Technical consultation to assess comparative efficacy of vector control products

Meeting report,
5 and 9 June 2023

World Health Organization

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Contents

Abbreviations

CI	confidence interval
GLP	good laboratory practice
GST	glutathione S-transferase
ITN	insecticide-treated net
IRS	indoor residual spraying
kdr	knockdown resistance
NIM	non-inferiority margin
OR	odds ratio
PBO	piperonyl butoxide
s.l.	sensu lato
s.s.	sensu stricto
WHO	World Health Organization

Executive summary

Four vector control products (three insecticide-treated nets [ITNs] and one indoor residual spray [IRS] product) were assessed for comparative efficacy against the first-in-class product in their respective intervention classes, as classified by the World Health Organization (WHO) vector control evaluation process.

Each of the three candidate nets (DuraNet Plus©, Yorkool® G3 and PermaNet® Dual) was assessed as being non-inferior to the first-in-class comparator in terms of the primary end-point of mosquito mortality. Based on the non-inferiority assessment of the primary end-point data, all three nets were considered to be covered by the WHO recommendation for the intervention class to which they belong. Data on the secondary end-point of blood feeding were also reviewed, although these data were not used for decision-making; their inclusion in this report is to ensure that programmes have access to these data.

The IRS product under assessment, VECTRON™ T500, contains an active ingredient (broflanilide) not covered by a WHO recommendation for vector control. The non-inferiority assessment of the candidate product found that it induces levels of mosquito mortality comparable to the active comparator, Actellic 300CS, on both mud and concrete substrates inside experimental huts. Therefore, it was advised that WHO should extend its IRS recommendation for malaria to include the insecticide broflanilide and that the candidate product be covered under this proposed revision.

1. Welcome and opening remarks

The Head of the Vector Control and Insecticide Resistance Unit of the Global Malaria Programme, Dr Jan Kolaczinski, opened the meeting. He reviewed the conclusions from the most recent meeting on comparative assessment of vector control products, along with the most recent report from the Malaria Policy Advisory Group, reiterating the need for the Global Malaria Programme to move forward with the implementation of the comparative effectiveness process and to provide any remaining clarification needed on how this process complements the WHO vector control evaluation and guideline development process.

Dr Kolaczinski thanked all those serving as temporary advisors and participants in the technical consultation for their support for WHO's work, as well as those manufacturers and researchers who had submitted data for analysis.

Prior to the meeting, Dr Seth Irish, Technical Officer within the Vector Control and Insecticide Resistance Unit of the Global Malaria Programme, assessed the "Declaration of interests for WHO experts" forms submitted by the temporary advisors of the technical consultation. Based on the assessment, it was decided that none of the declarations constituted conflicts of interest in this context, with the exception of Mr Olukayode Odufuwa, who had worked on the assessment of Yorkool® G3 and was therefore excluded from the session discussing this product. The full declarations of interest statement (see Annex 1) was read out at the meeting.

2. Background

Since 1 January 2017, WHO has been implementing a new process for evaluating vector control products *(1)*. The process aims at providing enhanced assurance of product safety, quality and efficacy (both entomological and epidemiological) to better meet the needs of WHO Member States. The assessment of individual products for their quality, safety and entomological efficacy is overseen by the WHO Prequalification Team for Vector Control Products, while the WHO technical departments, namely the Global Malaria Programme and the Department of Control of Neglected Tropical Diseases, draw on the Vector Control Advisory Group to review epidemiological data in order to assess the public health value of new vector control interventions. A positive determination of public health value provides the basis for the WHO guideline development process, overseen by the Guidelines Review Committee *(2)*, and the associated formulation of WHO recommendations.

In parallel with WHO's move to a new evaluation process for vector control products, the Global Malaria Programme revised its process for developing recommendations and companion documents *(3)*. This revised process provides better predictability and enhanced clarity on which malaria interventions are recommended and how they should be deployed, and supports the uptake of guidance. One of the outputs of this process, the first edition of the consolidated *WHO guidelines for malaria (4)*, was released in 2021 and has since been updated and expanded. A series of preferred product characteristics documents have been developed to communicate identified unmet public health needs and associated evaluation requirements.

Over the past six years, the evaluation process for vector control products has continued to evolve. When available, new implementation experience has been incorporated into the process. As a part of this evolution, the WHO Global Malaria

Programme and Department of Control of Neglected Tropical Diseases, with the support of the Vector Control Advisory Group, have reviewed and reduced the overall number of intervention classes. With fewer intervention classes that are broader in scope, the number of epidemiological trials required to bring new products to market has been reduced. At the same time, this has considerably increased the potential diversity of products within a class, raising the question of whether products grouped together in a specific class perform similarly to the "first-in-class" product that established the class and should therefore be considered to be covered by the same WHO recommendation.

This uncertainty was recognized by WHO and its advisory groups as early as 2017 and, based on technical consultation *(5)*, WHO embarked on a process to explore the use of comparative effectiveness to address this uncertainty. A notice of intent to this effect was published by WHO in 2018 *(6)*, followed by a study protocol in 2019 *(7)*. The process was further explored with the generation of data for mosquito nets treated with a pyrethroid insecticide and the synergist piperonyl butoxide (PBO) *(8)*. For IRS, comparative effectiveness data were used to expand the WHO recommendation for IRS to neonicotinoid insecticides in 2017, and the need for comparative data for other new types of insecticides is explicitly referenced in the associated preferred product characteristics *(9)*.

Based on these encouraging practical experiences and in the context of an ever-increasing diversity of vector control products, the WHO Malaria Policy Advisory Group has repeatedly recommended that WHO require comparative efficacy data, including data from non-inferiority assessments, as a routine component of vector control evaluation for second-in-class products *(10, 11)*. In March 2023, to address this identified need, which has re-emerged with the recent arrival of a number of new vector control products, the Global Malaria Programme posted a call for data from comparative evaluations of ITN and IRS products. The present convening was held to review the data submitted to the Global Malaria Programme in response to the data call. The convening had the following objectives:

1. Review the datasets formally submitted to WHO, covering two pyrethroid-PBO nets, one pyrethroid-chlorfenapyr net and one IRS product.
2. Review the combined non-inferiority estimates for each product based on a standardized analysis of the individual studies conducted on each product.
3. Discuss the findings based on the evidence provided.
4. Formulate recommendations to WHO, including on whether or not the existing WHO recommendation for IRS should be extended to cover broflanilide insecticides, which have not previously been used for vector control.

Assessment of the data submitted to WHO in response to the data call was performed based on WHO guidance provided in the study protocol *(7)* and in the study report of the 2021 technical consultation on pyrethroid-PBO nets *(8)*.

The present technical consultation was convened virtually on 5 and 9 June 2023. The meeting was chaired by Professor Azra Ghani. The temporary advisors were introduced, and Dr Kolaczinski provided an overview of the background and objectives of the meeting.

The first day saw presentations of trial data from studies on DuraNet Plus© and Yorkool® G3 (both pyrethroid-PBO net products). The second day started with a brief summary of day-one outcomes, followed by presentations of trial data from

studies on VECTRON™ T500 (a broflanilide IRS product) and PermaNet® Dual (a pyrethroid-chlorfenapyr net). During each session, a description of the trial was given (including the geography and ecology of the site, insecticide resistance profile of the mosquito populations, etc.) and the comparative efficacy results generated by the study investigators were presented for each of the studies. For each product, Dr Joseph Challenger from Imperial College London (acting independently through Imperial Consultants) presented the results of the WHO-commissioned independent analyses of the study data, following the presentations on the individual trials.

