# Stillbirths: the hidden burden of malaria in pregnancy

Published Online
September 26, 2017
http://dx.doi.org/10.1016/S2214-109X(17)30378-9

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Globally, most stillbirths are preventable.[1] An estimated 2·6 million third-trimester stillbirths occur annually, and over 90% of these stillbirths result from modifiable medical conditions. Such disorders include chronic non-communicable diseases such as obesity, hypertension, and diabetes; obstetric conditions such as advanced maternal age and post-term pregnancies; and infections such as malaria and syphilis. Given the epidemiology of these factors, stillbirths occur at the highest rates in southern Asia (25·5 per 1000 births) and sub-Saharan Africa (28·7 per 1000 births). Despite this burden, stillbirth was a somewhat neglected tragedy up until the past 5 years in the landscape of maternal and child health,[2] which has more commonly focused on improving neonatal and under-5 survival.[1] With sustained progress towards meeting goals established for these groups, renewed attention has been directed towards the measurement and prevention of stillbirth as a component of the Every Newborn Action Plan (ENAP) from WHO and UNICEF.[3] The ENAP, launched in 2014 and endorsed by 194 member states of the World Health Assembly, named as one of two explicit goals an end to preventable stillbirths by 2035.[3] Although the strategy to achieve this goal is primarily a renewal of focus on improving access to skilled care at birth, the ENAP has deservedly established the prevention of stillbirth on the global health agenda.

Antenatal malaria prevention strategies vary throughout the tropics: in malaria-endemic Africa, programmes are founded on the use of insecticide-treated bednets, intermittent preventive therapy with antimalarials, and effective case management, whereas programmes elsewhere are more varied and use combinations of insecticide-treated bednets with active or passive case detection and case management.[4] Malaria in pregnancy can have devastating consequences for the developing fetus, resulting in preterm delivery and intrauterine-growth retardation, and is believed to be a major contributor to spontaneous abortions and stillbirths. The magnitude of this effect on pregnancy loss has not been well documented, and it is also unclear how this effect might be modified by the intensity of malaria transmission, which determines the extent of acquired protective immunity among pregnant women and thus their risk of complications of antenatal malaria infections.[5]

In *The Lancet Global Health*, Kerryn Moore and colleagues[6] confirm that antenatal malaria is a major cause of stillbirth. The authors did a systematic review and meta-analysis of 59 studies to estimate the contribution to stillbirths of *Plasmodium falciparum* and *P vivax* infections during pregnancy. Their analysis expands our understanding of the previously underestimated burden of the consequences of antenatal malaria, and has implications for Africa and other malaria-endemic regions. First, the study definitively and comprehensively measures the elevated risk of stillbirth conferred by *P falciparum* malaria during pregnancy. Across nearly 20 studies, antenatal infections that were detected and treated increased the odds of stillbirth by 1·47 times, whereas in over 30 studies, infections at delivery in the mother increased the odds of stillbirth by 1·81 times and malaria in the placenta increased the odds of stillbirth by 1·95 times. By calculating population-attributable fractions, the authors estimate that in Africa, where stillbirth and *P falciparum* malaria coexist most commonly, between 132 000 and 221 000 stillbirths per year might result from antenatal *P falciparum* malaria, representing 12% and 20% of all stillbirths in this region. *P vivax* malaria, which is endemic throughout the tropics outside of Africa, was associated with a 2·81 times increased odds for stillbirth, but this association was not significant and based on only three studies.

Another interesting finding reported by Moore and colleagues was that the risk of stillbirth conferred by *P falciparum* malaria is modified by the intensity of malaria transmission. Compared with studies done in moderately-to-highly endemic areas, the malaria-associated increase in stillbirth in low-to-intermediate areas was roughly doubled. Why is this important? As we move towards malaria elimination, protective immunity will wane in populations with pre-existing immunity. These low levels of protective immunity in pregnant women result in more severe clinical manifestations of malaria, including higher densities of placental infections in settings with more sustained levels of transmission.[7] Thus, as infection becomes less common because of decreasing transmission, the clinical severity of those infections, including the risk of stillbirth, might increase. Furthermore, reductions in

protective immunity might shift the burden of malaria in pregnancy more widely across all gravidae rather than being concentrated in first and second pregnancies. For these reasons, malaria is likely to remain an important risk factor for stillbirth in the foreseeable future. Therefore, even in areas where transmission has decreased considerably, protection of pregnant women from malaria will remain crucial.

In the past 15 years, programmes that protect susceptible populations with vector control measures, highly-effective treatment, and targeted prophylaxis have substantially reduced malaria-associated deaths in Africa.[8] However, these new data by Moore and colleagues highlight a hidden burden of malaria mortality, because stillbirths are not captured in standard estimates of infant and under-5 mortality. These data suggest that accelerated progress in perinatal survival rates by reducing stillbirths can be achieved by investment in strategies to enhance the effectiveness and uptake of antenatal malaria prevention, which remain low in many areas.[9] Recognition of this hidden burden of malaria might also provide a previously hidden opportunity to reduce the immiserating burden of stillbirth in malaria-endemic areas.

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We declare no competing interests.



1 Lawn JE, Blencowe H, Waiswa P, et al. Stillbirths: rates, risk factors, and acceleration towards 2030. *Lancet* 2016; **387:** 587–603.
2 Mullan Z, Horton R. Bringing stillbirths out of the shadows. *Lancet* 2011; **377:** 1291–92.
3 WHO, UNICEF. Every newborn: an action plan to end preventable deaths. Geneva: World Health Organization, 2014.
4 Menendez C, D'Alessandro U, ter Kuile FO. Reducing the burden of malaria in pregnancy by preventive strategies. *Lancet Infect Dis* 2007; **7:** 126–35.
5 Desai M, ter Kuile FO, Nosten F, et al. Epidemiology and burden of malaria in pregnancy. *Lancet Infect Dis* 2007; **7:** 93–104.
6 Moore KA, Simpson JA, Scoullar MJL, McGready R, Fowkes FJI. Quantification of the association between malaria in pregnancy and stillbirth: a systematic review and meta-analysis. *Lancet Glob Health* 2017; published online Sept 26. http://dx.doi.org/10.1016/S2214-109X(17)30340-6.
7 Mayor A, Bardaji A, Macete E, et al. Changing trends in *P falciparum* burden, immunity, and disease in pregnancy. *N Engl J Med* 2015; **373:** 1607–17.
8 Gething PW, Casey DC, Weiss DJ, et al. Mapping *Plasmodium falciparum* mortality in Africa between 1990 and 2015. *N Engl J Med* 2016; **375:** 2435–45.
9 van Eijk AM, Hill J, Larsen DA, et al. Coverage of intermittent preventive treatment and insecticide-treated nets for the control of malaria during pregnancy in sub-Saharan Africa: a synthesis and meta-analysis of national survey data, 2009–11. *Lancet Infect Dis* 2013; **13:** 1029–42.