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Doctopic: Review and Opinion

Malaria vector control in sub-Saharan Africa: complex trade-offs to combat the growing threat of insecticide resistance

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Mass distribution of insecticide-treated nets (ITNs) has been a key factor in reducing malaria cases and deaths in sub-Saharan Africa. A shortcoming has been the over-reliance on pyrethroid insecticides, with more than 2·13 billion pyrethroid ITNs (PY ITNs) distributed in the past two decades, leading to widespread pyrethroid resistance. Progressive changes are occurring, with increased deployment of more effective pyrethroid-chlorfenapyr (PY-CFP) or pyrethroid-piperonyl butoxide (PY-PBO) ITNs in areas of pyrethroid resistance. In 2023, PY-PBO ITNs accounted for 58% of all ITNs shipped to sub-Saharan Africa. PY-PBO and PY-CFP ITNs are 30–37% more expensive than standard PY ITNs, equating to an additional US$132–159 million required per year in sub-Saharan Africa to fund the shift to more effective ITNs. Several countries are withdrawing or scaling back indoor residual spraying (IRS) programmes to cover the shortfall, which is reflected by the number of structures sprayed by the US President's Malaria Initiative decreasing by 30% from 5·67 million (2021) to 3·96 million (2023). Benin, located in West Africa, is a prime example of a country that ceased IRS in 2021 after 14 years of annual spraying. Our economic evaluation indicates that IRS in Benin cost $3·50 per person protected per year, around five times more per person protected per year compared with PY-PBO ($0·73) or PY-CFP ITNs ($0·76). Although costly to implement, a major advantage of IRS is the portfolio of at least three chemical classes for prospective resistance management. With loss of synergy to PBO developing rapidly, there is the danger of over-reliance on PY-CFP ITNs. As gains in global malaria control continue to reverse each year, current WHO projections estimate that key 2030 malaria incidence milestones will be missed by a staggering 89%. This Personal View explores contemporary malaria vector control trends in sub-Saharan Africa and cost implications for improved disease control and resistance management.

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Introduction

The core vector control interventions recommended by WHO to reduce malaria transmission are universal coverage with insecticide-treated nets (ITNs) or indoor residual spraying (IRS) of houses.[1] ITNs are widely used by households across much of sub-Saharan Africa and have proved successful at driving the reduction of malaria transmission.[2] Between 2000 and 2015, it is estimated that vector control averted 663 million clinical cases of malaria in sub-Saharan Africa, with ITNs contributing to 68% of that decline.[2] Pyrethroid insecticides were the exclusive chemical class used on ITNs, with an estimated 2·13 billion pyrethroid ITNs delivered in sub-Saharan Africa between 2004 and 2022.[3] While the global malaria mortality rate halved between 2000 and 2015, progress has stalled and even begun to reverse in recent years coinciding with growing pyrethroid resistance, plateauing ITN coverage metrics and exacerbated by disruption during the SARS-CoV-2 pandemic.[4,5] If changes to malaria control are not implemented imminently, WHO projections indicate that key 2030 malaria morbidity and mortality milestones, outlined in the Global Technical Strategy for Malaria 2016–2030, will be missed by 89% and 88%, respectively.[6]

Selection pressure from multiple sources including decades of agricultural pesticide use coupled with large-scale distribution of pyrethroid ITNs (PY ITNs), sometimes in combination with pyrethroid IRS, inevitably led to a gradual intensification of pyrethroid resistance in major malaria vector species.[7–9] As a result, pyrethroid resistance across sub-Saharan Africa is ubiquitous and entrenched, with high intensity pyrethroid resistance reported across many countries.[10–12] Mass distribution of PY ITNs continues to further intensify phenotypic resistance, even in established resistant malaria vector populations.[13] Evidence of pyrethroid resistance starting to compromise PY ITN operational performance was first documented in West Africa more than 15 years ago.[14,15] Fears of widespread ITN failure were tempered by several studies, including a large-scale WHO-coordinated study, which indicated that ITNs continue to provide personal protection with no association between net effectiveness and pyrethroid resistance status.[16–18] However, a subsequent study in Malawi reported a loss of protective effect when using aged PY ITNs (1–2 years old) in an area of moderate pyrethroid resistance.[19] More recent cluster randomised controlled trials (cRCTs) in Benin, Tanzania, and Uganda (where high intensity pyrethroid resistance was present) showed that PY ITNs continued to provide some protection, but their performance was sub-optimal in all locations.[20–23]

