Effects of malaria interventions during pregnancy on low birth weight in Malawi

Owen Nkoka, MS[1], Ting-Wu Chuang, PhD[2], Yi-Hua Chen, PhD[3, *]

[1]School of Public Health, College of Public Health, Taipei Medical University, Taipei, Taiwan

[2]Department of Molecular Parasitology and Tropical Diseases, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

[3]School of Public Health, College of Public Health, Taipei Medical University, 250 Wu-Hsing St., Taipei 110, Taiwan

*Address for correspondence: Yi-Hua Chen, Professor

Tel.: 886-2-27361661, ext6528

E-mail: yichen@tmu.edu.tw

Word count: Abstract: 250 words Text: 3000 words; 4 tables; 36 references, 21 pages

Conflict of interests

The authors declare that there are no conflict of interest.

Financial Disclosure

No financial disclosures were reported by the authors of this paper

Abstract

Introduction: In malaria-endemic countries, malaria during pregnancy (MIP) is associated with adverse birth outcomes, including low birth weight (LBW) (i.e., <2.5 kilograms (kg)). However, the effects of the widely promoted and recommended approaches of intermittent preventive treatment for malaria in pregnancy (IPTp) and insecticide-treated nets (ITNs) for pregnant women on LBW have been insufficiently examined. Thus, this analysis investigated the independent and combined effects of IPTp and ITNs on LBW among Malawian children.

Methods: Using pooled datasets from 2004, 2010, and 2015–16 Malawi Demographic and Health Surveys, a total of 18,285 births were analyzed between August and December 2019. Binomial generalized linear regression models with a log-link function were conducted to explore the associations under consideration.

Results: The overall LBW prevalence was 10.3%. LBW was lower in children whose mothers used adequate IPTp [adjusted prevalence ratio (APR) = 0.88, 95% confidence interval (CI) = 0.79–0.99] or used ITNs (APR = 0.89, 95% CI = 0.79–0.99) than their respective counterparts. LBW was 20.0% lower among children whose mothers adequately used both IPTp and ITN compared with those without IPTp or ITN use (APR = 0.80, 95% CI = 0.68–0.93). Iron supplement consumption and survey year were significant effect modifiers on IPTp and LBW relationship.

Conclusions: There were evident benefits of independent and combined use of IPTp and ITN on LBW, thereby supporting the use of these interventions during pregnancy. The reduced protective effects of IPTp over time highlight the need for innovative MIP preventive methods.

Keywords: Insecticide treated nets, intermittent preventive treatment for malaria; low birth weight

Introduction

Low birth weight (LBW) (<2.5 kg) is a major contributor of neonatal and early childhood morbidity and mortality,[1] and later life conditions such as cardiovascular diseases.[2] Globally, the prevalence of LBW is approximately 15.5%, with 96.5% of these cases occurring in developing countries and the highest prevalence reported in sub-Saharan Africa (15%).[3] In malaria-endemic countries, malaria in pregnancy (MIP) is associated with adverse effects on pregnancy outcomes. Approximately 11 million pregnancies were exposed to malaria in 2018, out of which, 872,000 children with LBW were delivered, whereas nearly 100,000 infant deaths are due to malaria-related LBW.[4,5] Based on these associations, guidelines recommend the use of intermittent preventive treatment for malaria in pregnancy using sulfadoxine–pyrimethamine (IPTp-SP) and insecticide-treated nets (ITNs) in malaria-endemic countries to prevent MIP and its consequences.[6,7]

