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Evaluating the impact of two next-generation long-lasting insecticidal nets on malaria incidence in Uganda: an interrupted time-series analysis using routine health facility data

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ABSTRACT

Introduction Malaria remains a significant public health challenge globally, particularly in sub-Saharan Africa, where progress has stalled in recent years. Long-lasting insecticidal nets (LLINs) are a critical preventive tool against malaria. This study investigated the effectiveness of newer-generation LLINs following a universal coverage campaign in Uganda.

Methods Health facility data collected 36 months prior to LLIN distribution and 24 months after LLIN distribution were used from 64 sites that took part in a cluster-randomised trial comparing two newer-generation LLINs (pyrethroid-piperonyl butoxide and pyrethroid-pyriproxyfen). Using an interrupted time-series approach, we compared observed malaria incidence with counterfactual scenarios if no LLINs were distributed, adjusting for precipitation, vegetation, seasonality and care-seeking behaviour. Analyses were also stratified by LLIN type and study-site level estimates of transmission intensity.

Results Overall, malaria incidence decreased from 827 cases per 1000 person-years in the predistribution period to 538 per 1000 person-years in the postdistribution period. Interrupted time-series analyses estimated a 23% reduction in malaria incidence (incidence rate ratio [IRR]=0.77, 95% CI 0.65 to 0.91) in the first 12 months following distribution relative to what would be expected had no distribution occurred, which was not sustained in the 13–24 month post-distribution period (IRR=0.97, 95% CI 0.75 to 1.28). Findings were similar when stratified by LLIN type. In the first 12 months following distribution, LLIN effectiveness was greater in the high-transmission sites (IRR=0.67, 95% CI 0.54 to 0.86) compared with the medium- (IRR=0.74, 95% CI 0.59 to 0.92) and low-transmission sites (IRR=0.87, 95% CI 0.56 to 1.32).

Conclusion This study demonstrated a modest reduction in malaria incidence following the distribution of newer-generation LLINs that was sustained for only 12 months, highlighting the need for improved strategies to maintain net effectiveness. Adjusting the frequency of universal coverage campaigns based on local malaria transmission intensity may enhance control efforts.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Despite major scale-up of long-lasting insecticidal nets (LLINs) across malaria-endemic areas, progress at reducing malaria burden has slowed, likely due to waning effectiveness of LLINs. While there is ample evidence that newer-generation LLINs are more effective than traditional pyrethroid LLINs, less epidemiological evidence exists on their real-world longitudinal impact on malaria cases averted.

WHAT THIS STUDY ADDS

⇒ We leverage data from a cluster-randomised trial comparing two newer-generation LLINs (pyrethroid-piperonyl butoxide and pyrethroid-pyriproxyfen) to estimate a counterfactual trend of malaria incidence over 24 months if LLINs had not been distributed and determine the impact of LLINs over time. We find that malaria incidence was reduced in the first year after nets were distributed, with no detectable impact after that.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings from this study underscore the need for improved strategies to maintain net effectiveness and suggest that adjusting the frequency of universal coverage campaigns based on local malaria transmission intensity may be warranted.

BACKGROUND

Major efforts towards malaria control in sub-Saharan Africa have been met with success, resulting in a 44% reduction in malaria incidence from 2000 to 2019.[1 2] Much of this

success has been attributed to the scale-up of long-lasting insecticidal nets (LLINs). Access to LLINs in sub-Saharan Africa has increased markedly in the past two decades, from 5% of households with at least one net in 2000 to 70% in 2022,[2] with many countries in sub-Saharan Africa now distributing LLINs free of charge in universal coverage campaigns (UCCs), typically conducted every 3 years. Recently, however, progress towards reducing malaria burden has stalled and even reversed course in some high-burden African countries.[2] Waning effectiveness of LLINs due to the spread of pyrethroid resistance, changing vector behaviours, poor net adherence and net attrition are likely contributing to this recent reversal in progress.[3–6] Widespread resistance to pyrethroid insecticides has led to the development and distribution of newer-generation nets, including those that combine pyrethroids with piperonyl butoxide (PBO), a pyrethroid synergist, or with different insecticides such as pyriproxyfen, an insect growth inhibitor.

Cluster-randomised controlled trials (CRTs) are considered the optimal method for comparing the efficacy and effectiveness of different LLINs and shaping policy recommendations. While there is ample evidence that newer-generation nets are more effective than traditional pyrethroid LLINs,[7] less epidemiological evidence of the real-world longitudinal impact of newer-generation nets on malaria burden (eg, cases averted over time) is available. Such evidence is essential for understanding the dynamics of malaria after LLINs are distributed, deciding on the duration between LLIN distribution campaigns, and estimating the cost-effectiveness of LLINs. The most rigorous method for quantifying the impact of LLIN distribution would be a CRT including an arm without LLIN distribution. However, such a study design would be unethical given the known benefits of LLINs, and therefore alternative study designs and analytical strategies are needed.

Uganda is one of the high malaria-burden countries in sub-Saharan Africa where progress has reversed in recent years. Coverage of LLINs in Uganda is the highest globally[8] due to repeated UCCs conducted approximately every 3 years by the Ministry of Health (MoH) since 2013. Nevertheless, malaria burden remains high, and between 2018 and 2022, reported annual malaria cases increased by 1.7 million from 10.9 million to 12.6 million.[2] Widespread resistance to pyrethroid insecticides across Uganda has led to the distribution of newer-generation LLINs, including pyrethroid-PBO and pyrethroid-pyriproxyfen LLINs. A CRT was embedded into the 2020–2021 UCC to compare these two newer-generation nets across 64 sites. In this trial, there were no significant differences between the two LLINs on the incidence of malaria among community members of all ages or parasite prevalence among children 2–10 years of age, over 24 months following LLIN distribution.[9] However, these results did not include estimates of the overall impact of LLIN distribution on malaria incidence over time. By leveraging interrupted time-series (ITS) methodologies,[10 11] we used up to 36 months of data prior to LLIN distribution to estimate a counterfactual trend of malaria incidence over 24 months if LLINs had not been distributed. We then compared observed malaria incidence to counterfactual incidence to generate effect estimates for the impact of LLINs over the 24 months post distribution, aiming to improve our understanding of the real-world effectiveness of newer-generation LLINs on malaria burden over time.