While ITNs have been the primary vector control tool in sub-Saharan Africa, IRS continues to have an important role, often in targeted high-transmission locations or in countries with a long-standing history of IRS. The landscape of IRS has changed substantially since the era of dichlorodiphenyltrichloroethane (DDT) house-spraying as the fulcrum of the WHO-led Global Malaria Eradication Programme (1955–69).[24,25] Following years of inertia, availability of cheap and long-lasting pyrethroid insecticides led to increased IRS across sub-Saharan Africa in the 2000s, often as a complementary measure to PY ITNs.[26] There have been numerous publications highlighting the danger of relying on a small arsenal of public-health products. In 2002, the head of

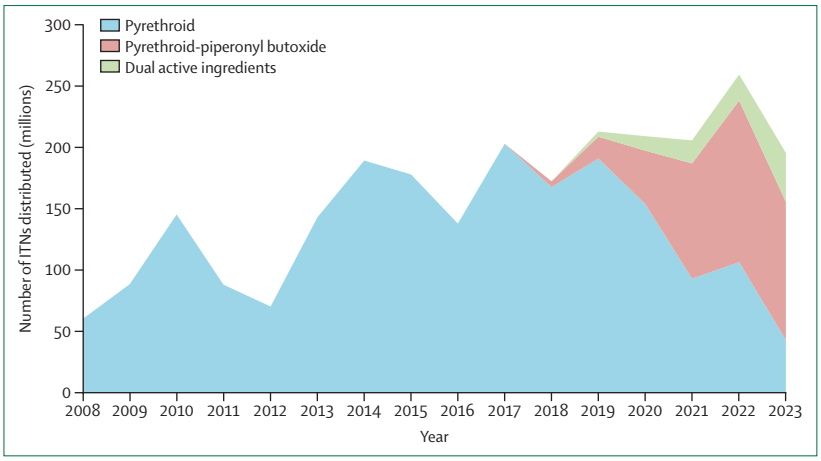

Figure 1: **Number and type of insecticide-treated nets delivered to sub-Saharan Africa per year**
Figure adapted from The Alliance for Malaria Prevention.[3] ITN=insecticide-treated nets.

the WHO Pesticide Evaluation Scheme issued a call for action, stating that "Mobilizing public resources and establishment of partnerships to support research and development of public health insecticides is crucial in the post-DDT and post-pyrethroid era."[27] In recent years, several new classes of insecticide for IRS and ITN have been developed, which has led to a pronounced change in malaria vector control practices.[28]

This Personal View explores contemporaneous trends in the malaria vector control landscape in sub-Saharan Africa and the cost implications associated with use of new chemical classes for improved malaria vector control and resistance management.

Pyrethroid-piperonyl butoxide insecticide-treated nets are a decade too late

Pyrethroids were the sole insecticide class used on ITNs for more than 20 years in sub-Saharan Africa before alternative products became available. The synergist piperonyl butoxide (PBO) was commercially developed in the USA in the 1950s for various uses, including pest control.[29] PBO has no direct insecticidal effect, but when combined with pyrethroids, enhances their activity against mosquitoes by inhibiting mixed function oxidase resistance mechanisms.[30] PermaNet3.0 was the first pyrethroid-PBO ITN (PY-PBO ITN) to receive WHO interim recommendation in 2009.[31] However, it was not until 9 years later in 2018 when PY-PBO ITNs started to be distributed at scale to combat pyrethroid-resistant malaria vectors.[32] This lengthy delay in using PY-PBO ITNs could have been shortened by prioritising funding for large-scale field trials to establish the long-term effectiveness of PY-PBO ITNs in areas with pyrethroid-resistant malaria vectors. Pyrethroid-PBO ITNs only began to be distributed at scale following a landmark cRCT in Tanzania that showed a sustained reduction in malaria prevalence over a 2-year period by PY-PBO ITNs (odds ratio 0·40, 95% CI 0·20–0·81) compared with PY ITNs in an area of high intensity pyrethroid resistance.[21] This epidemiological evidence led to a revised WHO position in 2017 whereby PY-PBO ITNs were endorsed as a new class of vector control product.[33] Subsequently, a similar epidemiological effect of PY-PBO ITNs was reported from trials in Uganda.[23,34] The market share for PY-PBO ITNs in sub-Saharan Africa has substantially increased in recent years, rising to 58% of ITNs (112·6 million) delivered in 2023, and a concurrent decrease in PY ITNs to 22% (43·0 million; figure 1). In the 6 years from 2018 to 2023, a total of 404 million PY-PBO ITNs were delivered to sub-Saharan Africa.[32]

