Generating the evidence base for malaria elimination: the situation in Haiti

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Insecticide-treated bed nets (ITNs) are thought to be the key driver of the large reductions in malaria transmission observed over the past 10–15 years.[1] ITNs work particularly well where the local *Anopheles* vectors usually bite indoors late at night, on average halving cases of malaria disease.[2] However, the effect of ITN is less consistently shown in Latin America where some local mosquito vectors often bite outdoors (exophagic behaviour) or earlier in the evening before people go to bed. In *The Lancet Global Health*, Laura Steinhardt and colleagues[3] report the first evaluation of ITN in Haiti, where the goal is to eliminate malaria by 2020.

The ideal way to assess the effect of ITN on malaria transmission, as noted by the authors, is a cluster-randomised controlled trial. However, now that ITNs are a routine intervention against malaria, it is hard to have a control group without nets. In Haiti, such a study would also require an extremely large sample size in view of the low malaria incidence. In the face of these challenges, Steinhardt and colleagues used a case-control study design to measure association between ITN use and positivity for *Plasmodium falciparum* infection in patients with fever at health facilities following a mass distribution of ITNs. They found no significant effect of ITN despite using different indicators of ITN use and a sophisticated set of analyses designed to minimise confounding and bias. The authors conclude that "alternative malaria control strategies should be prioritised" in Haiti.[3]

Although the study is of a high quality given the constraints of the case-control design, we question whether it alone provides sufficient evidence for this policy recommendation. Observational studies of ITNs are notoriously fraught with challenges. Even in settings in which randomised trials show ITN provide good protection, it is not unusual for case-control analyses to find a lack of protection or even ITN use being associated with increased risk of malaria. This counterintuitive finding can happen because people who live in houses more exposed to mosquitoes are more likely to use ITNs, or, when cases are recruited in health facilities, because individuals who have good health-seeking behaviour are more likely to use nets than those who tend to not attend health facilities. What is commendable about the Haiti study[3] is the lengths to which Steinhardt and colleagues went to control for such factors. These efforts included campaigns to encourage anyone with fever to come to free health facilities and a propensity scoring analysis, for which individuals were matched on a range of demographic, health behavioural, and socioeconomic indicators, enabling comparison of people who were similar with respect to many risk factors but not their recent ITN use. Nonetheless, even well conducted observational studies can fail to capture the true effect of interventions. For example, in sub-Saharan Africa where the impact of ITNs has been well established by cluster randomised trials,[2] a multi-country, individually-matched analysis[4] of cross-sectional data found that only two of seven country datasets showed a significant association between ITN use and reduced parasite prevalence, and two showed no reduction at all.

Another complication in areas approaching local elimination such as Haiti is high spatiotemporal variation in transmission.[5] Steinhardt and colleagues made every effort to match malaria exposure in cases and controls by comparing individuals experiencing fever close in time and living in the same commune. Nevertheless, a commune still equates to a relatively large geographical area relative to the focality of malaria transmission.[6] Cases could have also acquired infection outside the local area. The lack of recent entomological data from the study sites on biting times and exophagy of the primary vector, *Anopheleles albimanus*, hampers interpretation of the results. These data gaps are currently being addressed. Historical data suggest that although outdoor biting is more common, a non-negligible proportion of bites occurs indoors.[7] Existence of indoor biting is suggested by the finding in Steinhardt's study[3] that good-quality roofing material on houses (but not other socioeconomic indicators) was protective against malaria. Furthermore, some randomised studies[8] of ITNs in areas where *A albimanus* is the primary vector have shown significant effect, although this effect is not consistent across studies.[9] Steinhardt reported surprisingly low ITN use given the recent mass distribution of ITN and issues around this low use might need further investigation. Such coverage

is probably too low to substantially suppress the vector population, which can be an important component of the impact of ITNs on malaria transmission.[10]

Steinhardt's study emphasises the difficulty of measuring the effect of ITN in low-transmission settings. Nevertheless, the quantification of ITN effect in different settings is essential to inform malaria elimination. Observational studies like this[3] need to be considered together with good-quality local entomological monitoring and evidence from other relevant studies of ITNs. Indeed, ITNs have been shown to be effective in parts of Southeast Asia with exophagic vectors.[2] The Haiti context highlights the absence of a one-size-fits-all solution for malaria control and the difficulties of providing the evidence-base for locally appropriate strategies against diverse vectors.

L C Okell, T S Churcher
MRC Centre for Outbreak Analysis & Modelling, Department of Infectious Disease Epidemiology, Imperial College London, London, UK
l.okell@imperial.ac.uk

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