METHODS

Data source

This study leveraged data from a network of health facility surveillance sites established in 2006 through collaboration between the MoH/National Malaria Control Division and Uganda Malaria Surveillance Program (UMSP).[12] The Ugandan public health system is decentralised and is comprised of seven levels of care, ranging from village-based community health workers to national referral hospitals. A 2024 study found that, while diagnosis and treatment of malaria in the Ugandan public sector should theoretically be free, patients spent on average US$10.10 to diagnose and treat suspected malaria at public health facilities.[13] UMSP operates within selected level III/IV health facilities across Uganda that serve approximately 20 000 people, referred to as Malaria Reference Centers (MRCs). At each MRC, individual-level patient data are entered into an electronic database using a standardised register form. Patient information includes demographics (age, sex and village/parish of residence), whether malaria was suspected, malaria laboratory testing results (either rapid diagnostic test (RDT) or microscopy), diagnoses and treatments prescribed. UMSP supports health facilities to ensure high-quality data, including training, supervision and adequate stocks of laboratory supplies. This study used data from 64 MRCs included in a CRT assessing the impact of two newer-generation LLINs on malaria incidence.[9] We included 36 months of data pre-2020–2021 LLIN distribution (baseline) and 24 months of data post-LLIN distribution; if a site had less than 36 months of baseline data available, we included the maximum amount available (see online supplemental table 1 for the number of months contributed by each site). Given the variable contribution of each site to the baseline period and the fact that nets were also distributed in 2017–2018, we conducted a sensitivity analysis to determine whether limiting the baseline period to 24 and 12 months pre-LLIN distribution impacted the results. Furthermore, we ran an additional sensitivity analysis excluding any site with less than 6 months of baseline data.

Study setting and long-lasting insecticide-treated net distribution

Details of the parent CRT have been previously reported.[9] Briefly, in 2020–2021, the Ugandan MoH implemented a UCC, distributing LLINs free-of-charge across the

country. An estimated 27 789 044 LLINs were distributed to 11 287 392 households, achieving 94% coverage of households receiving at least one net.[14 15] As part of this campaign, a CRT (LLINEUP2) designed to evaluate the impact of two different LLINs, pyrethroid-PBO LLINs (PermaNet 3.0) and pyrethroid-pyriproxyfen LLINs (Royal Guard), was carried out. 32 districts with high malaria burden not receiving indoor residual spraying (IRS) and selected by the Uganda National Malaria Control Division to receive pyrethroid-PBO LLINs were included in the trial (figure 1).

A total of 64 clusters located within these 32 districts (two per district) were randomised to receive either pyrethroid-PBO or pyrethroid-pyriproxyfen LLINs. A 'fried egg' approach was used to measure the impact of the LLINs within the clusters, with the 'white' defined as subcounties receiving LLINs, and the 'yolk' as geographically smaller, prespecified target areas around MRCs, where outcomes were measured. In total, 1 329 273 LLINs were allocated for distribution to these, including 632 359 pyrethroid-pyriproxyfen LLINs and 696 914 pyrethroid-PBO LLINs. LLINs were delivered to these subcounties by the Ugandan MoH and partners, adhering to this randomisation scheme.

Measures

The outcome measure for this analysis was monthly malaria incidence in MRC target areas.[16] Target areas were defined as a group of one or more villages around each MRC, based on the assumption that most patients living within this area with malaria would seek care at the MRC. To validate this assumption, we conducted cross-sectional surveys in randomly selected households from November 2021 to March 2022. Of those who were treated for malaria in the last six months, 81% went to the MRC. Villages were included if they met the following criteria: (1) did not contain another public health facility, (2) were in the same subcounty as the MRC and (3) had similar malaria incidence to the village where the MRC is located. Populations of the MRC target areas were determined during enumeration surveys conducted 12 months after the LLIN distribution. The numerator for monthly incidence estimates within target areas was defined as the monthly count of laboratory-confirmed malaria cases among patients residing in the target area (adjusted for target area residents with suspected malaria who did not undergo laboratory testing (assuming that the test positivity rate for those not tested is the same for those tested), and for patients with confirmed malaria whose village of residence was unknown (assuming that the proportion of patients residing in the catchment area is the same among those with village missing as it is for those with village not missing)). The denominator was defined as the population of the target areas estimated during enumeration surveys, with a constant growth factor of 0.29% per month.[17]

We adjusted for time-varying variables that impact malaria burden and case detection. These include target area-level monthly precipitation lagged by 1 month,[18] enhanced vegetation index,[19] an indicator variable for calendar month (to account for seasonality) and a monthly count of patients not suspected of having malaria visiting the MRC from the target area (to adjust for care-seeking behaviours over time).

Statistical analysis

An ITS segmented regression approach was taken to estimate the impact of the LLIN distribution on malaria incidence over a 24-month period. The following segmented regression model was estimated:

$$Y_{ct} = \beta_0 + \beta_1 T + \beta_2 X_{ct} + \beta_3 T X_{ct} + \beta_4 R_{ct}$$

where Y_{ct} is the outcome (malaria incidence) in cluster c at time t, T is the time elapsed since the start of the study in months, X_{ct} is a dummy variable indicating the pre-LLIN distribution period (0) or postintervention period (1) for cluster c at time t, and R_{ct} is the vector of covariates for cluster c at time t. β_0 represents the baseline outcome level at the start of the study (t=0), β_1 represents the change in outcome associated with a 1-month increase in the pre-LLIN period, β_2 represents the level change in the outcome after the LLIN distribution, and β_3 represents the additional change in the slope after the LLIN distribution. Poisson regression using a generalised estimating equation was used to model the count of malaria cases in cluster c at month t, with an offset of the logged population denominator. We included an autoregressive order of 1 correlation structure to account for autocorrelation over time at the cluster level. The resulting ITS model was used to estimate the counterfactual (unobserved) trend of malaria incidence in the absence of the LLIN distribution for each month by setting X_{ct} to zero. Incidence rate ratios were calculated by comparing the observed incidence to the counterfactual incidence, with bootstrapped 95% CIs.

Our primary analysis estimated the impact of the LLIN distribution pooled across study arms. A secondary analysis allowed the slope change to differ by LLIN arm by including a three-way interaction term to determine whether the impact of the LLIN distribution differed by net type. We conducted an additional analysis with a three-way interaction term including a categorical variable for baseline incidence to estimate whether the impact of the LLINs differed across transmission intensities. Baseline incidence was defined by dividing the sites into quartiles and categorising them into low (100–412 per 1000 person-years (PY)), medium (412–765 per 1000 PY) and high (765–2440 per 1000 PY, the upper two quartiles).