In terms of insecticide resistance management, PY-PBO ITNs cannot be viewed as a new chemical class. Given the high intensity of pyrethroid resistance in many countries and multiple resistance mechanisms present, loss of complete synergy with PBO could develop rapidly. Susceptibility bioassays have already shown that PBO does not fully synergise some pyrethroids in parts of Malawi,[35] Togo,[36] Cameroon,[37,38] Niger,[39] Benin,[40] Burkina Faso,[41] Tanzania,[42] Mali,[11] Guinea-Bissau,[43] Guinea,[44] Mozambique,[45] Uganda,[46] and Ghana.[7] These bioassay data are a crucial proxy to establish where such ITNs are suitable for distribution. However, there is currently little basis for deciding what threshold of mortality in synergist susceptibility tests predicts the potential loss of ITN operational field performance. There are also indications that PBO has a lower wash resistance than pyrethroids and the quantity of PBO on ITNs can diminish substantially 1–2 years after distribution.[47] Of greater concern are findings from a more recent cRCT trial in Tanzania, where PY-PBO ITNs provided limited additional effectiveness compared with standard PY ITNs for only 12 months, a much shorter duration than in previous cRCTs.[20] Entomology data indicated that permethrin resistance increased 56-fold in *Anopheles funestus* s.l. during the 3-year study, while multiple resistance mechanisms diminished the synergistic effect of PBO.[13] This study highlights the dynamic nature of insecticide resistance and the importance of regular monitoring of PBO synergism in susceptibility bioassays to guide decision making for PY-PBO ITN distribution. There is a real, imminent danger that repeated distribution of PY-PBO ITNs might result in partial or total loss of the synergistic effect and further exacerbation of pyrethroid resistance. Escalation of pyrethroid resistance and selection for associated cross-resistance mechanisms has negative long-term consequences for the design and development of novel insecticides for malaria vector control.

Dual active ingredient ITNs; over-reliance on chlorfenapyr

In recent years, new dual active ingredient ITNs treated with two different insecticide classes have been developed for improved control of pyrethroid-resistant malaria

vectors. Currently, there are two types of dual active ingredient net, pyrethroid-pyriproxyfen (PY-PPF) and pyrethroid-chlorfenapyr (PY-CFP) ITNs. As both nets contain new chemical classes intended to control pyrethroid-resistant malaria vectors, 24 months of epidemiological evidence was required from two cRCTs for review by the WHO Vector Control Advisory Group (VCAG) to establish whether there was public health benefit from their deployment.

Pyriproxyfen is an insect juvenile hormone analogue that works by inhibiting egg development, sterilising adult female mosquitoes and shows some level of mosquito mortality.[48] Initial laboratory and semi-field testing of PY-PPF ITNs produced promising results, with a combined effect in terms of mosquito mortality and substantial reductions in mosquito reproduction.[48–50] Three large-scale cRCTs of PY-PPF ITNs have since been conducted in Burkina Faso, Benin, and Tanzania. In Burkina Faso, results of a stepped wedge cRCT with Olyset Duo (PY-PPF) ITNs over an 18-month period showed a 12% reduction (rate ratio 0·88, 95% CI 0·77–0·99) in malaria incidence and a 51% reduction (rate ratio 0·49, 95% CI 0·32–0·66) in entomological inoculation rate when compared with PY ITNs.[51] Subsequent cRCTs in Benin and Tanzania were conducted with Royal Guard ITNs, which have similar specifications to Olyset Duo. In both trials, there was no evidence that Royal Guard ITNs provided any greater protection than PY ITNs after 24 months of use, with a malaria incidence hazard ratio of 0·86 (95% CI 0·65–1·14) in Benin and malaria prevalence odds ratio of 0·82 (95% CI 0·55–1·23) in Tanzania.[20,52] Subsequently, WHO issued a conditional recommendation in 2023 for the deployment of PY-PPF ITNs, noting issues around their poor cost-effectiveness compared with PY ITNs.[1] Of concern was the finding in Tanzania that wild *An. funestus* s.s. and *An. gambiae* s.s. became resistant to the sterilising effects of pyriproxyfen, with the intensity of pyrethroid resistance also increasing over the 3 years following ITN distribution.[13] Meta-analysis by Barker and colleagues indicated that PY-PPF ITNs provided no significant reduction in malaria case incidence compared with PY ITNs (incidence rate ratio 0·9, 95% CI 0·73–1·13).[53] It should be noted that Olyset Duo is no longer produced commercially, while Royal Guard has WHO prequalification and two further PY-PPF ITNs (DuraActive and Miranet Combi) are under assessment.

