Effectiveness of pyriproxyfen-pyrethroid and chlorfenapyr-pyrethroid long-lasting insecticidal nets (LLINs) compared with pyrethroid-only LLINs for malaria control in the third year post-distribution: a secondary analysis of a cluster-randomised controlled trial in Benin

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Summary

Background Malaria continues to kill approximately 650 000 people each year. There is evidence that some second-generation insecticide-treated nets, which combine insecticide formulations with different modes of action, are protective against malaria while the nets are new; however, evidence for their impact over 3 years is scarce. In this study, we report the third-year results of a cluster-randomised controlled trial assessing the long-term effectiveness of dual-active ingredient long-lasting insecticidal nets (LLINs).

Methods This is a secondary analysis of a cluster-randomised controlled trial, carried out between May 23, 2019, and April 30, 2023, in southern Benin. Restricted randomisation was used to assign 60 clusters (villages or groups of villages with a minimum of 100 households) to the three study groups (1:1:1) to evaluate the efficacy of pyriproxyfen-pyrethroid LLINs and chlorfenapyr-pyrethroid LLINs compared with pyrethroid-only LLINs (reference) against malaria transmission. The study staff and communities were masked to the group allocation. The primary outcome was malaria incidence measured over the third year after LLIN distribution, in a cohort of children aged 6 months to 9 years at the time of enrolment, in the intention-to-treat population. Here, we present the data of the third year post-LLIN distribution. The trial was registered with ClinicalTrials.gov, NCT03931473.

Findings Study net use declined over the 3 years and was consistently lowest in the pyriproxyfen-pyrethroid LLIN group (at 36 months: 889 [39·4%] of 2257 participants *vs* 1278 [52·2%] of 2450 participants for the chlorfenapyr-pyrethroid LLIN group and 1400 [57·6%] of 2430 participants for the pyrethroid-only LLIN group). The cohort of children for the third year of follow-up (600 per group) were enrolled between April 9 and 30, 2022. Mean malaria incidence during the third year after distribution was 1·19 cases per child-year (95% CI 1·09–1·29) in the pyrethroid-only LLIN reference group, 1·21 cases per child-year (1·12–1·31) in the pyriproxyfen-pyrethroid LLIN group (hazard ratio [HR] 1·02, 95% CI 0·71–1·44; p=0·92), and 0·96 cases per child-year (0·88–1·05) in the chlorfenapyr-pyrethroid LLIN group (HR 0·80, 0·56–1·17; p=0·25). No adverse events related to study nets were reported by participants.

Interpretation During the third year, as was also observed during the first 2 years, the pyriproxyfen-pyrethroid LLIN group did not have superior protection against malaria cases compared with the standard LLIN group. In the third year, people living in the chlorfenapyr-pyrethroid LLIN group no longer benefited from greater protection against malaria cases and infections than those living in the pyrethroid-only LLIN group. This was probably influenced by lower study net use than previous years and the declining concentration of partner insecticides in the nets.

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Introduction

Long-lasting insecticidal nets (LLINs) treated with a pyrethroid insecticide have been instrumental in the fight against malaria for the past two decades. This core malaria intervention is estimated to have contributed to 68% of the 663 million malaria clinical cases averted between 2000 and 2015.[1] A second generation of LLINs combining an insecticide and a synergist or a mixture of insecticides with two different modes of action have been manufactured,[2–4] to control malaria vectors that have developed resistance to standard pyrethroid insecticides and threaten to derail control efforts.[5]

In recent years, three new classes of LLIN have been developed for improving malaria control. The first are

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Research in context

Evidence before this study

We searched PubMed on July 4, 2023, without language or date restrictions. We used the terms "randomised controlled trial" AND "malaria" AND "insecticide-treated net" OR "long-lasting insecticidal net", combined with either "pyriproxyfen" OR "chlorfenapyr". We found three published cluster-randomised trials (RCTs), reporting the efficacy of chlorfenapyr-pyrethroid long-lasting insecticidal nets (LLINs) on malaria incidence or prevalence, and two of those studies also evaluated pyriproxyfen-pyrethroid LLINs. One of the studies published was the first 2 years of the present RCT conducted in Benin, where we reported a 46% reduction in malaria case incidence in children younger than 10 years in the chlorfenapyr-pyrethroid LLINs group compared with those in the standard pyrethroid-only LLIN group; this reduction was 44% in the same age group in the second trial conducted in Tanzania. Based on these trials, WHO issued a public health recommendation for chlorfenapyr-pyrethroid LLINs to be deployed in areas where malaria vectors are resistant to pyrethroids. Neither trial reported any superior effect of the pyriproxyfen-pyrethroid LLINs compared with standard pyrethroid-only LLINs on epidemiological indices at 24 months post-distribution. The third trial—the only one showing significant reduction in malaria indices for pyriproxyfen-pyrethroid LLINs—was conducted in Burkina Faso, where the authors showed a 12% reduction in malaria case incidence in children receiving pyriproxyfen-pyrethroid LLINs compared with those who received standard pyrethroid-only LLINs. The RCTs conducted in Tanzania reported the third-year results and found that chlorfenapyr-pyrethroid LLINs were still more effective despite low usage compared with standard-pyrethroid LLINs, with a 43% reduction in odds of malaria prevalence.