Reflexivity

The research team included early career and senior researchers from both the Global North and Global South. A structured reflexivity statement can be found in online supplemental appendix S1.

RESULTS

Across the 64 sites included in the analysis, a total of 3 565 639 outpatient visits were recorded over the study

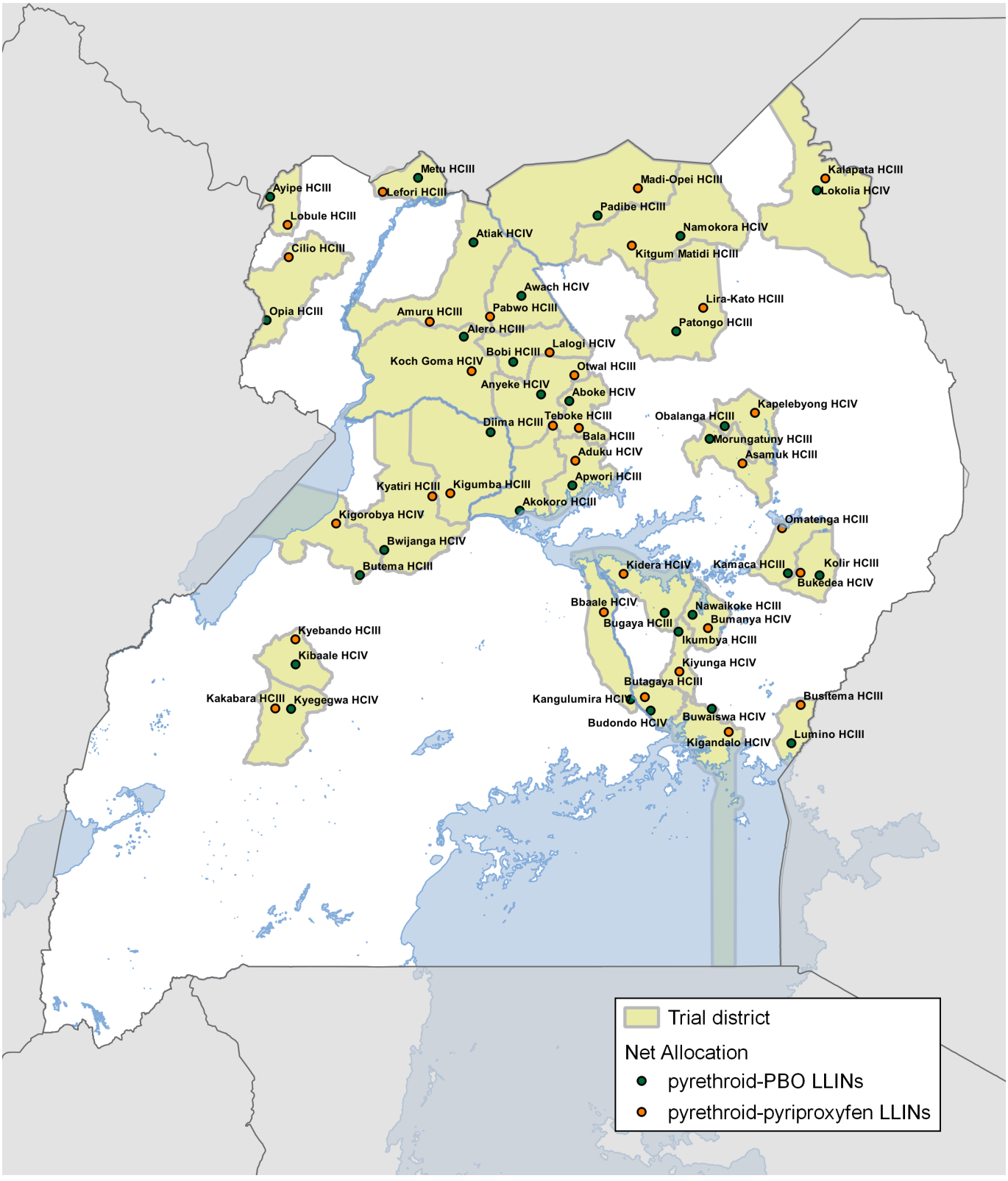

Figure 1 Map of 64 Malaria Reference Centers and their net allocations. LLINs, long-lasting insecticidal nets; PBO, piperonyl butoxide.

period; 1 505 974 in the pre-LLIN distribution period and 2 059 665 in the post-LLIN distribution period. Of these visits, 822 835 were observed within the pyrethroid-PBO arm and 683 139 within the pyrethroid-pyriproxyfen arm in the predistribution period and 997 735 and 1 061 930, respectively, in the postdistribution period (table 1, with greater detail in online supplemental table 2). Of the 2 558 784 patients suspected of having malaria across the

Table 1 Descriptive statistics over the study period

Strata	Number of sites	Time period	Number of months, median (range)	Visits with malaria suspected (% total visits)	Diagnostic test performed (% with suspected malaria)	Laboratory-confirmed malaria (% tested for malaria)	Laboratory-confirmed malaria within target area, adjusted*	Malaria incidence within target area (per 1000 person-years)
All sites								
	64	Pre-LLIN distribution	12 (2–36)	1 084 694 (72)	1 079 267 (100)	67,3011 (62)	163 784	827
		Post-LLIN distribution	24 (24–24)	1 474 090 (72)	1 465 889 (99)	80,2870 (55)	189 486	538
Stratified by net type								
Pyrethroid-PBO	32	Pre-LLIN distribution	13 (4–36)	590 747 (71)	586 971 (99)	36,4421 (62)	95 340	769
		Post-LLIN distribution	24 (24–24)	701 861 (70)	697 064 (99)	37,7286 (54)	98 907	501
Pyrethroid-pyriproxyfen	32	Pre-LLIN distribution	11 (2–27)	493 947 (72)	492 296 (100)	30,8590 (67)	68,445	896
		Post-LLIN distribution	24 (24–24)	772 229 (73)	768 825 (100)	42,5584 (55)	90 579	576
Stratified by baseline transmission								
Low transmission	16	Pre-LLIN distribution	11 (2–29)	272 386 (62)	270 256 (99)	146 297 (54)	28 795	434
		Post-LLIN distribution	24 (24–24)	407 526 (60)	406 226 (100)	194 506 (47)	33 260	270
Medium transmission	16	Pre-LLIN distribution	12 (8–25)	413 238 (73)	411 151 (100)	263 870 (64)	63 498	774
		Post-LLIN distribution	24 (24–24)	548 078 (77)	545 064 (100)	314 312 (57)	71 831	556
High transmission	32	Pre-LLIN distribution	11 (3–36)	399 070 (79)	397 860 (100)	262 844 (66)	71 492	1261
		Post-LLIN distribution	24 (24–24)	518 486 (77)	514 599 (99)	294 052 (57)	84 395	778