The last session of each day was set aside for closed deliberations by the temporary advisors to inform the development of recommendations.

The agenda is included as Annex 2 and the list of participants as Annex 3.

3. Assessment of non-inferiority

3.1 ITNs

Three ITNs were evaluated during the meeting: two pyrethroid-PBO nets (DuraNet Plus©, manufactured by Shobikaa Impex Private Limited, and Yorkool® G3, manufactured by Tianjin Yorkool® International Trading) and one pyrethroid-chlorfenapyr net (PermaNet® Dual, manufactured by Vestergaard Sarl).

The epidemiological data supporting the WHO recommendation for pyrethroid-PBO nets were originally derived from a trial in the United Republic of Tanzania deploying Olyset™ Plus (Sumitomo Chemical Co., Ltd.) and a trial in Uganda assessing Olyset™ Plus and PermaNet® 3.0 (Vestergaard Sarl). These two nets were assessed by the WHO Prequalification Team for Vector Control Products and prequalified in January 2018. Olyset™ Plus was used as the active comparator for non-inferiority data generation in the experimental hut trials for the two candidate products, DuraNet Plus© and Yorkool® G3.

With regard to the pyrethroid-chlorfenapyr net, PermaNet® Dual, the epidemiological data underpinning the WHO recommendation for this intervention class were originally generated using Interceptor® G2 (BASF) as the first-in-class product. Interceptor® G2 was prequalified in 2018, following epidemiological assessments of this product conducted in Benin and the United Republic of Tanzania. In 2022, the Vector Control Advisory Group determined that the product provided public health value against malaria, and the WHO recommendation was developed by the Global Malaria Programme Guideline Development Group for vector control thereafter. PermaNet® Dual, the candidate product, was thus assessed against Interceptor® G2 as the active comparator.

As described in the meeting report of the 2021 technical consultation *(8)*, the following standard approach applied to all three of the ITN assessments reviewed during the present meeting. The mosquito mortality (the primary end-point) for the candidate net should be compared to the active comparator and reported as an odds ratio (OR) with the corresponding 95% confidence interval (CI). The candidate net should then be assessed against the comparator using a non-inferiority margin of 0.7 for the OR, meaning that the lower bound of the 95% CI for mortality should not fall below 0.7. An additional comparison to a standard reference product (in this case a pyrethroid-only net) should also be presented in order to validate the superiority of

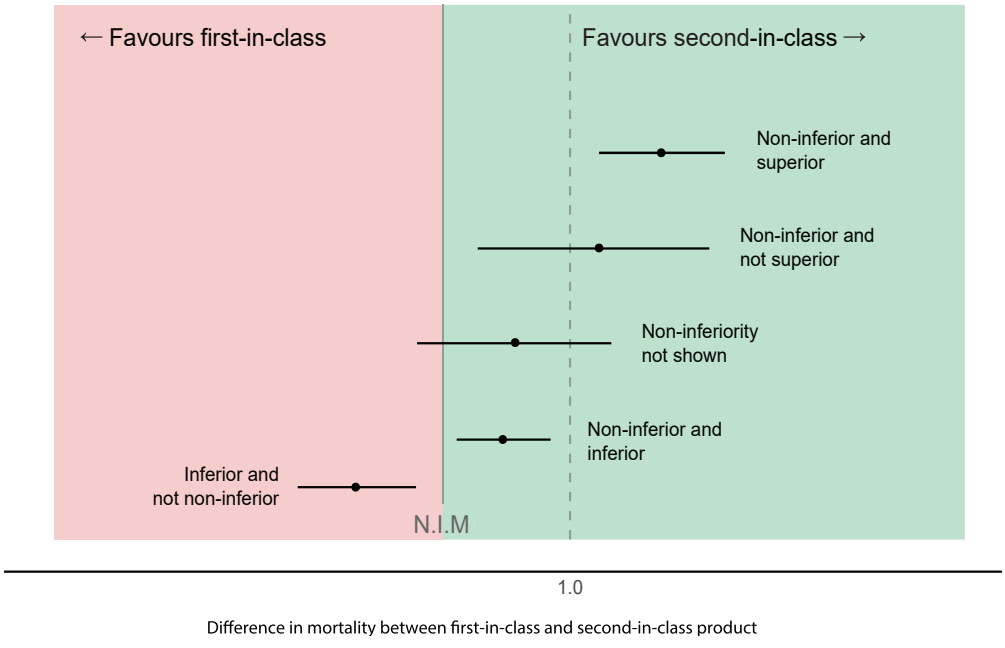
the candidate net over this comparator for the mosquito mortality end-point. For the secondary end-point of blood feeding, investigators should report the percentage of blood-fed mosquitoes for each net, with a CI and P value. If non-inferiority analyses are performed, a non-inferiority margin of 1.43 should be used (the inverse of 0.7), meaning that the upper bound of the 95% CI should not cross 1.43. This secondary end-point is used to provide further insight into the product's efficacy, but, while relevant to vector control programmes, should not be considered in the final decision by WHO's temporary advisors as to whether a product meets the WHO requirements for non-inferiority to the first-in-class product.

Following this approach, the data were analysed and reported by the trial investigators for each trial. In addition, the data were subjected to independent analyses by Imperial College London, commissioned by WHO. Dr Challenger presented the results of the independent analyses, which were performed using a logistic regression model in the widely used lme4 package in the statistical software package R *(12)*.

Dr Challenger explained how the OR between the candidate and comparator products in the trial was calculated, and how the entire CI of the mortality estimates had to fall above the non-inferiority margin of 0.7 for the candidate product to be considered non-inferior to the comparator (Fig. 1). By contrast, the inverted non-inferiority margin of 1.43 was used to investigate the non-inferiority of blood feeding, and the upper bound of the CI for the candidate net had to fall below this margin.

Using separate data for washed and unwashed nets, the model employed fixed effects for each treatment arm (based on the brand of net), hut, sleeper and day of collection. In cases in which the data were pooled for washed and unwashed nets, an additional fixed effect was included in the model to account for the washing condition.

Fig 1. Schematic figure depicting the various outcomes of comparative efficacy assessments for mortality



Note: Outcomes are based on where the CI falls relative to a non-inferiority margin (NIM) and the reference point of 1.0 (13).

3.1.1 DuraNet Plus©

Description of trials and comparative efficacy assessments

DuraNet Plus© (alpha-cypermethrin+PBO) was compared to both DuraNet© (alpha-cypermethrin-only) and Olyset™ Plus (permethrin+PBO) in three independent experimental hut studies between November 2018 and February 2019. The trial sites covered West and Central Africa, specifically, Benin, Cameroon and Côte d'Ivoire. All studies were conducted using the same methodology, the results of which were presented by Dr Corine Ngufor.

Study aims

- Assess the superiority of DuraNet Plus© over DuraNet© (which is a pyrethroid-only product and the positive control in the study).
- Assess the non-inferiority of DuraNet Plus© to Olyset™ Plus (which is a pyrethroid-PBO product and the first-in-class product in this intervention class).

Approach

Seven treatment groups were included in the studies, as outlined in Table 1. The same study design was used in all three trials.