Chlorfenapyr is a pyrrole compound with a non-neurotoxic mode of action that involves uncoupling of oxidative phosphorylation at the mitochondria, disruption of ATP production, cell death, and organism mortality.[54] Interceptor G2 is a PY-CFP ITN that received WHO prequalification in 2018,[28] followed by the "next in class" product PermaNet Dual, which received WHO prequalification in 2023, while further generic PY-CFP ITNs are under WHO prequalification consideration.[28] Two cRCTs conducted in Benin and Tanzania showed that malaria transmission was approximately 50% lower in PY-CFP ITN clusters than those with PY ITNs, 2 years after ITN distribution. In Benin, the malaria incidence hazard ratio over a two-year period following ITN distribution was 0·54 (95% CI 0·42–0·70, p<0·0001), while in Tanzania the malaria prevalence odds ratio was 0·45 (95% CI 0·30–0·67, p=0·001).[20] WHO subsequently issued a strong recommendation for the deployment of PY-CFP ITNs to prevent malaria in areas where mosquitoes have become resistant to pyrethroids.[1] Grouping together PY-CFP and PY-PPF ITNs under the same dual active ingredient classification is not helpful because of how different these nets are, and the malaria community should rather refer to these nets separately henceforth.

Increased cost burden of ITNs to control pyrethroid-resistant malaria vectors

The price of PY ITNs has been driven down from US$7–15 per net[55] in the 1980s and 1990s to around $2 per net because of competition from multiple manufacturers (there are currently 15 PY ITN products with WHO prequalification)[28] and low raw material and labour costs coupled with industrial scale production and stable demand.[56] Inevitably, PY-PBO ITNs and dual active ingredient ITNs are more expensive than conventional PY ITNs. Price listings for a Global Fund pooled procurement mechanism were $2·08 for a PY ITN compared with $2·71 for a PY-PBO ITN and $2·84 for a PY-CFP ITN (based on the commonly procured size of 180×190×150 cm rectangular net, including hooks, strings, and bag).[56] While this price change might appear to be modest, it represents a 30–37% increase in ITN cost. Given the large population at risk of malaria in sub-Saharan Africa and the short lifespan of ITNs, a substantial quantity is procured annually with a mean of 209 million ITNs delivered to sub-Saharan Africa per year (2018–23 data).[3] Based on current quantities and unit prices, it would cost an additional $132–159 million per year to switch from pyrethroid to PY-PBO or PY-CFP ITNs. The current Global Fund grant cycle has restricted increases in malaria budgets, which will impede the uptake of these more effective but more expensive ITNs.[57] While ITNs have been the primary strategy for malaria vector control in most of sub-Saharan Africa in recent decades, it is important to examine the role of IRS in the control of pyrethroid-resistant malaria vectors.[2]

Resistance management potential of IRS impeded by high cost

Insecticide formulations used for the US President's Malaria Initiative (PMI)-funded IRS campaigns have changed substantially over time. DDT is a persistent organic pollutant that should be phased out to meet the stipulations of the Stockholm Convention and should only be used for malaria vector control when there are no equally effective or efficient alternatives.[58] In keeping with this guidance, DDT has not been used in

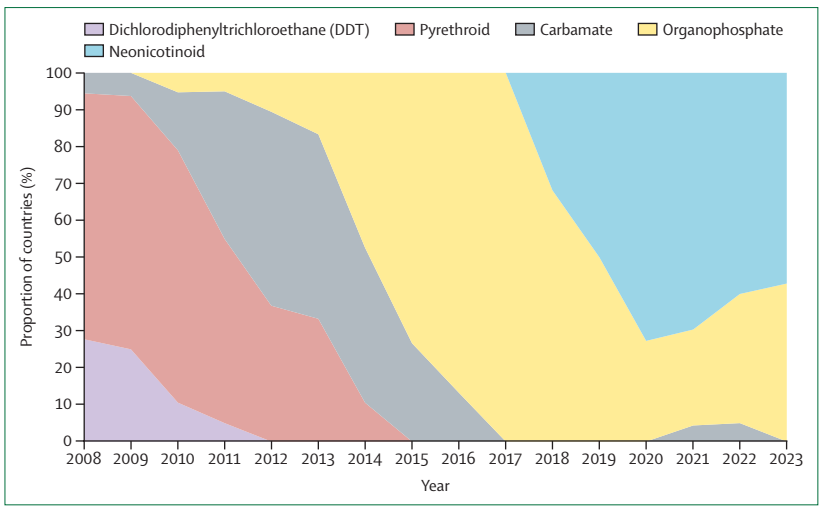

Figure 2: **Insecticide class used per year in President's Malaria Initiative-funded indoor residual spraying campaigns 2008–23 (proportion of countries that sprayed each insecticide class)**