*Adjusted for testing rate and missingness of village.
LLIN, long-lasting insecticidal net; PBO, piperonyl butoxide.

study period, 2 545 156 (99.5%) received a laboratory test for malaria, implying a 0.5% clinical diagnosis rate. Among those tested, 2 097 965 (82.0%) were diagnosed with RDTs, with the remaining diagnosed via microscopy. During the study period, missingness of patients' villages of residence was low (4.2%).

Malaria incidence within target areas averaged 827 cases per 1000 PY in the predistribution period and 538 per 1000 PY in the postdistribution period across all sites. Predistribution incidence was 769 cases per 1000 PY in the pyrethroid-PBO arm and 896 per 1000 PY in the pyrethroid-pyriproxyfen arm; these figures declined to 501 per 1000 PY and 576 per 1000 PY in the postdistribution period, respectively. A total of 16 sites were classified as low transmission, 16 sites as medium transmission and 32 as high transmission. In low-transmission sites, malaria incidence in target areas averaged 434 per 1000 PY in the predistribution period and 270 per 1000 PY in the postdistribution period. These figures were 774 per 1000 PY and 556 per 1000 PY in medium-transmission sites and 1261 per 1000 PY and 778 per 1000 PY in high-transmission sites, respectively.

Results from the ITS analysis comparing observed and counterfactual malaria incidence pooled across all sites in the 24 months after the LLIN distribution are shown in figure 2 and table 2. In the first 12 months after the distribution, observed malaria incidence was 23% lower than counterfactual incidence under the conditions of no LLIN distribution (IRR=0.77, 95% CI 0.65 to 0.91, table 2). In months 13–24 post distribution, observed malaria incidence was 3% lower than the counterfactual, but we could not rule out a null or positive association (IRR=0.97, 95% CI 0.75 to 1.28). These results were unchanged when varying the baseline period to 12 and 24 months (online supplemental figures 1 and 2), and when excluding the four sites with less than 6 months of baseline data (online supplemental figure 3).

Results stratified by LLIN type are shown in figure 3 and table 2. We detected no difference in the post-LLIN distribution change in slope between net types (three-way

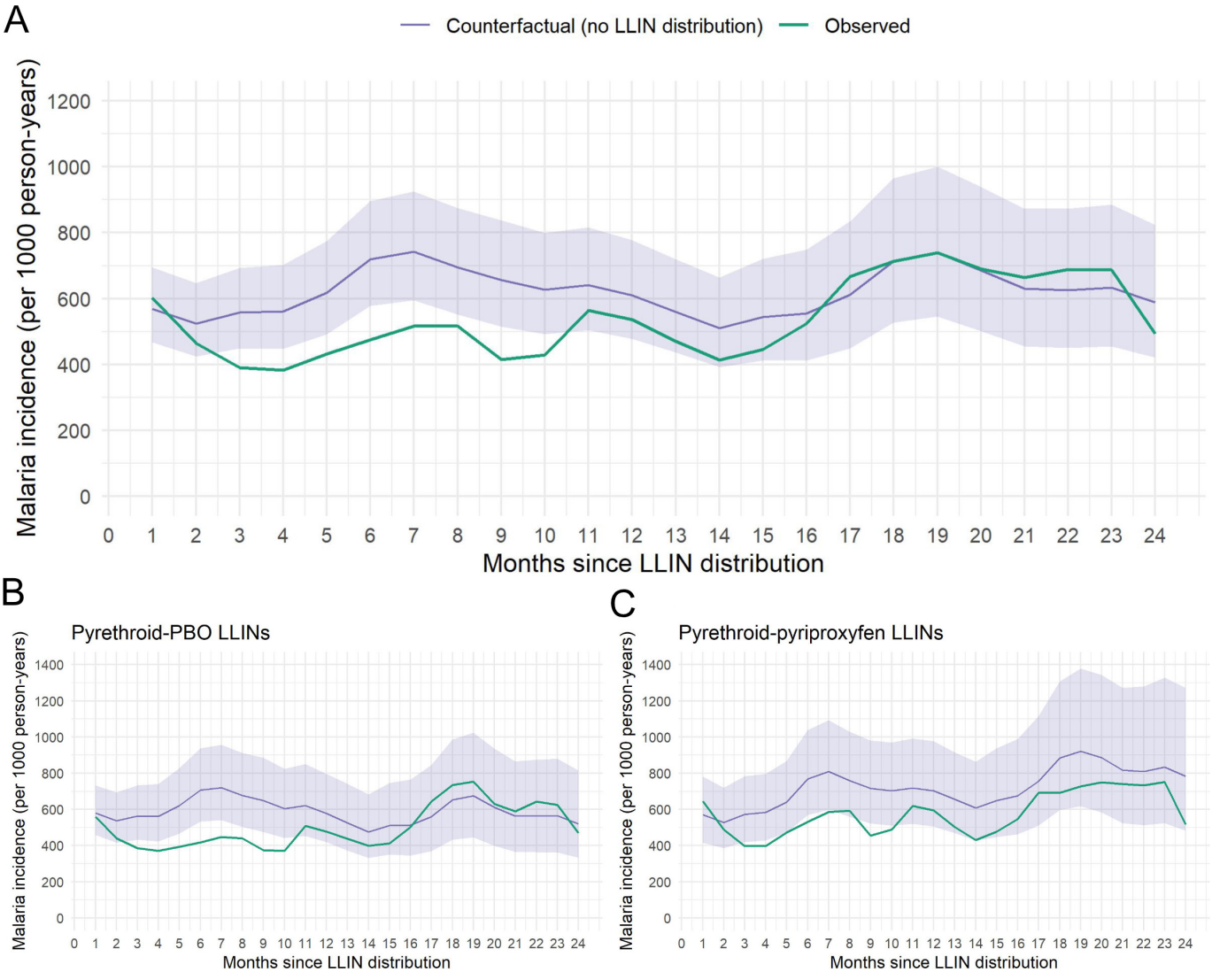

Figure 2 Observed and modelled counterfactual monthly malaria incidence over the 24 months after the long-lasting insecticidal net (LLIN) distribution (A) overall and (B/C) stratified by net type. PBO, piperonyl butoxide.