Table 1. Summary of the design of the experimental hut studies in Benin, Cameroon and Côte d'Ivoire used to generate data to enable the comparative efficacy assessment of DuraNet Plus©

Treatment	Active ingredients	Role in study	Condition of washing	Number of replicates
Untreated net	N/A (control)	Negative control	Unwashed (0x)	6
DuraNet©	Pyrethroid	Positive control	Unwashed (0x)	6
DuraNet©	Pyrethroid	Positive control	Washed (20x)	6
DuraNet Plus©	Pyrethroid+PBO	Candidate net	Unwashed (0x)	6
DuraNet Plus©	Pyrethroid+PBO	Candidate net	Washed (20x)	6
Olyset™ Plus	Pyrethroid+PBO	Active comparator	Unwashed (0x)	6
Olyset™ Plus	Pyrethroid+PBO	Active comparator	Washed (20x)	6

Regeneration times for each net were established according to WHO procedures. One net was washed in addition to those included in the hut trials and was used to perform bioassays and chemical analyses assessing the pre-trial quality of each ITN type. For each trial, mosquito collections were conducted six days a week, for a total of 54 nights per trial.

Mortality and blood-feeding rates were compared between treatments using logistic regression models with treatment arm, sleeper, hut, day of collection and wash status as fixed effects. P values (5% significance levels) were used to assess the superiority of DuraNet Plus© over DuraNet© for mortality and blood-feeding inhibition; 95% CIs of the OR were used to assess the non-inferiority of DuraNet Plus© to Olyset™ Plus for mortality and blood-feeding inhibition against the WHO predefined margin. All analyses were performed in Stata version 17 *(14)*.

Trial 1: Benin

General description

The study was conducted in Covè, Benin. The predominant species at this West African site were *Anopheles gambiae* sensu stricto (s.s.) and *An. coluzzii*. Mosquito populations at the trial site demonstrated high levels of resistance to pyrethroids, but pre-exposure of mosquitoes to PBO restored their susceptibility to this class of insecticides. The prevalent insecticide resistance mechanisms were knockdown resistance *(kdr)* and oxidases. Mosquitoes were susceptible to organophosphates and carbamates.

Outcomes

Point estimates for mortality and blood feeding are shown in Table 2, while findings from the comparative efficacy assessment are presented in Table 3. Analyses using pooled data demonstrated that DuraNet Plus© was superior to the pyrethroid-only positive control, DuraNet©, as well as to the active comparator, Olyset™ Plus, for mosquito mortality and blood feeding.

Table 2. Point estimates of pooled data from unwashed and washed nets for the respective products tested in the Benin trial, where *An. gambiae* s.s. and *An. coluzzii* were the predominant vectors

Outcome	Product	Role in study	Point estimate (%)	95% CI
Primary: Mortality (24 hours)	DuraNet©	Positive control	20.2	18.3–22.1
	Olyset™ Plus	Active comparator	14.2	12.8–15.6
	DuraNet Plus©	Candidate	29.4	26.9–31.9
Secondary: Blood feeding	DuraNet©	Positive control	25	22.9–27.1
	Olyset™ Plus	Active comparator	34.9	33.0–36.8
	DuraNet Plus©	Candidate	12.8	11.0–14.6

Table 3. Comparative efficacy assessment of DuraNet Plus© and respective reference nets, analysing the pooled data for washed and unwashed nets in Benin, where *An. gambiae* s.s. and *An. coluzzii* were the predominant vectors

Outcome	Reference	Candidate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (24 hours)	DuraNet©	DuraNet Plus©	1.78	1.48–2.15	Superiority	Superior
	Olyset™ Plus	DuraNet Plus©	2.81	2.34–3.38	Non-inferiority	Non-inferior
Secondary: Blood feeding	DuraNet©	DuraNet Plus©	0.39	0.32–0.49	Superiority	Superior
	Olyset™ Plus	DuraNet Plus©	0.23	0.19–0.28	Non-inferiority	Non-inferior

Trial 2: Cameroon

General description

The study was conducted in Mibellon, Cameroon. The predominant species at this West African site was *An. funestus*. Mosquito populations at the trial site demonstrated high levels of resistance to pyrethroids, but pre-exposure of mosquitoes to PBO restored their susceptibility to this class of insecticides. The prevalent resistance mechanisms were related to glutathione S-transferase (GST) and the resistant to dieldrin (RDL) gene. Mosquitoes were susceptible to organophosphates and carbamates.

Outcomes

For the study in Cameroon, point estimates for mortality and blood feeding are shown in Table 4, while findings from the comparative efficacy assessment are presented in Table 5. In this study, fewer mosquitoes were captured in the huts compared to in Benin. For the 24-hour mortality end-point using the pooled data from washed and unwashed nets, DuraNet Plus© was found to be superior to DuraNet© and non-inferior to Olyset™ Plus. In terms of blood feeding, the pooled data demonstrated that DuraNet Plus© was non-inferior to DuraNet© for blood-feeding protection, but was not considered superior (as the P value was only 0.075). Compared to the first-in-class comparator Olyset™ Plus, DuraNet Plus© was non-inferior for blood feeding.

Table 4. Point estimates of pooled data from unwashed and washed nets for the respective products tested in the Cameroon trial, where *An. funestus* was the predominant species

Outcome	Product	Role in study	Point estimate (%)	95% CI
Primary: Mortality (24 hours)	DuraNet©	Positive control	12.9	10.3–15.5
	Olyset™ Plus	Active comparator	21.5	18.4–24.6
	DuraNet Plus©	Candidate	27.8	24.2–31.4
Secondary: Blood feeding	DuraNet©	Positive control	42.2	38.3–46.1
	Olyset™ Plus	Active comparator	44.4	40.6–48.2
	DuraNet Plus©	Candidate	34.8	30.9–38.7

Table 5. Comparative efficacy assessment of DuraNet Plus© and respective reference nets, analysing the pooled data for washed and unwashed nets in Cameroon, where *An. funestus* was the predominant species

Outcome	Reference	Candidate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (24 hours)	DuraNet©	DuraNet Plus©	3.95	2.71–5.61	Superiority	Superior
	Olyset™ Plus	DuraNet Plus©	1.81	1.32–2.49	Non-inferiority	Non-inferior
Secondary: Blood feeding	DuraNet©	DuraNet Plus©	0.77	0.58–1.03	Superiority	Not superior but non-inferior
	Olyset™ Plus	DuraNet Plus©	0.66	0.49–0.87	Non-inferiority	Non-inferior

Trial 3: Côte d'Ivoire

General description

The study was conducted in M'be, Côte d'Ivoire. The predominant species at this West African site was *An. coluzzii*. Mosquito populations at the trial site demonstrated high levels of resistance to pyrethroids, but pre-exposure of mosquitoes to PBO was shown to restore their susceptibility to this class of insecticides. The prevalent resistance mechanisms were *kdr* and ace-1 genes, esterases, oxidases and GST. The mosquitoes were susceptible to organophosphates and carbamates. During the study, very high numbers of mosquitoes were captured in the huts.

Outcomes

The point estimates for mortality and blood feeding for the study in Côte d'Ivoire are shown in Table 6, while findings from the comparative efficacy assessment are presented in Table 7. Using pooled data from washed and unwashed nets, DuraNet Plus© was found to be superior to the pyrethroid-only positive control, DuraNet©, and the active comparator, Olyset™ Plus, for both mosquito mortality and blood feeding.