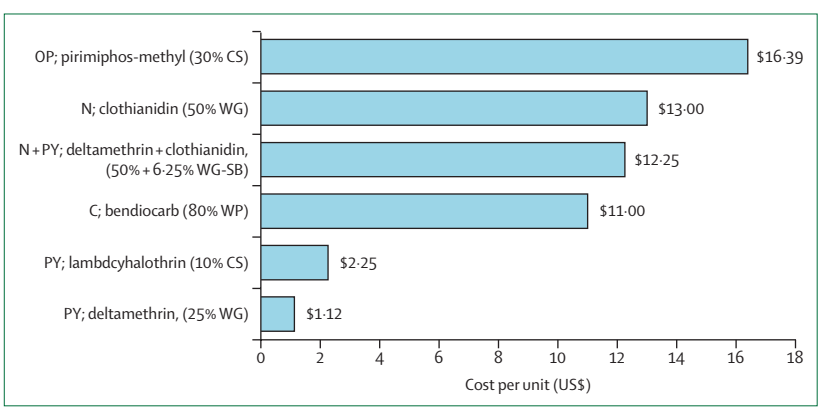

Figure 3: **Cost of insecticide per sachet or container equivalent to spray a surface of 250 m² at the recommended concentration[63]**

C=carbamate. CS=capsule suspension. N=neonicotinoid. OP=organophosphate. PY=pyrethroid. WG=water dispersible granules. WG–SB=water dispersible granules in a sealed water-soluble bag. WP=wettable powder.

US-PMI-funded IRS programmes since 2011. Figure 2 shows that pyrethroid insecticides were the dominant IRS insecticide in 2008, followed by gradual replacement with carbamate insecticide bendiocarb wettable powder (WP) in several countries due to concerns about the spread of pyrethroid resistance. Bendiocarb WP generally had a short residual duration and in many settings did not adequately cover the main malaria transmission periods, especially if there was more than one rainy season per year.[59] Given concerns over pyrethroid resistance and short residual duration of bendiocarb WP, the long-lasting organophosphate formulation pirimiphos-methyl capsule suspension (CS) came to dominate IRS campaigns in 2015. Formulations of the neonicotinoid clothianidin (SumiShield water dispersible granules and Fludora Fusion WP) received WHO prequalification in 2017 and 2018, respectively, and have been heavily used since, often in rotation with pirimiphos-methyl CS, as part of national resistance management plans.[28,60] In 2023, broflanilide WP (Vectron™ T500), a meta-diamide insecticide, received WHO prequalification following a series of laboratory and experimental hut studies that consistently showed a 12-month residual duration. In addition, perlite WP (Imergard; physical mode of action) and chlorfenapyr suspension concentrate (Sylando 240; pyrrole) are currently under WHO prequalification review. The portfolio of insecticide classes for IRS has never been stronger and effective insecticide resistance management by rotation of organophosphate, neonicotinoid, meta-diamide, and physical modes of action formulations are an exciting prospect. Given the dearth of effective ITN insecticide options, it would be prudent to preserve chlorfenapyr solely for ITNs and not for IRS to limit the speed of resistance development. Agricultural use of chlorfenapyr in sub-Saharan Africa is believed to be uncommon, but has the potential to accelerate the development of resistance in malaria vectors and is beyond the influence of malaria control programmes.[61]

While IRS is particularly appealing from a resistance management perspective given the various chemical classes, the high cost of IRS programmes has restricted coverage to a small proportion of the at-risk population. The unweighted mean cost per structure sprayed across all PMI IRS programmes per year was $19·62 in 2008 and gradually increased to $28·90 per structure in 2022.[62,63] However, economies of scale are the largest driver of unit costs for IRS programmes and the cost of campaigns for more than 200 000 structures was substantially lower at $13·13 in 2008 and $15·50 per structure sprayed in 2022.[62,63]

Insecticides are an important component of overall IRS campaign cost and vary substantially by chemical class and formulation. The cost for a sachet of pyrethroid is particularly low at $1–2, but is much more expensive for a unit of neonicotinoid at $12–13 or organophosphate formulations at $16 (figure 3). Higher insecticide costs are associated with scaling back of IRS coverage in some countries in recent years.[26] While insecticides only accounted for approximately 20% of mean IRS campaign costs in 2022, this increased to 36% for more efficient larger campaigns (for more than 200 000 structures).[62] Comparatively, total insecticide costs for campaigns in 2008 were 10–13% when cheaper pyrethroids were the dominant class sprayed.[63]

Cost-effectiveness is a key component of any public health decision making, particularly for malaria control commodities where the population at-risk of malaria transmission is large and increasing. While initiatives such as the Next Generation IRS project and the Innovative Vector Control Consortium have had some success in bringing new active ingredients to market and have stabilised prices, the cost of viable formulations is still more than ten times that of the cheapest pyrethroid IRS formulation.