Added value of this study

This is, to our knowledge, the second trial reporting the efficacy of chlorfenapyr-pyrethroid and pyriproxyfen-pyrethroid LLINs over 3 years of community use and the first one in west Africa. We are also reporting malaria case incidence rather than only prevalence as reported in the Tanzania study; incidence is less sensitive to changes in transmission over a short period of time. Longer efficacy of bednets up to at least 3 years as recommended by WHO will improve cost-effectiveness. Despite higher net usage in the chlorfenapyr-pyrethroid LLIN group than was observed in Tanzania in the third year (52·2% *vs* 23%), pyrethoid-chlorfenapyr LLINs did not reduce malaria prevalence and incidence compared with the standard-pyrethroid LLIN group, potentially due to low study power. No difference in efficacy was seen in the pyriproxyfen-pyrethroid LLIN group compared with standard pyrethroid-only LLINs at any year during the study.

Implications of all the available evidence

This trial shows that chlorfenapyr-pyrethroid LLINs were not sufficiently effective in the third year after distribution in a high-malaria transmission setting. Although they remained superior to pyrethroid-only LLINs in Tanzania's lower transmission setting, it is harder to maintain previous gains from when the nets were new, as population net coverage declines over time. This suggests that the superior efficacy of chlorfenapyr-pyrethroid LLINs might only last for 2 years, and that the apparent superior efficacy in the Tanzania trial up to 3 years, despite extremely low use, might be due to a carry-over effect or to the presence of other nets in the community. To capitalise on the new generation of nets, we need more information on their durability (physical and chemical) in communities. However, both trials showed a huge reduction in the use of trial nets over the 3 years, highlighting the need to rethink strategies for maintaining high coverage in high-risk communities. The WHO recommendation that a net should last for 3 years is not met by any nets on the market, yet this recommendation is the basis for the regularity of mass distributions. It is essential that the 3-year figure is reconsidered and that countries are empowered to make strategic decisions regarding distribution strategies.

nets treated with a synergist, piperonyl butoxide, which, when combined with a pyrethroid, enhances the killing effect of the partner insecticide in pyrethroid-resistant mosquitoes.[6,7] A second class of LLIN is a mixture of pyrethroid and a pyrrole insecticide, chlorfenapyr. Chlorfenapyr disrupts cellular respiration of the insect rather than affecting their nervous system as pyrethroids do.[8] The third net class combines a pyrethroid with pyriproxyfen, which disrupts insect reproductive hormone balance, inducing sterility in adult mosquito vectors.[2] The efficacy of these new-generation nets on malaria clinical outcomes compared with pyrethroid-only nets has been tested in several randomised controlled trials (RCTs) and showed a relatively small level of protection offered by pyriproxyfen-pyrethroid LLINs in one trial and no impact in another,[9–11] while chlorfenapyr-pyrethroid LLINs provided a consistently greater reduction in malaria incidence and prevalence.[10,11] In Benin, over the first 2 years following net distribution, there was very little evidence of any reduction in malaria case incidence in the pyriproxyfen-pyrethroid LLIN group but strong evidence of a reduction of 46% for the chlorfenapyr-pyrethroid LLIN group compared with the pyrethroid-only LLIN group.[11] Combined with previous evidence from Tanzania,[9,10] these findings enabled WHO to provide a "strong recommendation" to deploy chlorfenapyr-pyrethroid LLINs instead of pyrethroid-only LLINs in areas with pyrethroid resistance while conditional approval was given to pyriproxyfen-pyrethroid LLINs based on results from an earlier trial in Burkina Faso.[6,12]

Although evidence of efficacy over 2 years is enough for WHO policy recommendations,[13] bednets are typically

replaced every 3 years via mass distributions; therefore, the efficacy over 3 years is of key importance for the monitoring and evaluation of new-generation nets. In Tanzania, chlorfenapyr-pyrethroid LLINs were more cost-effective than other nets including standard pyrethroid-only LLINs, despite being slightly more costly from the provider's or funder's perspective.[10] Price reductions as volumes of chlorfenapyr-pyrethroid LLIN production increased and longer-lasting efficacy would further reduce this cost.[10] In the third year of the Tanzania RCT, malaria infection prevalence in children younger than 15 years was still lower in the chlorfenapyr-pyrethroid LLIN group than in the standard pyrethroid-only LLIN group despite very low usage of the nets.[14,15] However, it is not clear if, in this moderate transmission setting, the effect was a carry-over of the reduction achieved in the previous year or if the nets were still genuinely more effective. In addition, these findings need to be verified in a separate setting with higher malaria transmission and different malaria vector species.

This study reports on the third-year results of a cluster RCT assessing the effectiveness of two dual-active ingredient LLINs compared with pyrethroid-only LLINs on malaria case incidence and prevalence in an area of intense pyrethroid resistance in Benin.

Methods

Study design and participants

The trial was a three-group, cluster-randomised, superiority trial which took place in three districts (Covè, Zagnanado, and Ouinhi) in Zou department, southern Benin. The primary 24-month endpoint was reported previously;[11] this secondary analysis presents outcomes measured in the third year following net distribution. The area is a high malaria transmission region, with a peak of cases between May and October. At baseline in 2019, malaria prevalence across all age groups was 45·3% and there was an indoor entomological inoculation rate of 21·6 infected bites per person per month. The primary vectors in the setting are *Anopheles coluzzii* and *Anopheles gambiae* sensu stricto, both of which have been shown to be highly resistant to pyrethroid insecticides.[16] The only recent malaria control intervention conducted in the study area was an LLIN mass-distribution campaign (pyrethroid-only LLIN, PermaNet 2.0) in 2017, 3 years before the study implementation. As part of the national LLIN distribution process, the community received information about hanging, cleaning, and use of the nets.