Table 6. Point estimates of pooled data from unwashed and washed nets for the respective products tested in Côte d'Ivoire, where *An. coluzzii* was the predominant vector

Outcome	Product	Role in study	Point estimate (%)	95% CI
Primary: Mortality (24 hours)	DuraNet©	Positive control	9.2	7.8–10.6
	Olyset™ Plus	Active comparator	11.7	10.3–13.1
	DuraNet Plus©	Candidate	19.2	17.3–21.1
Secondary: Blood feeding	DuraNet©	Positive control	26.5	24.4–28.6
	Olyset™ Plus	Active comparator	25.8	23.9–27.7
	DuraNet Plus©	Candidate	17.6	15.8–19.4

Table 7. Comparative efficacy assessment of DuraNet Plus© and respective reference nets, analysing the pooled data for washed and unwashed nets in Côte d'Ivoire, where *An. coluzzii* was the predominant vector

Outcome	Reference	Candidate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (24 hours)	DuraNet©	DuraNet Plus©	2.54	2.02–3.18	Superiority	Superior
	Olyset™ Plus	DuraNet Plus©	2.38	1.71–3.33	Non-inferiority	Non-inferior
Secondary: Blood feeding	DuraNet©	DuraNet Plus©	0.53	0.44–0.64	Superiority	Superior
	Olyset™ Plus	DuraNet Plus©	0.58	0.48–0.70	Non-inferiority	Non-inferior

Independent data analysis

Dr Challenger presented the summary results, which showed that the independent analysis supported the results presented by the investigators (see Figs. 2 and 3 and Annex 4):

- In Benin, DuraNet Plus© was found to be non-inferior in all tests, using washed, unwashed and pooled data, for both the mortality and blood-feeding end-points.
- In Cameroon, DuraNet Plus© was found to be non-inferior in all tests, using washed, unwashed and pooled data, for both the mortality and blood-feeding end-points.
- In Côte d'Ivoire, all washed, unwashed and pooled data analyses demonstrated that DuraNet Plus© was non-inferior to Olyset™ Plus in terms of the mortality end-point. For blood feeding, however, DuraNet Plus© was non-inferior in the pooled data analysis, but not non-inferior in the unwashed comparison. This result was explained by the reduction of the efficacy of the Olyset™ Plus net after washing, a decline that was not observed with DuraNet Plus©.

Fig. 2. Non-inferiority margins for the primary end-point of mosquito mortality (pooled data for washed and unwashed nets) for the three studies assessing DuraNet Plus© as the candidate net compared to Olyset™ Plus as the active comparator

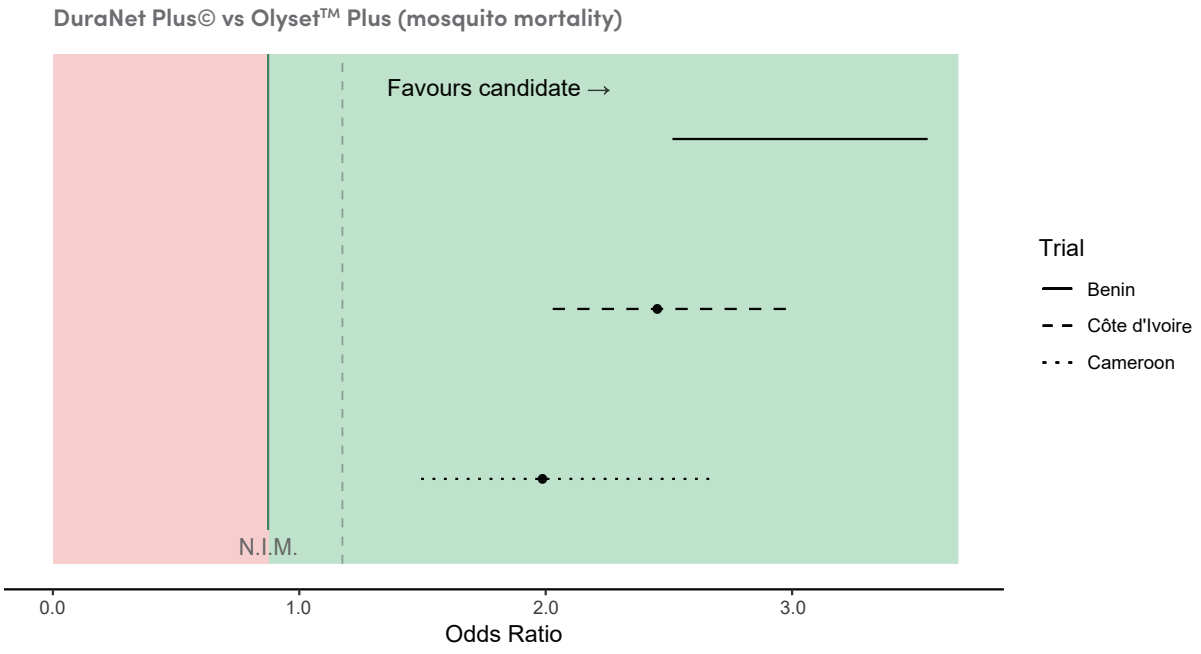
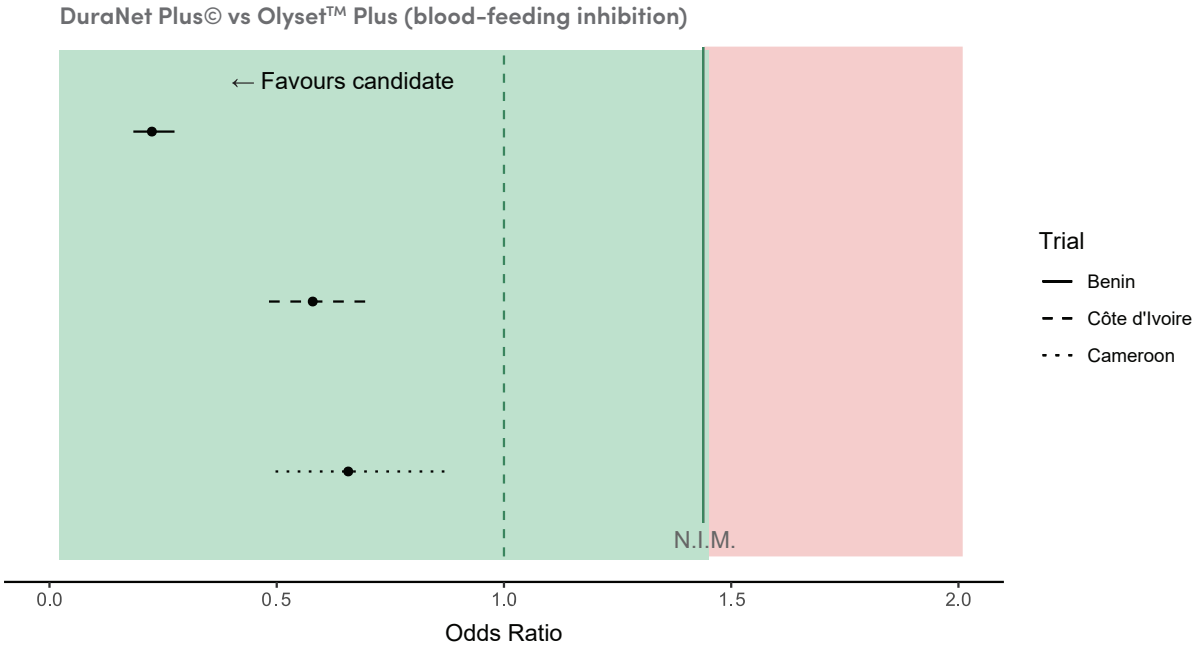


Fig. 3. Non-inferiority margins for the secondary end-point of blood feeding inhibition (pooled data for washed and unwashed nets) for each of the three studies comparing DuraNet Plus© to Olyset™ Plus



Discussion

No major points of discussion emerged with regard to this specific product comparison.