Table 2 Incidence rate ratios comparing observed malaria incidence to counterfactual malaria incidence modelled using interrupted time-series methods

Strata	Pre-LLIN distribution IRR (95% CI)	Months 1–12 post-LLIN distribution IRR (95% CI)	Months 13–24 post-LLIN distribution IRR (95% CI)
All sites			
	1.06 (0.89 to 1.34)	0.77 (0.65 to 0.91)	0.97 (0.75 to 1.28)
Stratified by net type			
Pyrethroid-PBO	0.91 (0.79 to 1.08)	0.71 (0.58 to 0.88)	1.01 (0.74 to 1.53)
Pyrethroid-pyriproxyfen	1.52 (0.97 to 2.19)	0.78 (0.62 to 0.98)	0.81 (0.54 to 1.53)
Stratified by baseline transmission			
Low transmission	1.32 (0.89 to 1.75)	0.87 (0.56 to 1.32)	1.69 (0.76 to 4.08)
Medium transmission	0.98 (0.85 to 1.15)	0.74 (0.59 to 0.92)	0.93 (0.65 to 1.46)
High transmission	1.22 (0.93 to 1.57)	0.67 (0.54 to 0.86)	0.73 (0.50 to 1.12)

LLIN, long-lasting insecticidal net; PBO, piperonyl butoxide.

p-value=0.18). In the first 12 months after the LLIN distribution, malaria incidence was 29% lower (IRR=0.71, 95% CI 0.58 to 0.88) in the pyrethroid-PBO arm and 22% lower (IRR=0.78, 95% CI 0.62 to 0.98) in the pyrethroid-pyriproxyfen arm comparing observed to counterfactual incidence. From months 13 to 24 post distribution, these effect estimates were attenuated and no significant difference was observed for the pyrethroid-PBO arm (IRR=1.01, 95% CI 0.74 to 1.53) nor for the pyrethroid-pyriproxyfen arm (IRR=0.81, 95% CI 0.54 to 1.53).

Results stratified by transmission intensity are shown in figure 3 and table 2. We detected a significant difference in the post-LLIN distribution change in slope between net types (joint three-way p-value=0.0004). In the first 12

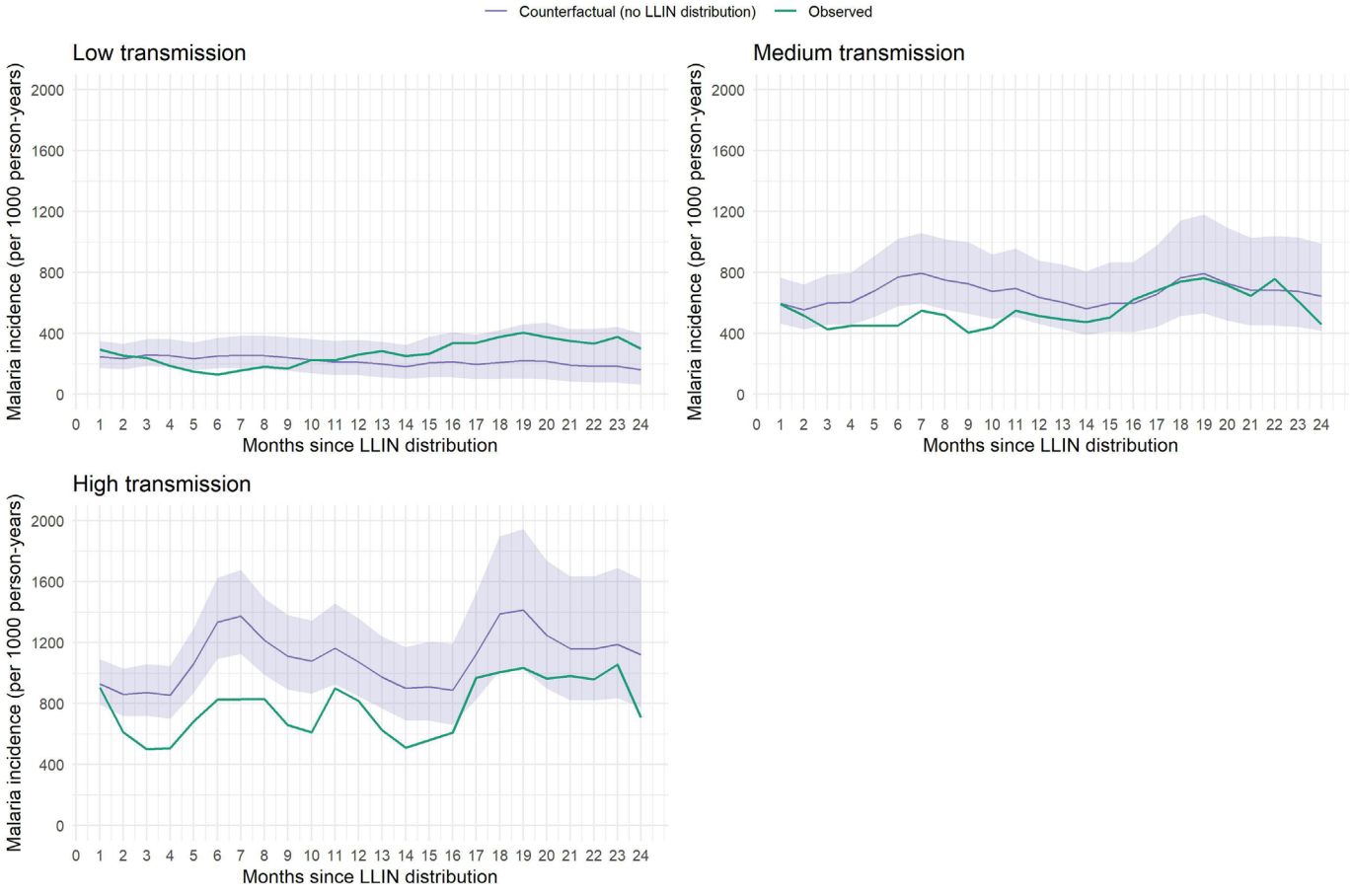

Figure 3 Observed and modeled counterfactual monthly malaria incidence over the 24 months after the long-lasting insecticidal net (LLIN) distribution, stratified by baseline malaria incidence.