However, only a few studies have examined the independent effects of either IPTp or ITN on LBW.[8] For instance, a randomized trial in Kenya reported the preventive effects of ITN on LBW among children whose mothers had used ITNs.[9] Moreover, limited population-based studies have examined the combined effects of IPTp and ITN on LBW.[10] Additionally, recent studies have raised concerns on the efficacy of IPTp because of the emerging resistance of *Plasmodium falciparum* to IPTp-SP,[10,11] thereby warranting continued monitoring of IPTp efficacy in malaria-endemic countries. Furthermore, although strong links between sociodemographic factors and LBW were reported,[12] there is a paucity of data regarding the moderating effects of these sociodemographics on the relationship between malaria interventions and LBW to identify high risk groups. The identification of effect modifiers is critical for formulating tailored malaria programs and innovative MIP preventive methods to specifically target the high-risk groups. Malawi is a malaria-endemic country and continues to experience high rates of LBW.[13,14] Therefore, the objective of this population-based study was to examine both the independent and combined effects, and the potential effect modifiers on the relationship of IPTp, ITN and LBW in Malawi between 2004 and 2015–16.

Methods

Study design and data source

A pooled analysis of cross-sectional data derived from the Malawi Demographic Health Survey (MDHS) of 2015–16, 2010, and 2004 was conducted. Comprehensive methods used in these surveys are described in detail elsewhere.[13,15,16] Briefly, using a stratified two-stage cluster design, the MDHS recruited a nationally representative sample. Data were collected from women aged 15–49 years through face-to-face interviews to obtain measures of population health and birth histories. The Malawi Health Sciences Research Committee and the International Classification Function under the Demographic and Health Survey program approved the survey. Informed consent for the surveys was obtained from each respondent at the start of each interview.

Overall, birth weight information was available for 33,002 births (under 5 years). The analysis was limited to the youngest child born in the preceding 36 months (to reduce recall on the outcome and main independent variables), singleton births, and births with complete information. The study excluded 7211 children who were not the youngest child, 1550 children who were not singletons, 5578 children aged ≥3 years, and 378 children with missing information. Subsequently, the final sample included 18,285 births for analysis.

Measures

Outcome: The dichotomized outcome variable LBW was defined as low (<2.5 kg) and normal (≥2.5 kg) according to the WHO guidelines.[17] Information on birth weight was based on both written records and mother's recall.[13,15,16]

Main independent variables: IPTp uptake and ITN use during the most recent pregnancy were considered.

The recommendations of IPTp have changed over time. Before 2012, 2 IPTp doses were recommended as the minimum optimal dose. However, concerns were raised about the efficacy of 2 IPTp doses and the recommendation changed to ≥3 IPTp doses.[18] Hence, the definition of adequate IPTp uptake was adapted accordingly. Specifically, for the 2004 and 2010 surveys, IPTp uptake was defined as the uptake of fewer than 2 IPTp doses (low uptake) or the uptake of 2 or more IPTp doses (recommended),[19] whereas for the 2015–16 survey, IPTp uptake was categorized as low uptake (<3 IPTp doses) and recommended uptake (≥3 or more IPTp doses).[18] Accordingly, all women with recommended IPTp uptake, regardless of the survey year, were categorized as having adequate IPTp uptake, whereas those with low uptake were categorized as having inadequate IPTp uptake.

ITN use, a dichotomized (yes/no) variable, was defined as sleeping under an ITN during the night before the survey. Considering the consistency of health behavior patterns, the response (i.e., ITN use or nonuse behavior) to this question was assumed to denote ITN usage during pregnancy period.[20]

Covariates: Based on their importance in the literature,[21] other potential covariates were considered, and they were categorized under the following three themes: *underlying factors*[21] included wealth,[13,15,16] educational level, employment status, residence, region, and survey year; *proximate factors* included body mass index (BMI) [measured as weight in kilograms divided by height in meters squared (kg/m^2) as per the WHO conventional classification, and BMI was categorized into three groups (underweight < 18.5, normal 18.5–24.9, overweight ≥25.0 kg/m^2)], preceding birth interval, number of antenatal care (ANC) visits (those with <4 visits were defined as having inadequate ANC visits while those with ≥ 4 visits were categorized as having adequate ANC visits)[22], iron tablet consumption during previous pregnancy, smoking, use of polluting cooking fuels (those who reported using wood, dung, crop residues, shrubs, coal, charcoal were categorized as using high polluting fuels or otherwise, were regarded as using low polluting fuels)[23], drinking water source (improved water source included piped water into dwelling, piped water to yard/plot, public tap or standpipe, tube well or borehole, protected dug well, protected spring and rainwater, otherwise water source was categorized as unimproved)[24], and access to improved sanitation (improved sanitation included flush toilet, piped sewer system, septic tank, flush/pour flush to pit latrine, ventilated improved pit latrine, pit latrine with slab, and composting toilet, otherwise sanitation was categorized as unimproved)[24]; and *gestational and fetal growth factors* such as age at birth, parity, and sex of the child.