The details of the trial have been published previously.[17] Briefly, all 123 villages in the study area were used to form 60 clusters. Each cluster had a core area of a minimum of 100 households and a buffer area to separate the core areas by at least 1000 metres. Interventions were delivered in core and buffer areas, but trial outcomes were only measured in the core areas.

Ethics approval was obtained from the Benin Ministry of Health ethics committee (6/30/MS/DC/SGM/DRFMT/CNERS/SA), the London School of Hygiene & Tropical Medicine ethics committee (16237), and the WHO Research Ethics Review Committee (ERC.0003153). The trial was independently monitored by a data safety monitoring board and a trial steering committee.

The primary epidemiological outcome was malaria case incidence estimated via active case detection in a cohort of children aged 6 months to 9 years at the time of enrolment. The primary outcome measured malaria case incidence up to 2 years following net distribution. A new cohort of children (30 randomly selected children per cluster) was enrolled in April, 2022, to monitor impact during the third year after the distribution. Children were eligible for inclusion if they were permanent residents in a trial cluster, had no serious illnesses, and written informed consent was given by their guardians.

Malaria infection prevalence (in all ages) was also measured in cross-sectional surveys at 6 months and 18 months after net distribution. This study reports results from the survey conducted 30 months post-net distribution. 72 individuals from the core of each cluster were randomly selected from census lists. The cross-sectional surveys collected data on malaria infection, measured using malaria rapid diagnostic test result, net ownership and use, sex of respondent, and household assets (as a proxy for socioeconomic status).

Indoor and outdoor *Anopheles* vector densities were measured using human landing catches in four randomly selected houses every 3 months in each cluster. This study reports the results from the final four entomological surveys.

Written informed consent or verbal assent (for those aged 10–18 years) was obtained for all participants; for children younger than 10 years, their guardians provided written consent. Written consent was also obtained from volunteers engaged with the entomological data collection, who were all older than 18 years and were vaccinated against yellow fever. All participation was voluntary, and participants could withdraw at any time.

Randomisation and masking

Restricted randomisation was used to randomly assign 60 clusters to one of three LLIN groups (1:1:1) and to ensure balanced cluster allocation between study groups with respect to population size, malaria infection prevalence (measured in the baseline survey), district, and socioeconomic status. Approximately 100 000 random allocations were generated using Stata 16 and ones that met the restriction criteria were retained (n=1183), with one randomly selected. The nets were designed to look as similar as possible to mask the net types from the participants and field workers. All data analyses were performed masked, with the net codes reshuffled before the third-year analysis to ensure third-year analyses were also performed masked.

Procedures

The nets tested in the trial were: Royal Guard (Disease Control Technologies, Greer, SC, USA), polyethylene netting (120 deniers incorporating 220 mg/m² pyriproxyfen and 220 mg/m² alpha-cypermethrin); Interceptor G2 (BASF SE, Ludwigshafen, Germany), polyester netting (100 deniers coated with 200 mg/m² chlorfenapyr and 100 mg/m² alpha-cypermethrin); and the reference net, Interceptor (BASF SE, Ludwigshafen, Germany), polyester netting (100 deniers coated with 200 mg/m² of alpha-cypermethrin). The nets were distributed in March, 2020, in conjunction with the Benin National Malaria Control Program. Net usage was assessed at 6, 9, 18, 24, 30, and 36 months post-distribution during household cross-sectional and coverage surveys. Insecticide content was assessed every year on 30 randomly selected nets per LLIN brand by gas chromatography with flame ionisation detection at the Centre Wallon de Recherches Agronomiques, Gembloux, Belgium.

The cohort of children for the third year of follow-up were enrolled between April 9 and 30, 2022, and follow-up continued until March 20, 2023, capturing malaria incidence during the third year after net distribution. During enrolment, children were treated with antimalarial drugs (artemether-lumefantrine) to clear any underlying malaria infection. Children were visited every 2 weeks during the transmission season (April–November) and had monthly visits by the study nurses during the dry season (December–March). Children were clinically examined and if they were febrile or had a history of fever in the past 48 h, were tested for malaria using a rapid diagnostic test (SD Bioline Malaria Ag P.f [HRP2/pLDH], Abbott Diagnostics Korea, Geonggi-do, South Korea). If the test was positive, they received treatment, in line with national guidelines.

During the 30-month cross-sectional survey, all participants were tested for malaria using a malaria rapid diagnostic test (CareStart malaria HRP2/pLDH [pf/pan] combo, DiaSys, Wokingham, UK) and treated if the test was positive. Children younger than 5 years were additionally tested for anaemia using a Hemocue device (HemoCue Hb 201+, Aktiebolaget Leo Diagnostics, Helsingborg, Sweden) for haemoglobin measurement. During the field data collection, study nets were labelled A, B, and C by using the study logo and loop colour as the field workers were masked to the type of the study net. During house visits, the nets were visually inspected with the consent of the household members to assess whether they had been hung.

Entomological monitoring continued as for the first 2 years. This paper reports results from collections made between June, 17, 2022, and May, 2, 2023, at 27, 30, 33, and 36 months post-net distribution. Entomological collections were conducted via human landing catches. Volunteers collected mosquitoes that landed on their legs between 1900 h and 0700 h for 1 night at four randomly selected houses in each cluster at each timepoint. Mosquitoes were morphologically sorted by species and a random sample of *Anopheles* spp (up to 30% from each nightly catch in each cluster) were tested for sporozoites using the ELISA circumsporozoite protein technique.