Conclusion

The results of the investigators' analyses and the independent analysis were consistent, and there was consensus among the WHO temporary advisors on the decision for this product. DuraNet Plus© was non-inferior to Olyset™ Plus for the mosquito mortality end-point, based on the pooled (washed and unwashed) data. This result was observed in all trial sites. For the secondary end-point of blood feeding, DuraNet Plus© was non-inferior to Olyset™ Plus in all analyses in the Benin and Cameroon trials. It was only for the comparison between unwashed nets in Côte d'Ivoire that DuraNet Plus© was not non-inferior to Olyset™ Plus. Nevertheless, the washed and the pooled data demonstrated the non-inferiority of DuraNet Plus© to the active comparator.

It was concluded that DuraNet Plus© had demonstrated non-inferiority to Olyset™ Plus, as per the WHO assessment criteria. The existing WHO recommendation for pyrethroid-PBO nets is therefore considered to be applicable to this product.

3.1.2 Yorkool® G3

Description of trials and comparative efficacy assessments

Yorkool® G3 (deltamethrin+PBO) was evaluated in two independent trials: one in Benin and the other in the United Republic of Tanzania. The candidate net was compared to Olyset™ Plus for the purpose of assessing non-inferiority and to PermaNet® 2.0 for assessing superiority. Dr Ngufor presented the data from the study

conducted in Benin, while Dr Sarah Moore presented the data from the study in the United Republic of Tanzania.

Study aims

- Assess the comparative efficacy (superiority) of Yorkool® G3 relative to PermaNet® 2.0 (which is a pyrethroid-only product and the positive control in the study).
- Assess the non-inferiority of Yorkool® G3 to Olyset™ Plus (which is a pyrethroid-PBO product and the first-in-class product in this intervention class).

Trial 1: Benin

General description

The study was conducted in Covè, Benin. The predominant species at this West African site were *An. gambiae* s.s. and *An. coluzzii*. Mosquito populations at the trial site demonstrated high levels of resistance to pyrethroids, but pre-exposure of mosquitoes to PBO was shown to restore their susceptibility to this class of insecticides. The prevalent resistance mechanisms were *kdr* and P450s. The mosquitoes were susceptible to organophosphates and carbamates. The study was conducted between Q4 2020 and Q1 2021. As in the DuraNet Plus© study carried out at this same site, all nets were prepared and washed according to WHO standard procedures.

Approach

A randomized Latin square design was used to rotate the nets through the huts throughout the course of the study. The treatments used in the study are presented in Table 8. Outcome measures included mortality rate at 24 hours and blood feeding. Mortality and blood-feeding rates were compared between treatments using logistic regression models with treatment arm, sleeper, hut, day of collection and wash status as fixed effects. P values (5% significance levels) were used to assess the superiority of Yorkool® G3 over PermaNet® 2.0 for mortality and blood-feeding inhibition; 95% confidence intervals of the OR were used to assess the non-inferiority of Yorkool® G3 to Olyset™ Plus for mortality and blood-feeding inhibition against the WHO predefined margins of 0.7 and 1.43, respectively. All analyses were performed in Stata version 17 *(14)*.

Table 8. Summary of the design of experimental hut studies in Benin used to generate data to enable the comparative efficacy assessment of Yorkool® G3

Treatment	Active ingredients	Role in study	Condition of washing	Number of replicates
Untreated net	N/A (control)	Negative control	Unwashed (0x)	6
PermaNet® 2.0	Pyrethroid	Positive control	Unwashed (0x)	6
PermaNet® 2.0	Pyrethroid	Positive control	Washed (20x)	6
Yorkool® G3	Pyrethroid+PBO	Candidate net	Unwashed (0x)	6
Yorkool® G3	Pyrethroid+PBO	Candidate net	Washed (20x)	6
Olyset™ Plus	Pyrethroid+PBO	Active comparator	Unwashed (0x)	6
Olyset™ Plus	Pyrethroid+PBO	Active comparator	Washed (20x)	6

Outcome

The point estimates for mortality and blood feeding for the study in Benin are shown in Table 9, while findings from the comparative efficacy assessment are presented in Table 10. Using pooled washed and unwashed data, Yorkool® G3 was determined to be superior to both the pyrethroid-only control, PermaNet® 2.0, and the active comparator, Olyset™ Plus, for 24-hour mortality. Comparisons using separate data from washed nets and unwashed nets supported this result.

Using pooled data for washed and unwashed nets, Yorkool® G3 was also found to be superior to both PermaNet® 2.0 and Olyset™ Plus for blood-feeding inhibition. It was noted, however, that when unwashed Yorkool® G3 nets were compared to unwashed Olyset™ Plus nets, the candidate product was not non-inferior to Olyset™ Plus (OR: 2.45; CI: 1.40–4.29). This observation is explained by the high levels of blood-feeding inhibition provided by unwashed Olyset™ Plus nets. After 20 washes, however, the efficacy of Olyset™ Plus declined more than that of Yorkool® G3. Indeed, after washing, Yorkool® G3 was not only non-inferior to Olyset™ Plus, but superior in terms of blood-feeding inhibition (OR: 0.40; CI: 0.30–0.54; $P < 0.001$).

Table 9. Point estimates of pooled data from unwashed and washed nets for the respective products tested in the Benin trial, where the predominant vectors were *An. gambiae* s.s. and *An. coluzzii*

Outcome	Product	Role in study	Point estimate (%)	95% CI
Primary: Mortality (24 hours)	PermaNet® 2.0	Positive control	9.7	7.8–11.6
	Olyset™ Plus	Active comparator	10.2	7.9–12.5
	Yorkool® G3	Candidate	19.8	16.3–23.3
Secondary: Blood feeding	PermaNet® 2.0	Positive control	55.0	51.9–58.1
	Olyset™ Plus	Active comparator	39.0	35.4–42.6
	Yorkool® G3	Candidate	21.0	17.4–24.6

Table 10. Comparative efficacy assessment of Yorkool® G3 and respective reference nets, analysing the pooled data for washed and unwashed nets in Benin, where the predominant vectors were *An. gambiae* s.s. and *An. coluzzii*

Outcome	Reference net	Candidate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (24 hours)	PermaNet® 2.0	Yorkool® G3	2.70	1.90–3.84	Superiority	Superior
	Olyset™ Plus	Yorkool® G3	2.22	1.54–3.22	Non-inferiority	Non-inferior
Secondary: Blood feeding	PermaNet® 2.0	Yorkool® G3	0.19	0.14–0.25	Superiority	Superior
	Olyset™ Plus	Yorkool® G3	0.40	0.30–0.54	Non-inferiority	Non-inferior

Trial 2: United Republic of Tanzania

General description

A comparative efficacy study of Yorkool® G3 and Olyset™ Plus was conducted in the United Republic of Tanzania and presented by Dr Moore. The experimental hut site was located in a perennial rice-growing area, with the huts situated between the rice-growing areas and the village. *An. arabiensis* was the predominant mosquito species in the area, but *An. funestus* was also present.