Statistical analysis

All analyses were performed using Stata version 15.0 (Stata Corp LP, College Station, TX, USA). The level of significance was set at $p < 0.05$ (two-tailed). The complex sample design of the surveys was considered, and the "svy" command was used to adjust for cluster effects and weights. Chi-squared tests were employed to assess the distribution of study characteristics based on IPTp uptake, ITN use, and LBW status.

In evaluating the independent effects of IPTp and ITN on LBW, the generalized linear models (GLM) with a log link function and a binomial distribution were used to report the crude and adjusted prevalence ratios (APR) and 95% confidence intervals (CIs). Furthermore, the two variables were combined into the following four groups: (1) adequate IPTp and ITN use (i.e., those who used recommended IPTp doses during pregnancy and those that reported sleeping under an ITN the night before the survey); (2) adequate IPTp and no ITN use; (3) inadequate IPTp and ITN use; and (4) inadequate IPTp and no ITN use. Group 4 was used as the reference group. A two-fold approach was used in model building. First, variables with *p*-value <0.1[25] in the unadjusted model were manually included in the multivariate GLM models using purposeful selection method.[26] Second, based on previous evidence, maternal BMI has been extensively linked to LBW [27,28] and thus, despite lacking significance in the bivariate analysis, it was carried forward for adjustment in the multivariate GLM analysis.

Interaction terms between IPTp or ITN and the sociodemographic factors associated with LBW were examined, and interactions with significant *p*-values ($p < 0.05$) were further

examined in subgroup analysis to assess potential moderation effects. Other non-significant interaction terms were excluded from further analyses.

Sensitivity analyses

Four sensitivity analyses were conducted by; (1) setting the cut-off for adequate IPTp dose as ≥ 2, and ≥ 3, and ≥4, respectively, across all survey waves to assess whether this may affect the results; (2) including only infants to examine the effects of the main independent variables on LBW to minimize recall bias on IPTp/LBW and to ensure the behavioral consistency on ITN usage in a shorter period; (3) including health behavior variables and designing a composite health behavior variable (good, moderate, and poor) from water treatment behaviors in households (yes/no) and the presence of handwashing facilities (yes/no) in 2010 and 2015-16 samples; (4) comparing the results for birth weight obtained by maternal recall vs written records.

Results

Distribution of study characteristics

Overall, 36.6% and 63.4% of birthweight data were collected through written records and mothers' recall, respectively.

Characteristics of the study participants based on the IPTp uptake and ITN use are displayed in Table 1. Overall, the prevalence of IPTp uptake and ITN use for the entire period was similar (i.e., 43.6% and 44.0%, respectively). Adequate IPTp and ITN use was more likely for women from wealthy households and who took iron tablets during the previous pregnancy (all $p < 0.05$). Significant differences were observed in other factors considered in the study based on IPTp uptake and ITN use and are listed in Table 1.

Table 2 presents the distribution of study characteristics according to the LBW status. The overall prevalence of LBW was 10.3%. An increasing trend in LBW rates was observed, with LBW rates of 8.3%, 10.2%, and 11.0% in 2004, 2010, and 2015–16, respectively. Higher proportions of infants with LBW were born to mothers who had inadequate IPTp uptake (11.0%), did not sleep under ITN (11.0%), and who were from poor households (12.2%) among others.

