+ parities
No malaria prevention in pregnancy	Reference	Reference
ITN ownership during all 6 months of pregnancy preceding birth, with no IPTp	1.020 (0.886 – 1.175)	1.071 (0.963 – 1.191)
IPTp of 2+ doses SP during pregnancy, with no ITNs	0.740*** (0.672 – 0.815)	0.742*** (0.684 – 0.805)
IPTp of 2+ doses SP during pregnancy or ITN ownership during all 6 months preceding birth, or both	0·792*** (0·732 – 0·856)	0·829*** (0·776 - 0·885)

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Results- neonatal mortality

Matched random effects Poisson regression of association of malaria prevention during pregnancy with neonatal mortality

n = 32 survey datasets, 135,266 live births	IRR (95% CI) 1st 2 parities	IRR (95% CI) 3+ parities
No malaria prevention in pregnancy	Reference	Reference
ITN ownership during all 6 months of pregnancy preceding birth, with no IPTp	0.997 (0.728 – 1.366)	0.847 (0.635 – 1.128)
IPTp of 2+ doses SP during pregnancy, with no ITNs	0.798* (0.660 – 0.964)	0.785* (0.669 – 0.922)
IPTp of 2+ doses SP during pregnancy or ITN ownership during all 6 months preceding birth, or both	0.820* (0.698 – 0.962)	0.839* (0.741 – 0.944)

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Discussion: *Take aways*

- Malaria prevention in pregnancy associated with 21% reduction in odds of LBW (1st 2 parities) under routine program conditions across Africa
  - Association [AOR=0.79; 95% CI=0.73 – 0.86) more modest than pooled trial data (RR=0.65; 95% CI=0.55-0.77)
  - Malaria prevention in pregnancy remained protective against LBW in 3rd or higher parities

- Malaria prevention in pregnancy associated with a 18% reduction in risk of neonatal mortality (1st 2 parities) under routine program conditions across Africa
  - Association [AOR=0.82; 95% CI=0.70-0.96] more modest than pooled trial data (RR=0.62; 95% CI: 0.37-1.05)- and much more modest than Menendez trial (RR=0.39; 95% CI: 0.16-0.93)
  - Malaria prevention in pregnancy remained protective against neonatal mortality in 3rd or higher parities

Discussion: *Take aways*

- Effect of ITNs and IPTp alone similar to exposure to both on LBW and neonatal mortality, compared to no exposure
  - No significant interaction of having both over one or the other
  - However- IPTp adds additional protection above ITNs in 1st 2 parities

- Findings support the continued effort to scale-up access of both IPTp and ITNs to pregnant women of all parities in areas of stable malaria transmission

- Results help bolster the 'plausibility' study design of the association of increased malaria prevention interventions with reductions in all-cause child mortality

- Likely still some confounding bias in this type of cross-sectional analysis, but exact matching brings crude point estimates closer to null in nearly all analyses

Thanks

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