months post distribution, we did not observe a significant difference in malaria incidence in low-transmission sites (IRR=0.87, 95% CI 0.56 to 1.32). We did, however, observe a 26% reduction in medium-transmission sites (IRR=0.74, 95% CI 0.59 to 0.92) and a 33% reduction in high-transmission sites (IRR=0.67, 95% CI 0.54 to 0.86). In months 13–24 post distribution, we did not observe a significant difference between observed and counterfactual malaria incidence in low-transmission sites (IRR=1.69, 95% CI 0.76 to 4.08), medium-transmission sites (IRR=0.93, 95% CI 0.65 to 1.46), nor in high-transmission sites (IRR=0.73, 95% CI 0.50 to 1.12), though we continued to observe a gradient of effectiveness by transmission intensity similar to that observed in the first year.

DISCUSSION

In this analysis, we used community-level malaria incidence data from a CRT to estimate the longitudinal impact of an LLIN UCC using newer-generation nets in Uganda. Our findings suggest that, in this setting, LLINs reduced malaria incidence by 23% in the first year after the UCC, after which effectiveness waned to undetectable levels through the second year post distribution. These findings were consistent across the two newer-generation net types distributed (pyrethroid-PBO and pyrethroid-pyriproxyfen), with similar effect sizes.

These findings point to a relatively modest and short-lived effectiveness of LLINs in this setting compared with what is generally expected of nets. The present study estimated the effectiveness of LLINs distributed in a 'real-world' setting, which may account for its more modest effect estimates compared with rigorously conducted CRTs that included control arms (ie, no bed nets).[20] However, such 'placebo-controlled CRTs' were conducted decades ago and the true effectiveness of bed nets may have waned over time. Other observational studies aimed at capturing LLIN effectiveness in 'real-world' settings have found similar results to this study. In observational studies comparing malaria burden pre- and post-UCC in Burundi and Madagascar, LLINs were associated with modest declines in malaria in the first year post UCC, but these declines were no longer detectable in years 2–3 post distribution.[21 22] In Rwanda, PBO nets continued to be effective in the second year post UCC, but standard nets did not.[23] In Malawi, a UCC of PBO and standard pyrethroid-treated nets was associated with reductions in malaria incidence in only the first malaria season post distribution, but not the second.[24]

Multiple factors may have contributed to the relatively modest impact and waning effectiveness of LLINs observed a year after LLIN distribution. First, the number of LLINs distributed during the UCC may have been inadequate, especially as this campaign was carried out during the early years of the COVID-19 pandemic. A 2023 analysis found that household coverage of the 2020–2021 UCC was high (94.1%).[14] However, although immediate postdistribution data were not available at all the sites, cross-sectional surveys were conducted at 12 of the sites 1–4 months post distribution as part of a separate study and revealed that only 60% of households reported adequate LLIN ownership (defined as at least one LLIN per two household members).[25] Second, post-distribution coverage studies in many settings have found that retention and use of nets are imperfect and reduce over time following distribution.[26–28] Indeed, findings from cross-sectional surveys conducted 12 and 24 months after the LLINEUP2 distribution found that adequate LLIN ownership dropped from 58% to 40%, and use (self-report of household residents sleeping under an LLIN the previous night) fell from 75% to 63%. Third, physical net integrity also degrades over time.[26–31] Findings from a trial nested within the previous 2017–2018 Ugandan UCC that included pyrethroid-PBO LLINs found that nets experienced an average 80% increase in holed area from 12 to 25 months post distribution.[32] An additional trial in Tanzania found that the functional survivorship of pyrethroid-pyriproxyfen nets was 1.9 years, with only 8.6% in serviceable condition by 36 months.[33] While holes found on nets may not markedly reduce the community effect of LLINs against mosquito populations, they may reduce personal protection from bites.[34] Furthermore, research suggests that perception of physical integrity is a primary driver for household net retention.[35] Fourth, reductions in net bioefficacy likely contributed to the observed waning. In previous CRTs in Uganda[32] and Kenya,[36] pyrethroid-PBO LLINs experienced steep reductions in bioefficacy in the second and third years, respectively, after distribution. While pyrethroid-pyriproxyfen LLINs have demonstrated high bioefficacy in laboratory and experimental hut studies,[37] little is known about the longitudinal bioefficacy of these nets in 'real-world' settings; trials in Tanzania and Benin are ongoing.[38 39] Disentangling the primary causes of declining LLIN effectiveness after a UCC is essential for designing interventions that improve their longevity. A 2020 modelling study that included data from seven trials of both conventional and pyrethroid-PBO nets found that non-use had a larger effect on LLIN impact compared with physical or chemical integrity.[6] More research is needed, including qualitative studies, to better understand factors contributing to changes in LLIN effectiveness over time.

We found no difference in the longitudinal impact of LLINs by net type. These findings reaffirm the results of the LLINEUP2 trial, which found no significant difference in 24-month malaria incidence.[9] We did, however, find that LLIN effectiveness differed by baseline transmission intensity, such that nets had greater impact in areas with higher baseline malaria incidence, with some additional evidence that effectiveness lasted longer in these areas. This finding echoes observational cohort data from sites with differing transmission intensity in Uganda.[40] These results are unsurprising, given that LLINs are likely to have the greatest impact in areas with more

malaria-infected mosquitoes. In Uganda, LLIN distributions are conducted on a country level. The findings from this study suggest that the location and frequency of future UCCs could vary depending on malaria burden in the administrative unit. Additional studies, including those focused on cost-effectiveness of LLIN distributions by transmission level, could help inform this.