Independent and combined effects of ITN and IPTp on LBW

LBW was 12.0% (APR = 0.88, 95% CI 0.79–0.99) and 11.0% (APR = 0.89, 95% CI 0.79 – 0.99) lower in children whose mothers took an adequate IPTp dose and slept under an ITN, respectively, compared with their respective counterparts (Table 3).

Table 3 further displays the combined effect of IPTp and ITN use during pregnancy on LBW. Children whose mothers had adequate IPTp uptake and did not use ITNs were 15%

less likely (APR = 0.85, 95% CI = 0.74–0.98) to have LBW compared with children having mothers without IPTp or ITN use. Similarly, the prevalence ratio of LBW was lower in children whose mothers only used ITN and did not adequately use IPTp (APR = 0.86, 95% CI = 0.75–0.99) compared with children having mothers without IPTp or ITN use. A more significant effect was observed in the group with combined adequate IPTp uptake and ITN use. Specifically, LBW was 20.0% lower in children whose mothers took adequate IPTp and used ITN (APR = 0.80, 95% CI = 0.68–0.93) compared with those having mothers without IPTp or ITN use.

Subgroup analysis

Significant interactions ($p < 0.05$) between IPTp uptake and other factors were observed; thus, a subgroup analysis was warranted. Notably, the protective effects of adequate IPTp uptake on LBW were observed among children whose mothers reported to have consumed iron supplements (APR = 0.84, 95% CI = 0.74–0.94), and were surveyed in 2004 (APR = 0.61, 95% CI = 0.46–0.82) (Table 4). Finally, the interactions between ITN usage and other investigated factors on LBW were non-significant.

Sensitivity analyses

Results were similar when the cut-off point for adequate IPTp dose was changed to ≥2, ≥3, and ≥4 across all survey waves. Restricting the sample to infants indicated that recall bias on the main independent variables and the outcome was minimal. The influence of using

both malaria interventions remained significant even after additionally controlling for other health behaviors in the model. There were differences in the results in the comparison between written records and mothers' recall of birth weight. Nevertheless, the direction of relationship remained consistent to indicate protective effects of the malaria interventions (all sensitivity analyses results are in the supplement).

Discussion

Based on literature review, this is the first population-based study to examine the association between IPTp, and ITN (independently and jointly) with LBW and the associated moderating factors. Notably, using both IPTp and ITN reduced the likelihood of LBW by 20.0% among Malawian children between 2004 and 2015–16. These two interventions (i.e., IPTp and ITN) also independently exerted preventive effects on LBW. The relationship between IPTp uptake and LBW was moderated by the survey year, and consumption of iron supplements during previous pregnancy.

An overall LBW prevalence of 10.3% was observed between 2004 and 2015–16 among children aged less than 3 years in Malawi. Consistent with reports between 2004 and 2015-16 on LBW among under-fives,[13,15,16] an increasing trend for LBW prevalence was observed from 2004 to 2015–16, although slight differences were observed between 2010 and 2015–16. In Malawi, there have been increased efforts in caring for infants with LBW through the Kangaroo Mother Care (KMC) program. KMC is a practice involving thermal

care through continuous skin-to-skin contact, support for exclusive breastfeeding, and early recognition or response to illness, and it has been reported to have the potential of preventing approximately half of all deaths in infants with LBW.[29] Therefore, the scale-up and continued efforts to improve the components of the KMC program in Malawi over the years have largely helped to increase the survival rate of infants with LBW, such that infants with LBW born in 2015–16 are more likely to have survived than those born in 2004. Nonetheless, LBW is still observed in Malawi; therefore, efforts to reduce LBW should be reinforced; thus, understanding the factors associated with LBW is crucial.