Approach

A Latin square design was used, with seven treatments. Two rotations were completed, meaning 98 data points. Table 11 outlines the treatments and experimental design used in the study. In conducting the study, all nets were washed and prepared as per WHO recommendations, following the instructed regeneration times.

Table 11. Summary of the design of experimental hut studies in the United Republic of Tanzania used to generate data to enable the comparative efficacy assessment of Yorkool® G3

Treatment	Active ingredients	Role in study	Condition of washing	Number of replicates
Untreated net	N/A (control)	Negative control	Unwashed (0x)	7
PermaNet® 2.0	Pyrethroid	Positive control	Unwashed (0x)	7
PermaNet® 2.0	Pyrethroid	Positive control	Washed (20x)	7
Yorkool® G3	Pyrethroid+PBO	Candidate net	Unwashed (0x)	7
Yorkool® G3	Pyrethroid+PBO	Candidate net	Washed (20x)	7
Olyset™ Plus	Pyrethroid+PBO	Active comparator	Unwashed (0x)	7
Olyset™ Plus	Pyrethroid+PBO	Active comparator	Washed (20x)	7

The investigators highlighted that the study was conducted with adequate statistical power and within the timeframe and budget of a standard experimental hut trial, in their view, providing justification that conducting non-inferiority trials is feasible as part of manufacturers' standard data generation process to support their submission for WHO prequalification.

Outcome

The point estimates for mortality and blood-feeding rates for the study in the United Republic of Tanzania are shown in Table 12, while the findings from the comparative efficacy assessment are presented in Table 13. Yorkool® G3 was assessed for non-inferiority to the first-in-class product, Olyset™ Plus. The presented analyses included only data relating to *An. arabiensis*, being the predominant species in the area. The candidate product was deemed non-inferior to Olyset™ Plus in terms of mortality at 24 hours, using the pooled data for washed and unwashed nets. As required, Yorkool® G3 was confirmed to be superior to the pyrethroid-only control.

Use of the candidate net, Yorkool® G3, permitted higher rates of blood feeding than the active comparator, and therefore Yorkool® G3 was not non-inferior to Olyset™ Plus. Compared to the pyrethroid-only net, Yorkool® G3 was superior. Nevertheless, it was noted that blood-feeding rates were low in all arms of the study, leading to large CIs surrounding the point estimates in the data.

Table 12. Point estimates of pooled data from unwashed and washed nets for the respective products tested in the trial in the United Republic of Tanzania, where the predominant vector was *An. arabiensis*

Outcome	Product	Role in study	Point estimate (%)	95% CI
Primary: Mortality (24 hours)	PermaNet® 2.0	Positive control	24.3	21.6–27.3
	Olyset™ Plus	Active comparator	37.4	34.0–40.9
	Yorkool® G3	Candidate	51.1	47.2–54.9
Secondary: Blood feeding	PermaNet® 2.0	Positive control	2.86	2.26–3.62
	Olyset™ Plus	Active comparator	1.77	1.30–2.41
	Yorkool® G3	Candidate	0.95	0.65–1.37

Table 13. Comparative efficacy assessment of Yorkool® G3 and respective reference nets, analysing the pooled data for washed and unwashed nets in the United Republic of Tanzania, where the predominant vector was *An. arabiensis*

Outcome	Reference	Candidate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (24 hours)	PermaNet® 2.0	Yorkool® G3	2.89	2.68–3.13	Superiority	Superior
	Olyset™ Plus	Yorkool® G3	1.75	1.62–1.88	Non-inferiority	Non-inferior
Secondary: Blood feeding	PermaNet® 2.0	Yorkool® G3	0.68	0.56–0.87	Superiority	Superior
	Olyset™ Plus	Yorkool® G3	1.87	1.43–2.39	Non-inferiority	Not non-inferior and inferior

The investigators noted, as a limitation of their study, that resistance testing for responsiveness to PBO was not performed synchronously with the study. The trial was performed during the coronavirus disease (COVID-19) pandemic, which meant that sourcing test papers from the testing centre in Malaysia was restricted. Nevertheless, the investigators considered that this issue had no impact on the outcomes of the study, given that pre-exposure to PBO was consistently shown to restore the pyrethroid susceptibility of wild mosquitoes in the area.

The investigators also reported that the chemical quality check of netting samples for the 20x washed nets showed that Olyset™ Plus and PermaNet® 2.0 were outside of the established WHO dose tolerance thresholds, meaning that there was lower bioavailability of the active ingredients to mosquitoes in the washed nets. Unwashed nets, however, were within the target thresholds.

Independent data analysis

Dr Challenger presented the results of the independent analysis (see Figs. 4 and 5 and Annex 4), which demonstrated the following:

- In Benin, Yorkool® G3 was non-inferior to Olyset™ Plus in terms of mosquito mortality in both the washed and unwashed tests; the pooled data supported this conclusion. The analysis of pooled data on blood feeding showed that Yorkool® G3 inhibited blood feeding more than Olyset™ Plus, with the results driven by the reduced efficacy of Olyset™ Plus after being washed 20 times; the relative efficacy of Yorkool® G3 remained consistent pre- and post-washing. Non-inferiority was not shown for blood feeding when comparing the unwashed nets.

- In the United Republic of Tanzania, Yorkool® G3 was found to be non-inferior to Olyset™ Plus in terms of mortality, when analysing the washed, unwashed and pooled data. By contrast, Yorkool® G3 did not demonstrate non-inferiority to Olyset™ Plus in terms of blood-feeding inhibition in the unwashed, washed and pooled data analyses.

Fig. 4. Non-inferiority margins for the primary end-point of mosquito mortality (pooled data for washed and unwashed nets) for the two studies assessing Yorkool® G3 as the candidate net compared to Olyset™ Plus as the active comparator