A key strength of this study is its outcome measure, malaria incidence measured continuously with high-quality data from local health facilities. We leveraged a network of established enhanced health facility-based surveillance sites embedded in public health facilities across Uganda. Health facility data can be challenging to work with due to high rates of clinical diagnosis and aggregate reporting,[2] but its utility lies in its wide geographic spread and longitudinal nature. The UMSP acts as an intervention in these public health facilities, improving data quality and case management: data are reported at the patient level, diagnostic testing rates are markedly high and missingness of variables is near-zero. Furthermore, by capturing data on where patients reside and identifying and enumerating target areas around the health facilities, we can continuously and robustly measure malaria incidence on a large scale, at a high temporal resolution, and for a relatively low cost, allowing for longitudinal measurement of the impact of interventions, including this LLIN UCC. We have demonstrated that incidence estimated using passive case detection at UMSP health facilities is highly correlated with incidence measured simultaneously in cohorts at the same locations at two sites.[41] This approach can be used in the future to estimate the impact of future UCCs or other interventions, including IRS.

This study is not without limitations. Importantly, due to resource constraints, we did not have data from the LLINEUP2 trial on physical integrity, chemical composition, bioefficacy, nor entomological outcomes; we could therefore not examine the potential contribution of each factor towards LLIN impact. In addition, we had varying amounts of baseline data from different MRCs, with as low as 2 months of baseline data contributing to the model for one MRC, which introduces uncertainty into our counterfactual model. Furthermore, incidence measured using passive case detection likely underestimates true malaria incidence due to patients seeking care in the private sector or simply not seeking care at all. Data from community-based cross-sectional surveys conducted 12 and 24 months following LLIN distribution indicated that 81% and 79% of household residents who reported being treated for malaria in the prior 6 months received care at their local MRC, respectively. Thus, while estimates of absolute incidence may underestimate the truth, we do not believe the degree of underestimation changed over time, suggesting that results from the ITS analysis remain valid.[9] Finally, the ITS model may be impacted by unmeasured confounding. For example, if changes in care-seeking due to the COVID-19 pandemic impacted changes in malaria incidence captured at health facilities, our results may be flawed. However, an analysis assessing the potential impact of the first year of the COVID-19 pandemic at MRCs found no impact of the pandemic on malaria cases and non-malarial visits at health facilities.[42]

CONCLUSIONS

In most high-burden countries in sub-Saharan Africa, UCCs are typically conducted every 3 years. There is mounting evidence from observational studies, however, that this timing is too infrequent given degradation in net retention, use, physical integrity and bioefficacy. This study further contributes to this literature, with longitudinal data on malaria incidence, suggesting that distributed newer-generation LLINs were effective for only 12 months after the distribution. Future work aimed at identifying factors that contribute to reductions in LLIN effectiveness is essential for designing interventions aimed at enhancing their longevity. Furthermore, international donors and National Malaria Control Programs may consider reducing the spacing between UCCs, particularly in areas with higher malaria burden, and bolstering continuous distributions through alternative avenues to ensure net effectiveness remains high.

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Ethics approval This study involves human participants. The LLINEUP2 trial protocol provided approval for the full trial, including the cross-sectional surveys, and was approved by the Makerere University School of Medicine Research & Ethics Committee (SOMREC ref 2020-193), Ugandan National Council for Science and

Technology (UNCST ref HS1097ES), the University of California San Francisco Human Research Protection Program Institutional Review Board (UCSF ref 20-31769) and the London School of Hygiene & Tropical Medicine Ethics Committee (LSHTM ref 22615). This study uses routine health facility data and does not require informed consent.