Outcomes

The primary outcome for the original trial was malaria case incidence (infrared frontal temperature ≥37·5°C or reported fever in the previous 48 h, and positive malaria rapid diagnostic test) in children enrolled in the active case detection cohort in the 2 years after net distribution. This paper presents malaria case incidence measured in the third year after net distribution as the primary outcome. Passive data from health facilities were also collected to capture malaria cases occurring between active visits. Secondary outcomes were malaria infection prevalence in all age groups, anaemia prevalence in children younger than 5 years (haemoglobin concentration <10 g/dL) at 30 months, and vector density (bites per person per night) measured indoors and outdoors during the third year of the trial. Adverse events were recorded during the cohort visits and during the cross-sectional surveys using a prespecified questionnaire.

Statistical analysis

As the results of the first 2 years of the trial were not available at the beginning of the third year, the sample sizes remained unchanged from the original design,[17] with 30 children per cluster in the incidence cohort and 72 people of any age in each cluster for infection prevalence, measured in a cross-sectional survey.

The analysis was identical to that done for the first 2 years of the study and is detailed in the original publication.[11] Briefly, our main analysis was an intention-to-treat comparison of malaria case incidence in each dual-active ingredient LLIN group compared with the reference group using a Cox proportional hazards regression allowing for correlation of multiple events per child and per cluster by adjusting standard errors using cluster-robust estimates of variance. The proportional hazards assumption was tested formally and graphically. Malaria infection prevalence and prevalence of anaemia were assessed separately using mixed-effects logistic regression models with cluster included as a random effect. Secondary per-protocol analyses were conducted for malaria case incidence and malaria infection prevalence, and only included children using the allocated study nets.

Indoor and outdoor malaria vector density was calculated for each household visit and analysed using mixed-effect generalised linear models with a negative binomial distribution with cluster and survey as random effects. To adjust for the increased risk of type I error due to multiple pairwise comparisons, the level of significance was adjusted using the Bonferroni

	Pyrethroid-pyriproxyfen LLIN group	Pyrethroid-chlorfenapyr LLIN group	Pyrethroid-only LLIN group
Study cluster characteristics			
Number of clusters	20	20	20
Total population in core and buffer areas	74 822	70 989	69 239
Median population in core area of clusters (IQR)	788 (475·5–1365·5)	857 (429·5–1163)	646 (390–1252)
Median number of people per household (IQR)	4 (2–6)	4 (2–5)	4 (2–6)
Median number of sleeping spaces per household (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
Household and participant characteristics in baseline cross-sectional survey			
Low socioeconomic status*	35·8%; 529/1479	36·2%; 533/1474	29·0%; 431/1487
LLIN ownership (at least one LLIN in the household)	96·4%; 1426/1479	97·1%; 1431/1474	95·1%; 1415/1488
LLIN use in all age groups the night before	95·8%; 1312/1370	94·9%; 1258/1326	96·5%; 1343/1392
Malaria infection prevalence in all age groups	43·1%; 636/1475	40·7%; 598/1468	46·5%; 690/1485
Anaemia prevalence in children aged 6 months to 4 years†	53·3%; 136/255	53·3%; 131/246	50·2%; 122/243
Entomological characteristics at baseline			
Median human biting density per person per night indoors‡ (IQR)	25·5 (13·5–43·5)	14·0 (7·0–29·5)	22·5 (9·5–40·5)
Mean indoor EIR per person per night (95% CI)	0·62 (0·20–1·04)	0·48 (0·19–0·77)	0·96 (0·43–1·49)
Child (aged 6 months to 9 years) characteristics at enrolment (third year)§			
Proportion of children younger than 5 years	62·3%; 374/600	59·7%; 358/600	60·0%; 360/600
Proportion of female children	48·2%; 289/600	49·7%; 298/600	48·0%; 288/600
Net usage the night before survey	99·5%; 552/555	98·2%; 540/550	99·5%; 570/573

Data are n or %; n/N unless otherwise stated. EIR=entomological inoculation rate. LLIN=long-lasting insecticidal net. *Proportion of households in the poorest tercile based on the wealth index of the entire study area. †Anaemia defined as haemoglobin concentration <10 g/dL. ‡Malaria vectors included *Anopheles gambiae sensu lato*, *Anopheles funestus* group, and *Anopheles nili* group. §Children were aged 6 months to 9 years at the time of enrolment; at the end of follow-up, some children were older than 9 years, but all were younger than 10 years.

Table 1: **Baseline characteristics**

correction. Post-hoc sensitivity analyses for malaria incidence and prevalence adjusted for baseline cluster-level variables used in restricted randomisation. Results are presented for the third year alone, and in combination with the results from the first and second years. This study is registered with ClinicalTrials.gov, NCT03931473.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

As reported previously,[11] the three groups did not differ in household characteristics, previous net ownership, entomological indicators, and epidemiological indicators at baseline (table 1). At enrolment for the third year of the evaluation, children were balanced for age, sex, and net use. The cohort of 600 children per group provided 1480 child-years of follow-up (figure). A total of 20 children (three deaths, 17 migrations) were lost to follow-up (four in the pyriproxyfen-pyrethroid LLIN group, five in the chlorfenapyr-pyrethroid LLIN group, and 11 in the pyrethroid-only LLIN group).