In this study, LBW was lower among children whose mothers had taken adequate IPTp. Walker and colleagues estimated that scaling up IPTp among women with ≥3 ANC visits would prevent an additional 215,000 LBW deliveries in Africa.[30] A 2011 meta-analysis conducted in malaria-endemic countries reported a 26% reduction in LBW owing to the use of IPTp.[31] Optimal IPTp doses have been shown to prevent MIP and maternal anemia.[9] In addition to preventing MIP and maternal anemia, IPTp with SP may improve birth outcomes (especially LBW), as the antimicrobial nature of SP may prevent and clear other pathogens that may deter fetal growth.[32] Earlier studies have demonstrated that infants of mothers with an infected placenta are two times more likely to be born with LBW.[33]

Moreover, this study revealed that children whose mothers used ITNs were also less likely to be born with LBW compared with those whose mothers had not used ITNs. A systematic review reported that ITN use is associated with a 50-g increment in birth weight.[34] The

results further revealed a 20.0% reduction in the likelihood of LBW among children whose mothers had adequate IPTp and ITN use. The use of both IPTp and ITN has been observed to be associated with a favorable effect on the mean hemoglobin levels and is associated with anemia prevention among pregnant women.[9] Malaria-associated anemia may affect oxygen supply to the fetus, thereby contributing to intrauterine growth restriction (IUGR).[35] Moreover, placental malaria has been reported to activate immune responses through the release of antibodies, cytokines, and macrophages, which in turn may stimulate early labor (preterm birth).[36] Independently or jointly, IUGR and premature birth (<37 gestation weeks) are leading causes of LBW. In addition, the adequate use of both IPTp and ITNs may reflect the health behaviors of women related to different health aspects that could influence pregnancy outcomes. Women who use IPTp and ITN are more likely to practice and understand the importance of favorable health behaviors that would eventually improve pregnancy outcomes. Nevertheless, after considering other nonmalaria specific health behaviors in the analysis, the effect of malaria-related health behaviors (IPTp uptake and ITN use) on LBW remained significant. This finding indicates the importance of malaria-related health behaviors (IPTp uptake and ITN use) in addition to other health behaviors and the need to integrate malaria prevention programs with programs aimed at reducing LBW.

Notably, the effects of IPTp on LBW were significant among children whose mothers were surveyed in 2004, and reported consuming iron supplements during pregnancy. Particularly, in the present study, considerable protective effects of SP were observed

among those surveyed in 2004 compared with those sampled in 2010 and 2015–16. This finding is of concern considering that a 2015 Malawian study reported the prevalence of the sextuple A581G mutation in malaria parasites and its negative effect on the efficacy of IPTp with SP.[37] Therefore, in addition to the combined use of IPTp and ITN to maximize protection, new interventions such as malaria vaccines may be vital and should be implemented in the future. Iron supplementation during pregnancy has been shown to reduce incidence of LBW in a randomized trial in Cleveland.[38] Severe maternal anemia increases the risk for premature births and subsequently, LBW. Coupled with the use of malaria interventions, children whose mothers consume iron supplements during pregnancy may receive a relatively greater protection.

Strengths and Limitations

This study used nationally representative samples; hence, the results can be generalized to the Malawian population. Several factors were controlled for, thereby strengthening the associations observed in this study. Several limitations should be noted. First, birth weight was based on both recall and written records. Additionally, the assessment of IPTp uptake during pregnancy was based on recall. Consequently, recall bias is a threat to this analysis and therefore findings should be carefully interpreted. Moreover, limiting the inclusion to the most recent birth and under 3 years would have helped reduce the recall bias. Second, the measure for ITN use was self-reported and was based on the assumption that the reported ITN use (for the night before the survey) may represent the use during pregnancy owing to the consistency of behavioral patterns.[18] However, ITN use reported in the survey

and the ITN use behavior during pregnancy could be different, thereby leading to misclassification. If women started to use ITN after having a baby with LBW (considering the vulnerability of the baby), the findings would be biased towards the null. Besides, self-reporting may lead to social desirability bias. Third, although the KMC program might have increased the survival of LBW babies over time, LBW babies are still at an increased risk of dying compared with normal weight babies.[39] Therefore, those children that might have died due to LBW may have been missed in the current sample and in turn, the results may have been compromised. Nevertheless, the observance of association between the malaria interventions and LBW provides valuable evidence to inform malaria programs. Fourth, causality could not be inferred because of the cross-sectional nature of the data.