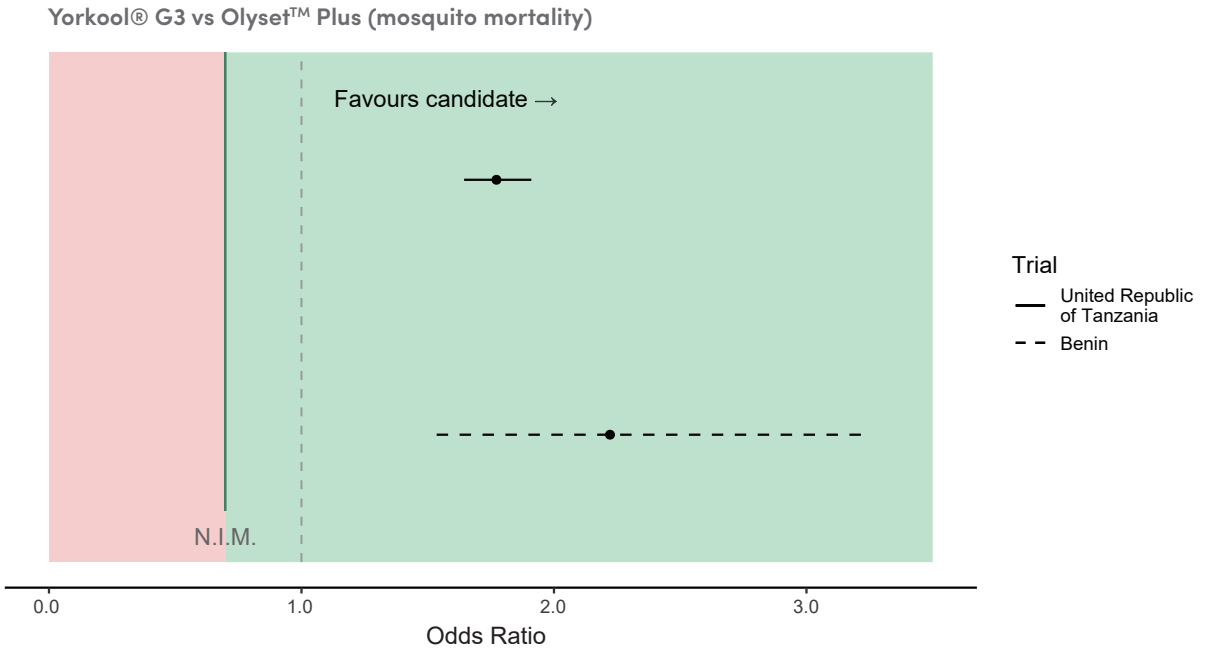
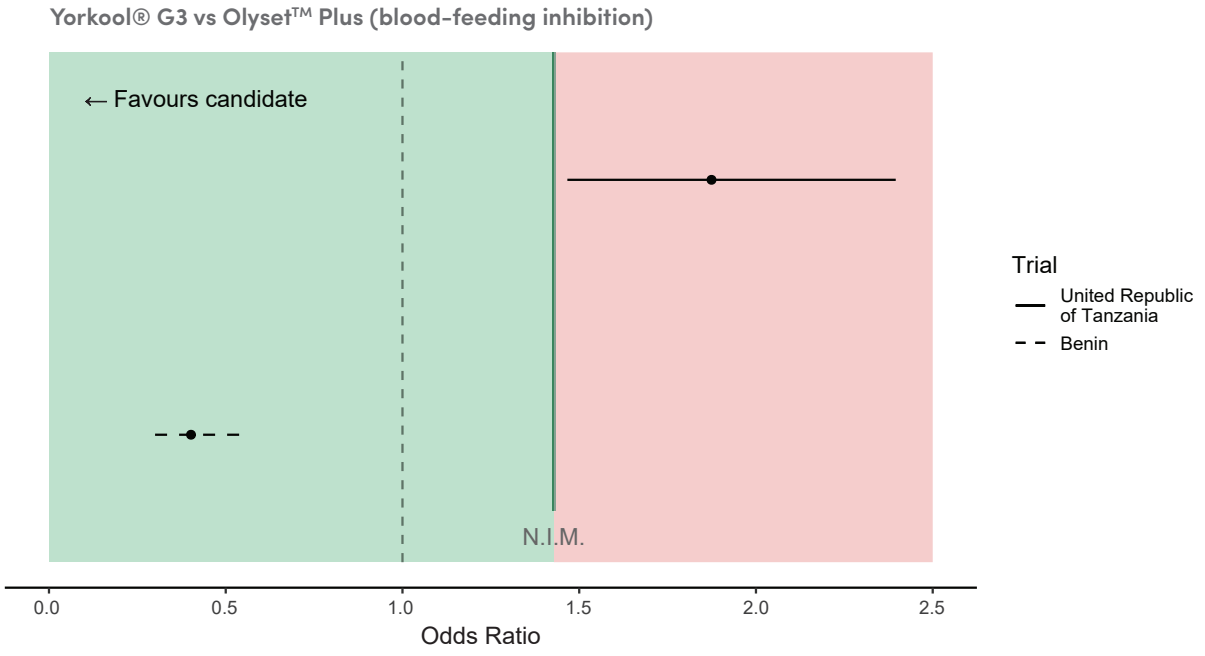


Fig. 5. Non-inferiority margins for the secondary end-point of blood feeding inhibition (pooled data for washed and unwashed nets) for each of the two studies comparing Yorkool® G3 to Olyset™ Plus



Discussion

The temporary advisors noted that the proportion of blood-fed mosquitoes across these studies was very low. Therefore, using this as the denominator for dead mosquitoes led to very large CIs and a lack of power to identify a difference. One advisor noted that the difference between permethrin, used in Olyset™ Plus, and deltamethrin, used in Yorkool® G3, may have caused the observed difference in the relative repellency of these nets when unwashed. Olyset™ Plus performed very well when unwashed, most likely because permethrin is an irritant to mosquitoes. After washing, however, the Olyset™ Plus nets were found to be less efficacious in terms of preventing blood feeding. The investigators noted that the study was conducted prior to 2021, when the most recent guidance was published on non-inferiority trials, and therefore some elements of the study analysis may not have been fully aligned with current WHO guidance.

Conclusion

The results of the investigators' analyses and the independent analysis were consistent, and there was consensus among the temporary advisors that Yorkool® G3 was non-inferior to Olyset™ Plus in terms of the mortality it induced. Yorkool® G3 did not demonstrate non-inferiority to Olyset™ Plus in terms of blood-feeding inhibition in the trial in the United Republic of Tanzania, when the data were pooled. In the Benin study, however, Yorkool® G3 was non-inferior to Olyset™ Plus after 20 washes and in the assessment of pooled data (but this result was driven by the strong results obtained with the washed nets).

Yorkool® G3 was confirmed to be non-inferior to Olyset™ Plus as per WHO assessment criteria. The existing WHO recommendation for pyrethroid-PBO nets is therefore considered to be applicable to this product.

3.1.3 PermaNet® Dual

Description of trials and assessment of non-inferiority

Two studies were conducted (one in Benin and one in Kenya) to enable the assessment of the efficacy of PermaNet® Dual compared to Interceptor® G2, the first-in-class net for pyrethroid-chlorfenapyr nets, and to a pyrethroid-only net as a control. Presentations were made by Mr Thomas Syme and Dr Eric Ochomo, respectively.

Study aims

- Assess the superiority of PermaNet® Dual over PermaNet® 2.0 (which is a pyrethroid-only product and the positive control in the study).
- Assess the non-inferiority of PermaNet® Dual to Interceptor® G2 (which is a pyrethroid-chlorfenapyr product and the first-in-class product in this intervention class).

Trial 1: Benin

Background

Mr Syme presented the work on the comparative efficacy trial conducted in Covè, Benin, comparing PermaNet® Dual to the first-in-class net, Interceptor® G2, and a control pyrethroid-only net, PermaNet® 2.0 (15). Although not pertinent for the purpose of assessing non-inferiority, PermaNet® 3.0 (a pyrethroid-PBO net) was also included

in the study. The primary vectors in this area were *An. coluzzii* and *An. gambiae* s.s. These populations were pyrethroid-resistant, but susceptible to carbamates and organophosphates. The predominant resistance mechanisms were *kdr* L1014F and P450s.