Study bednets were distributed between March 19 and 22, 2020, with 52 463 (97·1%) of 54 030 households receiving at least one net per household. The proportion of households with at least one study net decreased progressively over the 3 years of the evaluation, regardless of the type of net, but was lowest in the pyriproxyfen-pyrethroid LLIN group 36 months after distribution (340 [67·3%] of 505 households *vs* 400 [79·1%] of 506 households for the chlorfenapyr-pyrethroid LLIN group and 411 [80·6%] of 510 households for the pyrethroid-only LLIN group). The trend was similar for study net use, with 889 (39·4%) of 2257 participants in the pyriproxyfen-pyrethroid LLIN group, 1278 (52·2%) of 2450 participants in the chlorfenapyr-pyrethroid LLIN group, and 1400 (57·6%) of 2430 participants in the pyrethroid-only LLIN group reporting using a net the night before the survey 36 months after net distribution (appendix 2 p 2). Although usage of the study net dropped, overall LLIN usage (study net and other LLINs) remained relatively constant throughout the 3 years following distribution, decreasing from 90·6% (2210 of 2439 participants) to 83·8% (1892 of 2257) in the pyriproxyfen-pyrethroid LLIN group, 95·1% (2230 of 2345) to 82·2% (2014 of 2450) in the chlorfenapyr-pyrethroid LLIN group, and 93·1% (2254 of 2422) to 83·4% (2027 of 2430) in the pyrethroid-only LLIN group from 9 months to 36 months post-distribution (appendix 2 p 2).

See **Online** for appendix 2

The chemical content on the nets was also assessed. Pyriproxyfen content in Royal Guard was 90 mg/m² at 24 months versus 289 mg/m² when new (69% reduction),

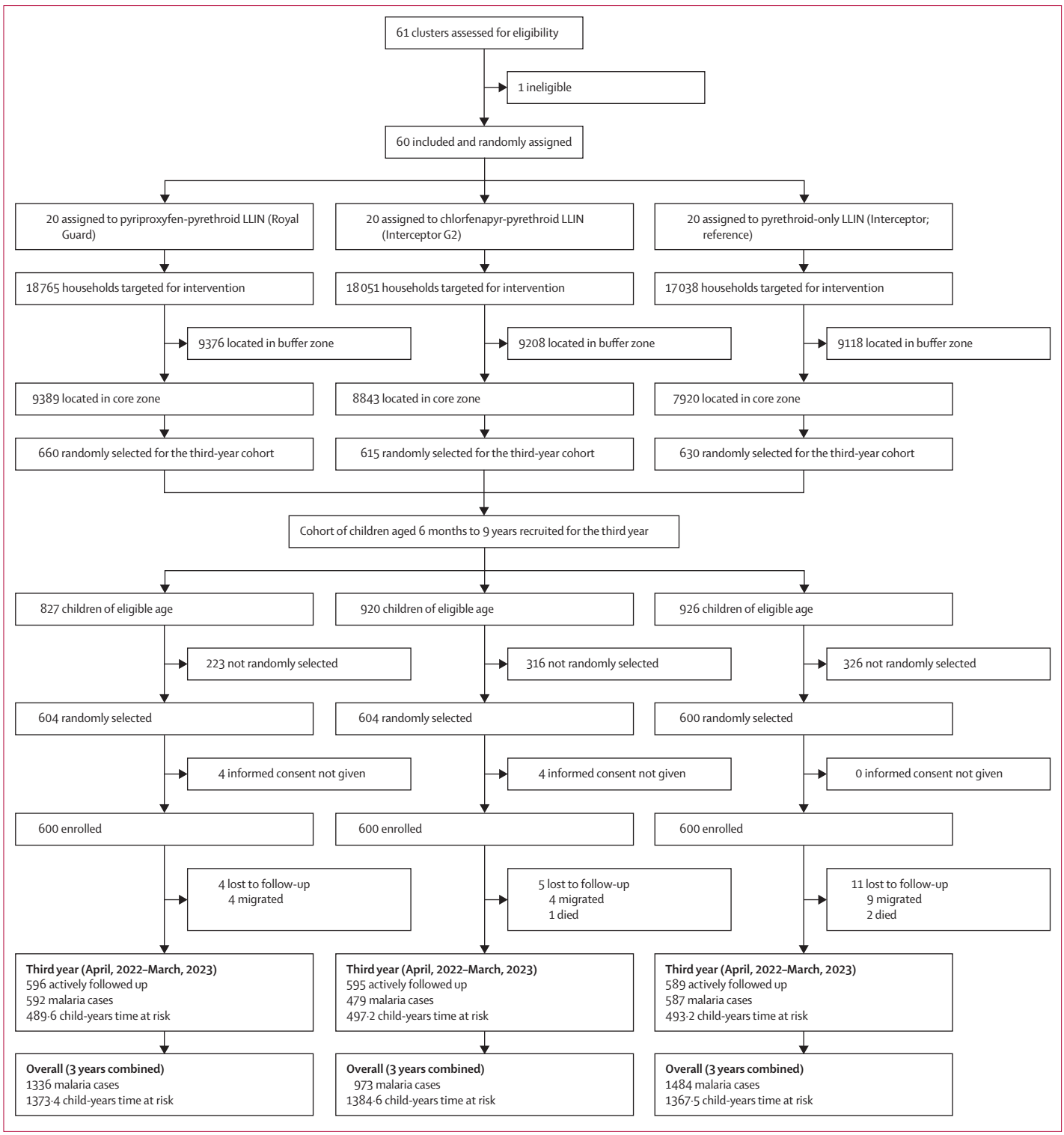

Figure: **Study flow chart**
LLIN=long-lasting insecticidal net.

while chlorfenapyr concentrations in Interceptor G2 were 52 mg/m² and 208 mg/m² (75% reduction) for the same time period.