Conclusion

The evidence-based findings were observed to affirm the importance of the strengthened and continued implementation of MIP interventions to reduce the incidence of LBW in Malawi. The reduced effects of IPTp on LBW in later survey years underscore the need for innovative MIP preventive methods such as community based scheduled screening and treatment of malaria during pregnancy. Integrating malaria programs with initiatives aimed at reducing the incidence of LBW in Malawi may prove beneficial.

Acknowledgements

We acknowledge the International Classification of Functioning Disability and Health (ICF) for the permission to use the MDHS data set for analysis.

This study did not receive any funding from government or non-governmental agencies.

ON conducted the data analysis, interpreted the data and drafted the manuscript. TWC assisted in the literature review and provided suggestions for manuscript preparation. YHC conceived and designed this study and supervised all critical data analysis and manuscript preparation. All authors have read and approved the manuscript.

No financial disclosures were reported by the authors of this paper.

References

1. Cates JE, Westreich D, Unger HW, et al. Intermittent preventive therapy in pregnancy and incidence of low birth weight in malaria-endemic countries. *Am J Public Health.* 2018;108(3):399-406. https://doi.org/10.2105/AJPH.2017.30425.
2. Smith CJ, Ryckman KK, Barnabei VM, et al. The impact of birth weight on cardiovascular disease risk in the Women's Health Initiative. *Nutr Metab Cardiovasc Dis*. 2016;26(3):239-245. https://doi.org/10.1016/j.numecd.2015.10.015.
3. Blencowe H, Krasevec J, de Onis M, et al. National, regional, and worldwide estimates of low birthweight in 2015, with trends from 2000: a systematic analysis. *Lancet Glob Health*. 2019;7(7):e849-e860. https://doi.org/10.1016/S2214-109X(18)30565-5.
4. Dombrowski JG, de Souza RM, Silva NRM, et al. Malaria during pregnancy and newborn outcome in an unstable transmission area in Brazil: A population-based

record linkage study. *PloS One*. 2018;13(6). https:doi.org/10.1371/journal.pone.0199415.

5. WHO. World malaria report 2019. Geneva: World Health Organization; 2019. https://www.who.int/publications-detail/world-malaria-report-2019. Accessed April 10, 2020.

6. World Health Organisation (2004) A strategic framework for malaria prevention and control during pregnancy in the Africa region. Brazzaville: WHO Regional Office for Africa. https://www.who.int/malaria/publications/atoz/afr_mal_04_01/en/. Accessed April 10, 2020

7. A Agarwal K, Alonso P, Chico RM, et al. Global Call to Action to scale-up coverage of intermittent preventive treatment of malaria in pregnancy: seminar report. *Malar J*. 2015;14:206-206. https://doi.org/10.1186/s12936-015-0730-3.

8. Tongo OO, Orimadegun AE, Akinyinka OO. Utilisation of malaria preventive measures during pregnancy and birth outcomes in Ibadan, Nigeria. *BMC Pregnancy Childbirth*. 2011;11(1):60. https://doi.org/10.1186/1471-2393-11-60.

9. Njagi JK, Magnussen P, Estambale B, Ouma J, Mugo B. Prevention of anaemia in pregnancy using insecticide-treated bednets and sulfadoxine-pyrimethamine in a highly malarious area of Kenya: a randomized controlled trial. *Trans R Soc Trop Med Hyg*. 2003;97(3):277-282. https://doi.org/ 10.1016/s0035-9203(03)90141-6.

