Burkitt lymphoma (BL), first described by Dennis Burkitt in Uganda in 1958, appears to be associated with intense exposure to *Plasmodium falciparum* infection in areas where the infection is holoendemic, especially in children aged 5 to 10 years. Although *P falciparum* is not considered carcinogenic to humans per se, the geographic association between the incidence of malaria and that of BL suggests that malaria coinfection with Epstein-Barr virus (EBV) may be an indirect risk factor for BL.

While studies suggest that cumulative *P falciparum* infections at the population level and antimalarial antibody titers at the individual level are associated with the incidence of BL, Schmit et al embarked on a 2-step approach to assess whether the use of antimalarial insecticide–treated bed nets (ITNs) could have downstream beneficial effects for reducing the burden of BL. First, they sought to calculate pooled estimates of BL incidence in sub-Saharan African countries where malaria is endemic before and after the large-scale introduction of ITNs using retrievable data and to compare trends in BL incidence over time. Second, they investigated a possible association of mean ITN use at the population level with BL incidence in children and adolescents.

With strict exclusion criteria for cases with confounders and using 2 data sets (13 publications and 10 International Agency for Research on Cancer reports) and 76 location- and time-specific BL incidence rates (1990-2017) from a total of 5226 BL cases, Schmit et al found that the BL incidence rates were estimated to be 44% lower in the period after large-scale ITN introduction. Stratified by country, the pooled BL incidence rates were reduced from 1.4 per 100 000 person-years before to 0.8 per 100 000 person-years after ITN introduction. However, large differences in estimated BL incidence rates were also observed between countries before and after the introduction of ITNs. For example, the estimated incidence of BL in Mali and Malawi before the introduction of ITNs was between 0.1 and 6.0 per 100 000 person-years, while the estimated incidence of BL in Ethiopia and Malawi after the introduction of ITNs was between 0.1 and 8.5 per 100 000 person-years. Schmit et al concluded that the greatest decline in BL incidence (ranging from 71% to 92%) was observed in countries with the highest mean ITN use since 2000, particularly in Maputo, Mozambique, followed by Brazzaville, Congo, and The Gambia.

Since the latency period between malaria exposure and the onset of BL is not known (as children are exposed to both EBV and malaria in the early years) and repeated malaria infections in childhood may increase the risk of BL, Schmit et al hypothesized that ITN use each year would be a poor indicator of BL incidence. Therefore, they used mean ITN use in the population to examine the association with BL incidence. A significant association was observed between the increasing use of ITNs in the population and the decrease in BL incidence in children and adolescents after accounting for potential confounders. In addition, the baseline prevalence of malaria was positively associated with BL incidence.

Bhatt et al studied the association of malaria control with *P falciparum* infection in Africa between 2000 and 2015, finding that the infection incidence decreased by 40% and that ITN interventions made the greatest contribution to preventing 68% of malaria cases. Although there is a reasonable hypothesis that the introduction of ITNs may have indirectly contributed to the reduction in malaria exposure and thus to the reduction in the incidence of BL, no resilient association has been found thus far between the use of ITNs and the incidence of BL, to our knowledge.
As the incidence of BL is higher in countries where malaria is endemic, 1 hypothesis is that most interventions to reduce malaria transmission may affect the incidence of BL. As explained by Schmit et al., interventions such as mass distribution of chloroquine, vector control, the use of bed nets, and indoor spraying with insecticides may have a mixed temporal relationship between intervention exposure and the development of BL. Nevertheless, 3 interventions to reduce the burden of malaria from 2000 onward should be recognized: diagnosis and prompt treatment with artemisinin-based combination therapies (ACTs) and the introduction of ITNs. The World Health Organization (WHO) has been advocating ACTs for the treatment of uncomplicated malaria since 2001, and it is evident that malaria morbidity and mortality decreased by 60% between 2000 and 2019. Thus, the synergistic effects of rapid diagnosis, ACTs, and probably also the use of ITNs since the early 2000s may have contributed to the lower incidence of BL.

Burkitt lymphoma is a monoclonal B-cell cancer, and possible carcinogenic mechanisms during malaria infection have already been well described. The interaction of \textit{P. falciparum} and B cells is considered a key factor. B-cell activation and hypergammaglobulinemia in malaria are well described both experimentally and clinically. Epstein-Barr viremia is also significantly associated with the development of BL\(^8\) and can cause chronic recurrent or reactivating infections. A recent systematic review and meta-analysis also showed that the highest prevalence of EBV infection in patients with BL was found in sub-Saharan Africa at 77\%.\(^9\) The reactivation of EBV may be attributable to \textit{P. falciparum}, as studies have shown that EBV DNA levels were elevated in the plasma of children with malaria compared with those without malaria, suggesting that EBV can reactivate viral replication during malaria episodes.\(^10\)

Schmit et al.\(^5\) used only available data from registries and a small number of publications, mainly from East, southern, and West Africa, while large parts of Central Africa, such as Angola, the Democratic Republic of Congo, Gabon, and the Central African Republic have not been covered. The WHO Roll Back Malaria initiatives also started the distribution and use of ITNs in Central Africa in a similar period. Since EBV also contributes to the development of BL, Schmit et al.\(^5\) could have used incidence of EBV infection from the available registries as data points to see whether reduced incidence of the infection also contributes to reduced BL incidence in populations in regions where malaria is endemic. Since BL is categorized into the clinical types of endemic, sporadic, and immunodeficiency-associated BL, investigation of an association between BL incidence and the use of ITNs among patients with HIV infection could provide additional value. However, populations selected based on specific known risk factors for BL, such as HIV infection, were excluded from their study.

Overall, the results of the study by Schmit et al.\(^5\) support the notion that the use of ITNs in malaria control programs has potential added value in reducing BL incidence and associated burden. More robust studies of other multifactorial interventions, particularly the use of ACTs, could have important implications for the composite of synergistic effects and BL incidence.
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REFERENCES