Scaling back IRS programmes to fund more expensive ITNs

US-PMI-funded IRS reached peak coverage in 2010 when 7·6 million structures were sprayed, mostly with inexpensive pyrethroid insecticides. The coverage decreased to 4·2 million structures in 2015 driven primarily by a shift to a more expensive long-lasting organophosphate. Subsequently, there has been a modest increase in structures sprayed due to increased budgets for IRS, reaching 5·7 million structures in 2018, which has been largely maintained since. A major shift has taken place recently, with a 30·2% decrease in structures sprayed in the 2 years from 2021 (5·67 million) to 2023 (3·96 million; appendix p 3).

Several countries have withdrawn IRS completely, including notable countries with a long-standing history of IRS (Benin, Malawi, Mali, Mozambique, Senegal, and Tanzania) and high burden countries, which only recently initiated IRS programmes (Burkina Faso and Côte d'Ivoire). Figure 4 shows that peak IRS coverage for these eight countries was in 2012 when 2·52 million structures were sprayed, mostly with pyrethroids, decreasing to 1·27 million in 2015 coinciding with a shift to more expensive formulations, predominantly pirimiphos-methyl CS. From 2015 to 2021, the number of structures sprayed remained stable at 1·5–2 million, followed by a substantial decrease to an expected zero structures to be sprayed in 2024. The primary reason reported was the need to prioritise resources to fund the transition from pyrethroid to PY-PBO, PY-CFP, or PY-PPF ITNs.[64–66]

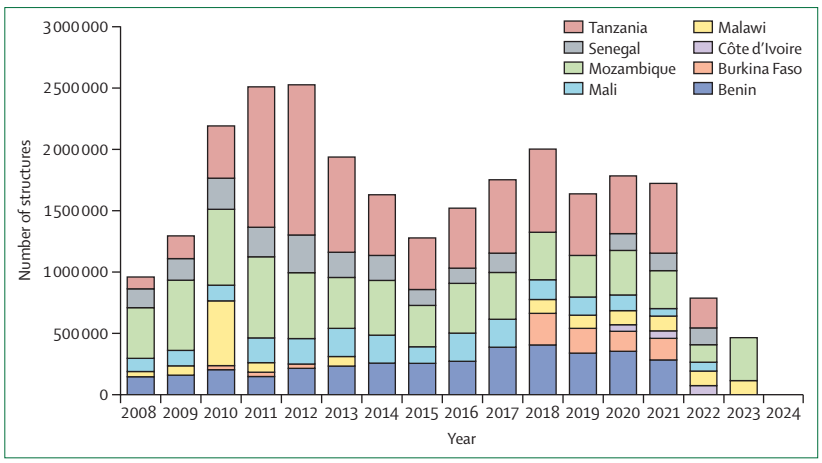

Figure 4: **Trend in number of structures sprayed over time for countries that have recently withdrawn indoor residual spraying**

Uncertain rationale for co-deployment of IRS with ITNs

Universal coverage with ITNs has become the standard of care in much of sub-Saharan Africa while IRS has been conducted in strategic locations, usually in addition to ITNs. As both ITNs and IRS target mosquitoes that are host-seeking or resting indoors, respectively, it is uncertain whether there is additional benefit in co-deploying both interventions. Such a combination could be beneficial from a resistance–management perspective only when two different insecticides are used for which there is no existing resistance in the mosquito population.[67] Since pyrethroid resistance is widespread throughout sub-Saharan Africa, the model in the past decade has been for non-pyrethroid IRS to compensate for the sub-standard killing effect of PY ITNs. PY ITNs continued to provide some personal protection as a physical barrier and chemical repellent, while non-pyrethroid IRS provided an additional mass killing effect.[68] A cRCT in Tanzania in 2013 clearly showed that IRS with a carbamate used in combination with PY ITNs provided additional protection against pyrethroid-resistant malaria vectors compared with PY ITNs alone.[69] Several subsequent studies have indicated that non-pyrethroid IRS provided additional impact when used together with PY ITNs.[70–74] However, IRS might not provide additional benefit when combined with effective PY-PBO and PY-CFP ITNs. Some combinations of insecticides might even reduce mosquito mortality via an antagonistic effect, with pro-insecticides such as pirimiphos-methyl and chlorfenapyr (that require cytochrome P450 enzymes to induce toxicity) inhibited by PBO.[40,75] A recent cRCT in Tanzania showed that pirimiphos-methyl IRS in areas with PY-PBO ITNs provided no additional benefit compared with use of PY-PBO ITNs alone.[21] Further cRCTs are needed to establish whether this result is mirrored with PY-CFP ITNs. Practically, the high cost of non-pyrethroid IRS plus PY-CFP ITNs mean that this approach is unlikely to be implemented widely. WHO does not recommend co-deployment of ITNs and IRS with priority given to delivering either ITNs or IRS at optimal coverage and to a high standard rather than introducing the second intervention to compensate for deficiencies of the first.[1]