10. Kayentao K, Garner P, van Eijk AM, et al. Intermittent preventive therapy for malaria during pregnancy using 2 vs 3 or more doses of sulfadoxine-pyrimethamine

and risk of low birth weight in Africa: systematic review and meta-analysis. *JAMA*. 2013;309(6):594-604. https://doi.org/ 10.1001/jama.2012.216231.

11. Beeson JG, Simpson JA. The potential benefit of scaling up malaria prevention to reduce low birth weight in Africa. *PLOS Medicine*. 2017;14(2):e1002244. https://doi.org/ 10.1371/journal.pmed.1002244.

12. Siyoum M, Melese T. Factors associated with low birth weight among babies born at Hawassa University Comprehensive Specialized Hospital, Hawassa, Ethiopia. *Ital J Pediatr*. 2019;45(1):48-48.

13. National Statistical Office - NSO/Malawi and ICF Macro. 2011. Malawi demographic and health survey 2010. Zomba, Malawi: NSO/Malawi and ICF Macro. https://dhsprogram.com/pubs/pdf/FR247/FR247.pdf. Accessed April 10, 2020.

14. Malawi ministry of health malaria strategic plan 2011–2015 towards Universal Access. National Malaria Control Programme Community Health Sciences Unit. https://endmalaria.org/sites/default/files/malawi2011-2015.pdf. Accessed April 10, 2020.

15. National Statistical Office - NSO/Malawi and ORC Macro. 2005. Malawi demographic and health survey 2004. Calverton, Maryland: NSO/Malawi and ORC Macro. https://www.dhsprogram.com/pubs/pdf/FR175/FR-175-MW04.pdf. Accessed April 10, 2020.

16. National Statistical Office - NSO/Malawi and ICF. 2017. Malawi demographic and health survey 2015-16. Zomba, Malawi: NSO and ICF. https://dhsprogram.com/pubs/pdf/FR319/FR319.pdf. Accessed April 10, 2020.

17. World Health Organization. International statistical classification of diseases and selated health problems. 10th revision. Geneva: World Health Organization; 2004. https://apps.who.int/iris/handle/10665/42980. Accessed April 10, 2020.

18. WHO. Intermittent preventive treatment of malaria in pregnancy using sulfadoxine pyrimethamine (IPTp-SP): updated WHO policy recommendation (October 2012). Geneva: World Health Organization; 2012. https://www.who.int/malaria/publications/atoz/who_iptp_sp_policy_recommendation/en/. Accessed April 10, 2020.

19. WHO. Intermittent preventive treatment of malaria in pregnancy (IPTp) with sulfadoxine–pyrimethamine (SP). Geneva: World Health Organization;2012. https://www.who.int/malaria/publications/atoz/who_iptp_sp_policy_recommendation/en. Accessed April 10, 2020.

20. Mbengue MAS, Bei AK, Mboup A, et al. Factors influencing the use of malaria prevention strategies by women in Senegal: a cross-sectional study. *Malar J*. 2017;16(1):470. https://doi.org/10.1186/s12936-017-2095-2.

21. Singh U, Ueranantasun A, Kuning M. Factors associated with low birth weight in Nepal using multiple imputation. *BMC Pregnancy Childbirth*. 2017;17(1):67. https://doi.org/10.1186/s12884-017-1252-5.

22. WHO. Recommendations on antenatal care for a positive pregnancy experience. Geneva: World Health Organization; 2016. http://apps.who.int/iris/bitstream/10665/250796/1/9789241549912-eng.pdf. Accessed April 10, 2020.

23. Milanzi EB, Namacha NM. Maternal biomass smoke exposure and birth weight in Malawi: Analysis of data from the 2010 Malawi Demographic and Health Survey. *Malawi Med J.* 2017;29(2):160-165.https://doi.org/10.4314/mmj.v29i2.16.