During the third year after net distribution, 1658 malaria cases were recorded through active detection. Malaria case incidence was 1·19 per child-year (95% CI 1·09–1·29)

	Number of clinical malaria episodes	Follow-up time, child-years	Incidence, cases per child-year (95% CI)	Hazard ratio	95% CI	p value*
Third year after distribution						
Pyrethroid-only LLIN group	587	493·2	1·19 (1·09–1·29)	1 (ref)	..	..
Pyrethroid-pyriproxyfen LLIN group	592	489·6	1·21 (1·12–1·31)	1·02	0·71–1·44	0·92
Pyrethroid-chlorfenapyr LLIN group	479	497·2	0·96 (0·88–1·05)	0·80	0·56–1·17	0·25
Overall (3 years combined)						
Pyrethroid-only LLIN group	1484	1367·5	1·09 (1·03–1·14)	1 (ref)	..	..
Pyrethroid-pyriproxyfen LLIN group	1336	1373·4	0·97 (0·92–1·03)	0·91	0·71–1·18	0·50
Pyrethroid-chlorfenapyr LLIN group	973	1384·6	0·70 (0·66–0·75)	0·64	0·50–0·83	0·0006

Each intervention is compared with the pyrethroid-only LLIN group for the same timepoint. Hazard ratios derived from Cox proportional hazards model with robust estimates of variance to account for clustered design. LLIN=long-lasting insecticidal net. Ref=reference (control group). *A p value <0·025 was considered statistically significant after Bonferroni correction.

Table 2: **Malaria case incidence in children aged 6 months to 10 years during the third year after distribution (active visits, intention-to-treat analysis)**

	Malaria infection					Anaemia in children younger than 5 years				
	n/N	Prevalence	OR	95% CI	p value*	n/N	Prevalence	OR	95% CI	p value*
Pyrethroid-only LLIN group	386/1474	26·2%	1 (ref)	..	..	76/244	31·2%	1 (ref)	..	..
Pyrethroid-pyriproxyfen LLIN group	422/1485	28·4%	1·12	0·78–1·61	0·55	82/242	33·9%	1·12	0·65–1·95	0·68
Pyrethroid-chlorfenapyr LLIN group	331/1469	22·5%	0·82	0·57–1·19	0·30	85/240	35·4%	1·21	0·69–2·09	0·50

Anaemia defined as a haemoglobin concentration <10 g/dL. OR=odds ratio. LLIN=long-lasting insecticidal net. Ref=reference (control group). *A p value <0·025 was considered statistically significant after Bonferroni correction.

Table 3: **Malaria infection and anaemia prevalence at 30 months after distribution (intention-to-treat analysis)**

in the pyrethroid-only LLIN reference group, 1·21 per child-year (1·12–1·31) in the pyriproxyfen-pyrethroid LLIN group (hazard ratio [HR] 1·02, 95% CI 0·71–1·44; p=0·92), and 0·96 per child-year (0·88–1·05) in the chlorfenapyr-pyrethroid LLIN group (HR 0·80, 0·56–1·17; p=0·25; table 2 and appendix 2 p 6). Findings were similar when including malaria cases detected passively (appendix 2 p 3). Considering the 3 years combined, overall malaria case incidence was significantly lower in the chlorfenapyr-pyrethroid LLIN group (HR 0·64, 0·50–0·83; p=0·0006), but not in the pyriproxyfen-pyrethroid LLIN group (HR 0·91, 0·71–1·18; p=0·50), compared with the pyrethroid-only LLIN group (table 2).

At 30 months post-intervention, malaria infection prevalence in the chlorfenapyr-pyrethroid LLIN group was lower compared with the pyrethroid-only LLIN group, but the difference was not statistically significant (22·5% [331 of 1469 participants] *vs* 26·2% [386 of 1474]; odds ratio [OR] 0·82, 95% CI 0·57–1·20; p=0·30; table 3; appendix 2 p 6). There was no significant reduction in malaria prevalence between the pyriproxyfen-pyrethroid and pyrethroid-only LLIN groups (28·4% [422 of 1485 participants] *vs* 26·2% [386 of 1474]; OR 1·12, 0·78–1·61; p=0·55). Per-protocol analysis (individuals who slept under the allocated study nets the night before) showed similar findings to the intention-to-treat analysis (appendix 2 p 5). The post-hoc analysis adjusting for covariates used in the randomisation did not change the interpretation of the results (appendix 2 pp 8–9).

No substantial reduction was also observed for anaemia prevalence in children younger than 5 years between either intervention group and the reference group with either intention-to-treat or per-protocol analysis (table 3). No side-effects related to the nets were reported by the participants during the third year.

A total of 48 452 mosquitoes were collected indoors and 57 662 outdoors during the third year of follow-up across the three study groups. Among these 106 114 mosquitoes, 30 941 (29·2%) were female anophelines (malaria and non-malaria vectors), of which 28 915 were malaria vectors. Most of these (n=28 571) were *A gambiae* sensu lato; the remaining mosquitoes belonged to the *Anopholes funestus* group (n=102), and *Anopholes nili* group (n=242). From the 28 571 *A gambiae* sensu lato malaria vectors, a subsample of 3027 mosquitoes randomly selected across the three study groups were molecularly speciated and were composed as follows: 1883 (62·2%) *A coluzzii*, 1131 (37·4%) *A gambiae* sensu stricto, and 13 (0·4%) hybrids (between *A coluzzii* and *A gambiae* sensu stricto). These proportions were similar in indoor and outdoor collections (of 1713 mosquitoes collected indoors, 1074 [62·7%] were *A coluzzii* and 632 [36·9%] were *A gambiae* sensu stricto; of 1314 mosquitoes collected outdoors, 809 [61·6%] were *A coluzzii* and 499 [38%] were *A gambiae* sensu stricto). During the third year, mean indoor vector density was 20·4 bites per person per night in the pyrethroid-only LLIN group, 14·5 bites per person per night in the chlorfenapyr-pyrethroid LLIN