Case study: cost analysis of vector control in Benin

Benin has made substantial progress in malaria control; however, cases have risen steadily from approximately 3·6 million in 2012 to 5·0 million in 2021.[4] ITNs are the primary method of malaria vector control in Benin with mass nationwide campaigns (financially supported by the The Global Fund to Fight AIDS, Tuberculosis and Malaria, US-PMI, and the Government of Benin) taking place every 3 years and supplemented by continuous distribution via antenatal care and immunisation systems. A total of 7·65 million ITNs were distributed nationwide in 2020 during the first digitised mass campaign,[76] followed by 8·9 million ITNs consisting of PY, PY-PBO, and dual active ingredient ITNs distributed in 2023.[32] The percentage of households with at least one ITN for every two people (universal coverage) increased from 7% in 2006 to 45% in 2011–12 and 61%

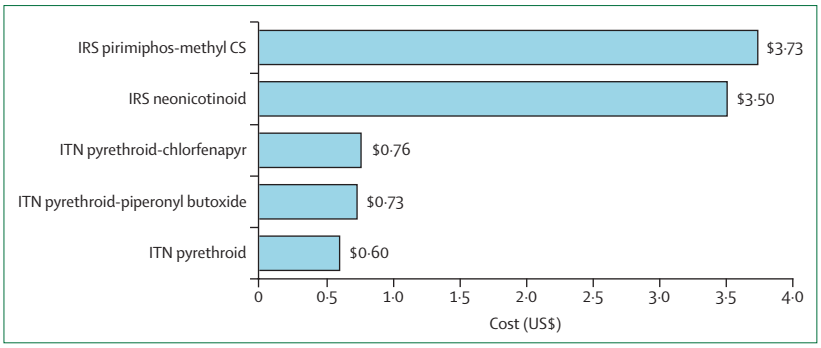

Figure 5: **Estimated cost in US$ per person protected per year by vector control method and type of insecticide**
CS=capsule suspension. IRS=indoor residual spraying. ITN=insecticide-treated net.

in 2017–18, with 92% of rural households owning at least one ITN.[77–79] IRS was implemented annually from 2008 to 2021, with the most recent campaigns targeting the high transmission regions of Alibori, Donga, and Atacora in northern Benin.[80] The scale of IRS campaigns in Benin has always been restricted to a small number of the at-risk population, with a range of 150 000–400 000 structures sprayed per year in high transmission areas.[64] The rationale for discontinuing IRS in Benin was based on several factors, including the high cost of IRS for limited coverage, epidemiological data from health facilities suggesting minimal effect, and the need for additional funding to distribute more expensive PY-PBO and PY-CFP ITNs.[81]

We calculated the cost for nationwide ITN distribution and targeted IRS in seven districts, based on current insecticide costs and recent operational costs of ITN and IRS campaigns in Benin. The estimated cost per person protected per year was five times greater for IRS with neonicotinoid ($3·50) or organophosphate ($3·73) insecticides compared with PY-PBO ($0·73) or PY-CFP ($0·76) ITNs (figure 5). Important assumptions in these calculations (that are routinely used when planning vector control campaigns) were that IRS provides protection for 12 months and ITNs for 3 years. However, the durability of ITNs varies considerably by net type and location, but is often far lower than what the policy presumes, with an estimated median net retention time of just 1·64 years (IQR 1·33–2·37) across sub-Saharan Africa.[5] Even when recalculated based on protection for 1·64 years, PY-CFP ($1·38) and PY-PBO ($1·33) ITNs are 2·5–3-fold cheaper per person protected per year than IRS with organophosphates ($3·73) or neonicotinoids ($3·50; appendix pp 4–6). The shift from cheap pyrethroids to more expensive organophosphate and neonicotinoid formulations has been linked to declining coverage in sub-Saharan Africa.[26] While this shift in cost is a contributory factor, the complex logistical arrangements for IRS and necessity of annual re-application due to short residual duration (1 year or less) lead to far higher logistical and programmatic costs than for ITN distribution. There is evidence of newer formulations, such as meta-diamides and neonicotinoids, surpassing WHO thresholds in bioassays for up to 2 years, which could considerably lower IRS costs.[82]

Although the cost difference between PY ITNs and PY-PBO or PY-CFP ITNs appears small at the individual level ($0·13–0·16 per person protected per year), when extrapolated to nationwide mass distribution in Benin this equates to an estimated additional $6·1–7·4 million (depending on the ratio of PY-PBO and PY-CFP ITNs procured). The estimated annual cost for IRS in seven districts (calculated based on 2020 operational costs) is $3·9–4·1 million. Therefore, cost-savings from IRS withdrawal are sufficient to cover the increased cost of nationwide PY-PBO and PY-CFP ITNs over a 3-year mass distribution cycle.