24. World Health Organization (WHO), United Nations Children's Fund (UNICEF). WHO and UNICEF Joint Monitoring Programme (JMP) for water supply and sanitation: types of drinking-water sources and sanitation. Geneva, Switzerland. http://www.wssinfo.org/definitions-methods/watsan-categories/. Accessed April 10, 2020.

25. Natama HM, Rovira-Vallbona E, Sorgho H, et al. Additional screening and treatment of malaria during pregnancy provides further protection against malaria and nonmalarial fevers during the first year of life. *Int J Infect Dis.* 2018;217(12):1967-1976.

26. Bursac Z, Gauss CH, Williams DK, Hosmer DWJScfb, medicine. Purposeful selection of variables in logistic regression. *Source Code Biol Med*. 2008;3(1):17.

27. Caulfield LE, Stoltzfus RJ, Witter FRJAJoPH. Implications of the Institute of Medicine weight gain recommendations for preventing adverse pregnancy outcomes in black and white women. *Am J Public Health***.**1998;88(8):1168-1174.

28. Razak F, Finlay JE, Subramanian SJTL. Maternal underweight and child growth and development. *Lancet*. 2013;381(9867):626-627.

29. Lawn JE, Mwansa-Kambafwile J, Horta BL, Barros FC, Cousens S. 'Kangaroo mother care' to prevent neonatal deaths due to preterm birth complications. *Int J Epidemiol*. 2010;39 Suppl 1:i144-154. https://doi.org/10.1093/ije/dyq031.

30. Walker PGT, Floyd J, Ter Kuile F, Cairns M. Estimated impact on birth weight of scaling up intermittent preventive treatment of malaria in pregnancy given sulphadoxine-pyrimethamine resistance in Africa: A mathematical model. *PLoS medicine.* 2017;14(2):e1002243-e1002243. https://doi.org/10.1371/journal.pmed.1002243.

31. Eisele TP, Larsen DA, Anglewicz PA, et al. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. Lancet Infect Dis. 2012;12(12):942-949. https://doi.org/10.1016/S1473-3099(12)70222-0.

32. White NJ. Intermittent Presumptive Treatment for Malaria. *PloS Medicine.* 2005;2(1):e3. https://doi.org/10.1371/journal.pmed.0020003.

33. Guyatt HL, Snow RW. Malaria in pregnancy as an indirect cause of infant mortality in sub-Saharan Africa. *Trans R Soc Trop Med Hyg*. 2001;95(6):569-576. https://doi.org/ 10.1128/CMR.17.4.760-769.2004.

34. Gamble CL, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No.: CD003755. DOI: 10.1002/14651858.CD003755.pub2.

35. Uneke CJ. Impact of placental *Plasmodium falciparum* malaria on pregnancy and perinatal outcome in sub-Saharan Africa: II: effects of placental malaria on perinatal outcome; malaria and HIV. *Yale J Biol Med.* 2007;80(3):95-103.

36. Sharma L, Shukla G. Placental Malaria: A new insight into the pathophysiology. *Front Med (Lausanne).* 2017;4:117-117. https://doi.org/10.3389/fmed.2017.00117.

37. Gutman J, Kalilani L, Taylor S, et al. The A581G mutation in the gene encoding *Plasmodium falciparum* dihydropteroate synthetase reduces the effectiveness of sulfadoxine-pyrimethamine preventive therapy in Malawian pregnant women. *J Infect Dis.* 2015;211(12):1997-2005. https://doi.org/10.1093/infdis/jiu836.

38. Cogswell ME, Parvanta I, Ickes L, Yip R, Brittenham GM. Iron supplementation during pregnancy, anemia, and birth weight: a randomized controlled trial. *Am J Clin Nutr*. 2003;78(4):773-781.

39. Wardlaw T, You D, Hug L, Amouzou A, Newby HJRh. UNICEF Report: enormous progress in child survival but greater focus on newborns urgently needed. *Reprod Health.* 2014;11(1):82.