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REFERENCES

1 Bhatt S, Weiss DJ, Cameron E, *et al*. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. *Nature New Biol* 2015;526:207–11.
2 World Malaria report 2023. Geneva World Health Organization; 2023.
3 Global plan for insecticide resistance management in Malaria vectors. Geneva World Health Organization; 2012.
4 Churcher TS, Lissenden N, Griffin JT, *et al*. The impact of pyrethroid resistance on the efficacy and effectiveness of bednets for malaria control in Africa. *Elife* 2016;5:e16090.
5 Killeen GF, Chitnis N. Potential causes and consequences of behavioural resilience and resistance in malaria vector populations: a mathematical modelling analysis. *Malar J* 2014;13:97.
6 Briet O, Koenker H, Norris L, *et al*. Attrition, physical integrity and insecticidal activity of long-lasting insecticidal nets in sub-Saharan Africa and modelling of their impact on vectorial capacity. *Malar J* 2020;19:310.
7 Gleave K, Lissenden N, Chaplin M, *et al*. Piperonyl butoxide (PBO) combined with pyrethroids in insecticide-treated nets to prevent malaria in Africa. *Cochrane Database Syst Rev* 2021;5:CD012776.
8 Uganda National Malaria Control Division. Uganda malaria indicator survey 2018-19. Kampala, Uganda, and Rockville, Maryland, USA NMCD, UBOS, and ICF; 2020.
9 Gonahasa S, Namuganga JF, Nassali MJ. LLIN Evaluation in Uganda Project (LLINEUP2) – Effect of long-lasting insecticidal nets (LLINs) treated with pyrethroid plus pyriproxyfen vs LLINs treated with pyrethroid plus piperonyl butoxide in Uganda: A cluster-randomised trial. *PLOS Glob Public Health* 2024;5:e0003558.
10 Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017;46:348–55.
11 Kontopantelis E, Doran T, Springate DA, *et al*. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ* 2015;350:h2750.
12 Sserwanga A, Harris JC, Kigozi R, *et al*. Improved malaria case management through the implementation of a health facility-based sentinel site surveillance system in Uganda. *PLoS One* 2011;6:e16316.
13 Snyman K, Pitt C, Aturia A, *et al*. Who pays to treat malaria and how much? Analysis of the cost of illness, equity and economic burden of malaria in Uganda. *Health Policy Plan* 2025;40:52–65.
14 Aguma HB, Rukaari M, Nakamatte R, *et al*. Mass distribution campaign of long-lasting insecticidal nets (LLINs) during the COVID-19 pandemic in Uganda: lessons learned. *Malar J* 2023;22:310.
15 Okiring J, Gonahasa S, Maiteki-Sebuguzi C, *et al*. LLIN Evaluation in Uganda Project (LLINEUP): modelling the impact of COVID-19-related disruptions on delivery of long-lasting insecticidal nets on malaria indicators in Uganda. *Malar J* 2024;23:180.
16 Okiring J, Epstein A, Namuganga JF, *et al*. Gender difference in the incidence of malaria diagnosed at public health facilities in Uganda. *Malar J* 2022;21:22.
17 United Nations, Department of Economic and Social Affairs, Population Division. World population prospects 2022: summary of results. 2022.
18 Funk C, Peterson P, Landsfeld M, *et al*. The climate hazards infrared precipitation with stations--a new environmental record for monitoring extremes. *Sci Data* 2015;2:150066.
19 Didan K. MOD13Q1 MODIS/Terra Vegetation Indices 16-Day L3 Global 250m SIN Grid. NASA LP DAAC; 2015.
20 Pryce J, Richardson M, Lengeler C. Insecticide-treated nets for preventing malaria. *Cochrane Database Syst Rev* 2018;11:CD000363.
21 Van Bortel W, Mariën J, Jacobs BKM, *et al*. Long-lasting insecticidal nets provide protection against malaria for only a single year in Burundi, an African highland setting with marked malaria seasonality. *BMJ Glob Health* 2022;7:e009674.
22 Girond F, Madec Y, Kesteman T, *et al*. Evaluating Effectiveness of Mass and Continuous Long-lasting Insecticidal Net Distributions Over Time in Madagascar: A Sentinel Surveillance Based Epidemiological Study. *EClinicalMedicine* 2018;1:62–9.
23 Kabera M, Mangala J-LN, Soebiyanto R, *et al*. Impact of Pyrethroid Plus Piperonyl Butoxide Synergist-Treated Nets on Malaria Incidence 24 Months after a National Distribution Campaign in Rwanda. *Am J Trop Med Hyg* 2023;109:1356–62.
24 Topazian HM, Gumbo A, Brandt K, *et al*. Effectiveness of a national mass distribution campaign of long-lasting insecticide-treated nets and indoor residual spraying on clinical malaria in Malawi, 2018-2020. *BMJ Glob Health* 2021;6:e005447.
25 Okiring J, Gonahasa S, Nassali M, *et al*. LLIN Evaluation in Uganda Project (LLINEUP2)—Factors associated with coverage and use of long-lasting insecticidal nets following the 2020–21 national mass distribution campaign: a cross-sectional survey of 12 districts. *Malar J* 2022;21:293.
26 Mansiangi P, Umesumbu S, Etewa I, *et al*. Comparing the durability of the long-lasting insecticidal nets DawaPlus. *Malar J* 2020;19:189.
27 Kilian A, Koenker H, Obi E, *et al*. Field durability of the same type of long-lasting insecticidal net varies between regions in Nigeria due to differences in household behaviour and living conditions. *Malar J* 2015;14:123.
28 Massue DJ, Moore SJ, Mageni ZD, *et al*. Durability of Olyset campaign nets distributed between 2009 and 2011 in eight districts of Tanzania. *Malar J* 2016;15:176.
29 Gnanguenon V, Azondekon R, Oke-Agbo F, *et al*. Durability assessment results suggest a serviceable life of two, rather than three, years for the current long-lasting insecticidal (mosquito) net (LLIN) intervention in Benin. *BMC Infect Dis* 2014;14:69.
30 Tan KR, Coleman J, Smith B, *et al*. A longitudinal study of the durability of long-lasting insecticidal nets in Zambia. *Malar J* 2016;15:106.
31 Morgan J, Abílio AP, do Rosario Pondja M, *et al*. Physical durability of two types of long-lasting insecticidal nets (LLINs) three years after a mass LLIN distribution campaign in Mozambique, 2008-2011. *Am J Trop Med Hyg* 2015;92:286–93.
32 Mechan F, Katureebe A, Tuhaise V, *et al*. LLIN evaluation in Uganda project (LLINEUP): The fabric integrity, chemical content and bioefficacy of long-lasting insecticidal nets treated with and without piperonyl butoxide across two years of operational use in Uganda. *Curr Res Parasitol Vector Borne Dis* 2022;2:100092.
33 Martin J, Lukole E, Messenger LA, *et al*. Monitoring of Fabric Integrity and Attrition Rate of Dual-Active Ingredient Long-Lasting Insecticidal Nets in Tanzania: A Prospective Cohort Study Nested in a Cluster Randomized Controlled Trial. *Insects* 2024;15:108.
34 Randriamaherijaona S, Briët OJT, Boyer S, *et al*. Do holes in long-lasting insecticidal nets compromise their efficacy against pyrethroid resistant Anopheles gambiae and Culex quinquefasciatus? Results from a release-recapture study in experimental huts. *Malar J* 2015;14:332.
35 Koenker H, Kilian A, Zegers de Beyl C, *et al*. What happens to lost nets: a multi-country analysis of reasons for LLIN attrition using 14 household surveys in four countries. *Malar J* 2014;13:464.
36 Gichuki PM, Kamau L, Njagi K, *et al*. Bioefficacy and durability of Olyset® Plus, a permethrin and piperonyl butoxide-treated

insecticidal net in a 3-year long trial in Kenya. *Infect Dis Poverty* 2021;10:135.
37 Ngufor C, Agbevo A, Fagbohoun J, *et al*. Efficacy of Royal Guard, a new alpha-cypermethrin and pyriproxyfen treated mosquito net, against pyrethroid-resistant malaria vectors. *Sci Rep* 2020;10:12227.
38 Protopopoff N, Mosha JF, Lukole E, *et al*. Effectiveness of a long-lasting piperonyl butoxide-treated insecticidal net and indoor residual spray interventions, separately and together, against malaria transmitted by pyrethroid-resistant mosquitoes: a cluster, randomised controlled, two-by-two factorial design trial. *Lancet* 2018;391:1577–88.
39 Ngufor C, Fongnikin A, Fagbohoun J, *et al*. Evaluating the attrition, fabric integrity and insecticidal durability of two dual active ingredient nets (Interceptor® G2 and Royal® Guard): methodology for a prospective study embedded in a cluster randomized controlled trial in Benin. *Malar J* 2023;22:276.
40 Katureebe A, Zinszer K, Arinaitwe E, *et al*. Measures of Malaria Burden after Long-Lasting Insecticidal Net Distribution and Indoor Residual Spraying at Three Sites in Uganda: A Prospective Observational Study. *PLoS Med* 2016;13:e1002167.
41 Epstein A, Namuganga JF, Kamya EV, *et al*. Estimating malaria incidence from routine health facility-based surveillance data in Uganda. *Malar J* 2020;19:445.
42 Namuganga JF, Briggs J, Roh ME, *et al*. Impact of COVID-19 on routine malaria indicators in rural Uganda: an interrupted time series analysis. *Malar J* 2021;20:475.