This cost analysis is specific for Benin, but some trends broadly align with multi-country observations indicating an economic cost of $0·59–1·65 per person year of protection from standard PY ITNs and an unweighted average of $7·66 ($3·79–16·31) per person protected by IRS with neonicotinoid or organophosphate formulations.[62,83]

While IRS is quite expensive, a major advantage is the portfolio of at least three chemical classes (organophosphates, neonicotinoids, and meta-diamides), with further new classes in advanced development,[84] which contrasts with ITNs where prospects for resistance management by rotation of different insecticide classes are highly restricted.

Study limitations

We primarily used US-PMI data to document IRS insecticide trends in sub-Saharan Africa, noting that campaigns from other funding sources might follow different trajectories. The US-PMI is a major funder of IRS in sub-Saharan Africa and is highly transparent regarding the online publication of IRS campaign data, hence our decision to use this data. The Global Fund are the other major funder of IRS for malaria control in sub-Saharan Africa, with 8·4 million households sprayed in 2022 in 17 countries. The Global Fund were approached for more detailed IRS data, but they were not forthcoming. Estimates of ITN cost for Benin in this study are based on the status quo of mass nationwide distribution every 3 years using a population divided by 1·8, with limited continuous distribution in the intervening years. It is recognised that this approach is insufficient to achieve targets of 80% population access and that in future, locally tailored quantification is needed that would increase cost calculations.[85]

Conclusion

Development of new IRS insecticides has proven far easier than ITN insecticides, yet the comparatively high cost has restricted IRS coverage to a small proportion of sub-Saharan Africa. Several agricultural insecticides have

been repurposed for IRS more easily due to similar application modality and low toxicological exposure risk. Development of new insecticides for ITNs has proven far more challenging given the need for wash resistance for several years of use and the greater potential for toxicological risk due to dermal and oral exposure.[86] While binders, cross-linkers, and fabric incorporation can be used to increase wash resistance, insecticides used for ITNs are required to have low water solubility to maintain their activity on nets, therefore rendering more soluble insecticide classes (eg, neonicotinoids) as unsuitable. A further barrier is the absence of financial incentive for companies to develop new insecticides for ITNs given the high research costs, low profit margins, and limited commercial protection with generic equivalent "me too" ITNs able to receive WHO prequalification listing, while bearing a fraction of the initial development costs.[87] Despite these challenges, efficacious ITNs continue to be the most cost-effective malaria control strategy and it is crucial that the long-term viability of ITNs is prioritised if malaria control and elimination targets are to be met.

Promising new vector control approaches in development include household spatial repellents and attractive targeted sugar baits, which are undergoing large-scale cRCTs in sub-Saharan Africa.[88,89] Preliminary data from Kenya showed protective efficacy of spatial repellents against malaria when used together with PY-PBO ITNs.[90] Despite enthusiasm regarding new vector control measures, these are complementary strategies and do not represent a silver bullet for malaria vector control. Insecticide-treated nets are estimated to have averted 450 million clinical cases of malaria between 2000 and 2015 and remain the primary vector control method used across sub-Saharan Africa now.[2] Based on current projections, WHO estimates that key 2030 malaria incidence milestones outlined in the Global Technical Strategy for Malaria will be missed by a staggering 89%.[6] While a portfolio of four types of ITN (pyrethroid, PY-PBO, PY-PPF, and PY-CFP) might appear to be reason for optimism, the reality is in stark contrast. The absence of a diverse ITN portfolio risks over-reliance on chlorfenapyr, with PY-PBO already becoming unviable in several locations due to rapidly evolving loss of PBO synergy and PY-PPF ITNs providing little or no public health benefit against pyrethroid-resistant mosquitoes. To enhance prospects for malaria control and elimination in sub-Saharan Africa, considerable funding is urgently needed both to develop a diverse range of insecticide classes for proactive resistance management and to support continent-wide roll-out of more expensive, but more cost-effective, ITNs. Considering the cost to develop a new insecticide is estimated at more than $250 million with more than 10 years of development time, rotational targeted IRS campaigns for resistance management might be worth maintaining in some locations despite the high associated funding required.[91,92]

Contributors

RMO and LAM conceived the manuscript topics, interpreted data, conducted data analysis, and wrote the manuscript. KLFC conducted economic analysis for insecticide-treated nets and indoor residual spraying interventions. FT contributed to the Benin case study. All authors read and approved the final manuscript. All authors had access to all the data in the study and had final responsibility for the decision to submit for publication. All authors accessed and verified the data.

Declaration of interests

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