	Indoor density					Outdoor density				
	Number of households analysed	Number of female Anopheles vectors	Mean Anopheles bites per night per person	Density ratio (95% CI)	p value*	Number of households analysed	Number of female Anopheles vectors	Mean Anopheles bites per night per person	Density ratio (95% CI)	p value*
Third year after distribution										
Pyrethroid-only LLIN group	320	6537	20·4	1 (ref)	..	320	4623	14·4	1 (ref)	..
Pyrethroid-pyriproxyfen LLIN group	320	5234	16·4	0·94 (0·46–1·88)	0·85	320	4262	13·3	1·10 (0·57–2·10)	0·79
Pyrethroid-chlorfenapyr LLIN group	320	4638	14·5	0·74 (0·37–1·48)	0·39	320	3621	11·3	0·71 (0·37–1·36)	0·30
Overall (3 years combined)										
Pyrethroid-only LLIN group	960	21246	22·2	1 (ref)	..	960	5932	18·8	1 (ref)	..
Pyrethroid-pyriproxyfen LLIN group	960	13904	14·5	0·68 (0·36–1·30)	0·25	960	3608	11·2	0·60 (0·31–1·16)	0·13
Pyrethroid-chlorfenapyr LLIN group	960	11073	11·5	0·52 (0·27–0·99)	0·0479	960	2637	8·3	0·48 (0·25–0·92)	0·0272

LLIN=long-lasting insecticidal net. Ref=reference (control group). *A p value <0·025 was considered statistically significant after Bonferroni correction.

Table 4: **Indoor and outdoor entomological outcomes during the third year of follow-up and over the 3 years of intervention**

group (density ratio 0·74, 95% CI 0·37–1·48; p=0·39), and 16·4 bites per person per night in the pyriproxyfen-pyrethroid LLIN group (density ratio 0·94, 0·46–1·88; p=0·85; table 4 and appendix 2 p 6). Outdoor vector density was in general lower than indoor, and ratios were similar between both the dual-active ingredient LLINs and the pyrethroid-only LLIN.

Discussion

In this study, we assessed the impact of two dual-active ingredient LLINs compared with standard pyrethroid LLINs on malaria incidence in children younger than 10 years, all-age-group malaria infection prevalence, and vector density in the third year following distribution of the nets. We found that chlorfenapyr-pyrethroid LLINs did not provide significantly better protection against any of these outcomes compared with standard pyrethroid-only LLINs in the third year of their use. This finding contrasted with the first 2 years of the trial, where reductions were observed in all outcomes in the chlorfenapyr-pyrethroid LLIN group.[11] There was no apparent reduction in malaria or vector density in the pyriproxyfen-pyrethroid LLIN group in the third year as was also shown in the second year post-distribution reported previously.[11]

Chlorfenapyr-pyrethroid LLINs only provided superior protection compared with standard pyrethroid-only LLINs in the first 2 years of use. A probable contributing factor for the lower efficacy in the third year was that chlorfenapyr-pyrethroid LLIN usage over the course of the trial declined from 83% after 9 months post-distribution to 52% at 36 months post-distribution. However, in the only other RCT of chlorfenapyr-pyrethroid LLIN conducted in Tanzania, usage of the chlorfenapyr-pyrethroid LLIN was lower than in our trial (31% in Tanzania *vs* 52% in Benin at 36 months); this RCT showed a sustained superior protection against malaria infection (43% reduction in odds) and vector density (54% reduction) compared with standard pyrethroid-only LLINs up to the third year.[15] This finding suggests that reduction in net usage might not be the only factor impacting the efficacy of chlorfenapyr-pyrethroid LLINs in the third year in Benin.

There was also a 75% reduction in chlorfenapyr content in these nets at 24 months when compared to the initial concentration, which was of a similar magnitude to that reported in Tanzania (82%) for the same timepoint. While the durability and bioefficacy studies of 36-month-old nets are ongoing in Benin, based on the 24-month results and the findings from the Tanzanian trial (92% reduction in insecticide content),[15] we would anticipate a substantial decline in insecticide content at 36 months also in the present RCT in Benin. Previous experimental hut studies of chlorfenapyr-pyrethroid LLINs showed relatively small reductions in *Anopheles* mortality when exposed to nets washed 20 times (aimed to mimic 3 years of use in the community) compared with new ones.[3,18,19] However, nets used in the community are exposed to more abrasive environments than in the laboratory, and reduction in chlorfenapyr content is much higher in the community and was associated with reduction in killing effect in recent experimental hut studies in Tanzania.[20] In the hut study, the superior impact of chlorfenapyr-pyrethroid LLIN on mosquito mortality compared with standard pyrethroid-only LLINs was evident for up to 2 years, with significant differences observed for up to 1 year only. The bioefficacy results of nets used by the community in Benin will be essential to confirm if the lower effect of the chlorfenapyr-pyrethroid LLIN observed during the third year is linked to a decline in insecticide on the nets. A previous study also conducted in Benin showed the key role of chemical content on the chlorfenapyr mixture nets' long-term efficacy.[3]

A possible explanation for the difference in results during the third year between the Benin and Tanzania RCTs might be the higher vector density and malaria transmission and incidence observed in our study area.[10,11] The effect sizes recorded during the first 2 years were of

similar magnitude in both settings, with the greatest impact seen when the nets were up to a year old. However, malaria infection returned to levels present before the implementation much quicker in Benin, which could be due to the transmission pressure resulting in a quicker resurgence than was observed in Tanzania.

In this paper, similar to the results of the first 2 years, the pyriproxyfen-pyrethroid LLIN did not provide additional protection against malaria infection or disease compared with pyrethroid-only LLINs in the third year. Although there was some evidence of an impact on indoor entomological outcomes in the pyriproxyfen-pyrethroid LLIN group in the first year, the effect declined and the reduction in indoor vector density was not sustained. Comparable findings were reported from the RCT in Tanzania assessing the same pyriproxyfen-pyrethroid LLIN brand.[15] In Benin, the use of pyriproxyfen-pyrethroid LLIN dropped more than the other brands of nets in the trial and only 39% of the participants declared using the net the previous night at 36 months post-distribution. Even at the start of the study, pyriproxyfen-pyrethroid LLIN usage was the lowest of the three brands of net, suggesting that the community might have preferred the softer polyester brands. In Benin, a study showed that the survivorship and attrition rate of Olyset nets made of polyethylene yarn (rough plastic-like fabric), similar to Royal Guard, was lower than predicted by assuming a 3-year service life.[21] Textile durability has been shown to depend on attitudes to net care, which differs across countries,[22] but if communities dislike certain net materials, they might be more likely to swap them for other nets, regardless of the net's physical condition.[23] Based on our RCT and the parallel Tanzania trial, WHO provided a conditional recommendation for the deployment of pyriproxyfen-pyrethroid LLINs, despite the very limited evidence for superiority found in the most recent two trials compared to pyrethroid-only nets.[12]

In our trial, study net usage decreased over the course of the trial (from 76·8% to 49·9%); however, overall net usage remained around 80% as standard pyrethroid-only LLINs were routinely distributed in health facilities by the government through antenatal care and the expanded programme for immunisation. The access to non-trial nets existing in the household might have played a role in the specific use of trial nets. A recent review showed that the main reported reason for a net not being used was that it was being saved for future use.[24] Similar observations were reported in Tanzania, where nets are additionally provided for free to primary school pupils through school net distribution programmes.[15] These additional nets are likely to have influenced the outcomes we measured in our trials, as high population coverage, of any type of nets, will result in community-level reductions in transmission. However, households are unlikely to retain any nets for the intended 3 years if they have physically deteriorated,[25] and the results from both the Benin and Tanzania RCTs highlight that 3 years after mass distributions, coverage of study nets is moderate to low. Continuous distribution strategies and more tailored approaches to maintain high net coverage will be key to improve impact,[26,27] particularly as none of the new generation of nets has been shown to provide superior efficacy to pyrethroid nets for the full distribution cycle of 3 years in this high-transmission setting. These continuous distribution strategies would allow rotation of new net classes, in line with insecticide resistance management strategies.[28] National malaria control programmes might also consider deploying other cost-effective strategies that could help boost vector control in the third year post-distribution.[29,30] In addition, understanding the obstacles and enablers related to bednet usage in communities will be important to tailor educational campaigns and distribution methods and increase use and care of nets.[24]

One of the main study limitations was the moderate to low study net usage during the third year of follow-up, which might explain the lack of impact offered by the two study nets at this timepoint. Our per-protocol analysis showed similar results to the intention-to-treat analysis but this might also have been impacted by the high usage of other, newer nets. In addition, our results might have been influenced by measurement bias in the intention-to-treat and selection bias in the per-protocol estimates. There was inconclusive effect for any reduction during this third year, which might have been the result of insufficient statistical power for a possibly smaller effect size and due to lower malaria incidence and prevalence in all three study groups in the third year, compared with baseline.

The study showed that in a high malaria transmission setting of west Africa, chlorfenapyr-pyrethroid LLINs no longer offered superior protection against malaria compared with pyrethroid-only LLINs in the third year post-distribution. Although low to moderate net usage is probably a contributing factor, chlorfenapyr decay on the net might also explain the lower efficacy observed in the third year. Regardless, until the quality of the nets is improved to meet the 3-year target for long-lasting efficacy, the use of continuous channels to distribute nets might mitigate the shortcomings of these nets and allow more tailored distributions based on transmission, to ensure an effective level of net coverage and insecticidal content at any one time.

Contributors

NP, JC, and CN conceived and designed the study with contributions from MR, IK, LAM, and MCA. JC and MA led the development of the analysis plan with input from BA, AS, and NP. MA, JC, NP, and MCA coordinated the trial implementation with local and national authorities. MA, BY, AS, CJA, and LA led the data collection in the field with CA and GGP, and oversight from MCA, JC, and NP. MA, JC, and NP wrote the data management plan and with ED developed collection tools and managed the data. MA, ED, LA, BA, AS, and JC did statistical analysis of the epidemiological and entomological outcomes with input from MCA

and NP. MA, JC, AS, and NP wrote the first draft of the manuscript with inputs from CN, MR, IK, and MCA. All authors have reviewed, read, and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. MA, ED, JC, and NP accessed and verified the data.

Declaration of interests

We declare no competing interests.

Data sharing

Data collected for the study, including de-identified participant data and data dictionaries, will be made available at the end of the third year of trial follow-up upon publication and reasonable request to the corresponding author.

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