Approach

The study tested nine nets and was conducted over 54 nights. This study, as outlined in Table 14, followed the same protocols as the other non-inferiority studies of ITNS conducted in Benin and presented in this report. Data were analysed using a generalized logistic regression model, performed in Stata version 17 *(14).*

Table 14. Summary of the design of experimental hut studies in Benin used to generate data to enable the comparative efficacy assessment of PermaNet® Dual

Treatment	Active ingredients	Role in study	Condition of washing	Number of replicates
Untreated net	N/A (control)	Negative control	Unwashed (0x)	6
PermaNet® 2.0	Pyrethroid	Positive control	Unwashed (0x)	6
PermaNet® 2.0	Pyrethroid	Positive control	Washed (20x)	6
PermaNet® 3.0	Pyrethroid+PBO	N/A for this analysis	Unwashed (0x)	6
PermaNet® 3.0	Pyrethroid+PBO	N/A for this analysis	Washed (20x)	6
PermaNet® Dual	Deltamethrin+ chlorfenapyr	Candidate net	Unwashed (0x)	6
PermaNet® Dual	Deltamethrin+ chlorfenapyr	Candidate net	Washed (20x)	6
Interceptor® G2	Alpha-cypermethrin+ chlorfenapyr	Active comparator	Unwashed (0x)	6
Interceptor® G2	Alpha-cypermethrin+ chlorfenapyr	Active comparator	Washed (20x)	6

The bioefficacy and quality of the nets were tested for quality assurance purposes. One net was randomly sampled from each treatment group and tested in cone bioassays and with chemical analyses. It was confirmed that all nets were within the specified WHO tolerance thresholds. Bioassays indicated that mosquito populations had a high intensity of pyrethroid resistance, although susceptibility was fully restored when mosquitoes were pre-exposed to PBO. Mosquitoes were susceptible to chlorfenapyr.

Overall, a total of 5967 mosquitoes were collected during the trial, representing an average of 12.3 mosquitoes per hut per night.

Outcome

The point estimates for mosquito mortality and blood feeding for the study in Benin are shown in Table 15, while the findings from the comparative efficacy assessment are presented in Table 16. This analysis, for which the authors only reported the 72-hour mortality end-point and pooled data, indicated that PermaNet® Dual was superior to the pyrethroid-only positive control, PermaNet® 2.0. PermaNet® Dual was also found to be superior in terms of blood-feeding inhibition. Compared to the active comparator, Interceptor® G2, the analysis showed PermaNet® Dual to be non-inferior in terms of mortality, but not in terms of blood-feeding inhibition.

Table 15. Point estimates of pooled data from unwashed and washed nets for the respective products tested in the Benin trial

Outcome	Product	Role in study	Point estimate (%)	95% CI
Primary: Mortality (72 hours)	PermaNet® 2.0	Positive control	17.3	15.3–19.3
	Interceptor® G2	Active comparator	79.0	76.8–81.2
	PermaNet® Dual	Candidate	75.8	73.4–78.2
Secondary: Blood feeding	PermaNet® 2.0	Positive control	50.6	48.0–53.2
	Interceptor® G2	Active comparator	26.2	23.8–28.6
	PermaNet® Dual	Candidate	34.5	31.9–37.1

Table 16. Comparative efficacy assessment of PermaNet® Dual and respective reference nets, analysing pooled data for washed and unwashed nets in Benin, where *An. gambiae* s.s. and *An. coluzzii* were the predominant vectors

Outcome	Reference net	Candidate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (72 hours)	PermaNet® 2.0	PermaNet® Dual	17.16	14.02–21.01	Superiority	Superior
	Interceptor® G2	PermaNet® Dual	0.88	0.72–1.07	Non-inferiority	Non-inferior
Secondary: Blood feeding	PermaNet® 2.0	PermaNet® Dual	0.50	0.42–0.59	Superiority	Superior
	Interceptor® G2	PermaNet® Dual	1.42	1.17–1.72	Non-inferiority	Not non-inferior and inferior

Trial 2: Kenya

Background

A comparative efficacy study on PermaNet® Dual was conducted in Siaya, Kenya, using an adaptation of the Ifakara experimental hut design. Dr Ochomo presented the objective of the study, which was to assess the non-inferiority of PermaNet® Dual to Interceptor® G2, using free-flying pyrethroid-resistant *An. gambiae* sensu lato (s.l.) and *An. funestus* mosquitoes, the predominant species in the area. The study also aimed to assess the superiority of PermaNet® Dual over PermaNet® 3.0 (pyrethroid-PBO net).

Approach

The study was designed using the Guidelines for laboratory and field-testing of long-lasting insecticidal nets *(16)* and the non-inferiority study protocol *(7)* as a basis. The investigators used a 7x7 Latin square study design (treatments presented in Table 17). Over the course of the study, they collected over 15 000 *An. funestus* mosquitoes (averaging 44 females per hut, per night). Both mosquito species of interest were fully susceptible to chlorfenapyr. Mortality was reportedly measured at 72 hours only, as opposed to 24 hours.

Table 17. Summary of the design of experimental hut studies in Kenya used to generate data to enable the comparative efficacy assessment of PermaNet® Dual

Treatment	Active ingredients	Role in study	Condition of washing	Number of replicates
Untreated net	N/A (control)	Negative control	Unwashed (0x)	6
PermaNet® 3.0	Pyrethroid+PBO	Positive control	Unwashed (0x)	6
PermaNet® 3.0	Pyrethroid+PBO	Positive control	Washed (20x)	6
PermaNet® Dual	Deltamethrin+ chlorfenapyr	Candidate net	Unwashed (0x)	6
PermaNet® Dual	Deltamethrin+ chlorfenapyr	Candidate net	Washed (20x)	6
Interceptor® G2	Alpha-cypermethrin+ chlorfenapyr	Active comparator	Unwashed (0x)	6
Interceptor® G2	Alpha-cypermethrin+ chlorfenapyr	Active comparator	Washed (20x)	6

Outcome

The point estimates for mortality and blood feeding for the study in Kenya are shown in Table 18, while the findings from the comparative efficacy assessment are presented in Table 19. The study determined that PermaNet® Dual was superior to PermaNet® 3.0. Compared to the active comparator, PermaNet® Dual was found to be non-inferior to Interceptor® G2 in terms of both end-points: mortality and blood feeding.

For blood feeding, PermaNet® Dual was shown to be non-inferior to Interceptor® G2 using the pooled data for washed and unwashed nets. Interestingly, compared to PermaNet® 3.0 (a pyrethroid-PBO net, a supplemental comparison made by the investigators), PermaNet® Dual was found to be inferior in terms of blood feeding.

Table 18. Point estimates of pooled data from unwashed and washed nets for the respective products tested in the Kenya trial

Outcome	Product	Role in study	Point estimate (%)	95% CI
Primary: Mortality (72 hours)	PermaNet® 3.0	Positive control	56	54–57
	Interceptor® G2	Active comparator	65	64–67
	PermaNet® Dual	Candidate	68	66–69
Secondary: Blood feeding	PermaNet® 3.0	Positive control	6	6–7
	Interceptor® G2	Active comparator	10	9–11
	PermaNet® Dual	Candidate	12	11–13

Table 19. Comparative efficacy assessment of PermaNet® Dual and respective reference nets, analysing pooled data for washed and unwashed nets in Kenya, where *An. gambiae* s.l. and *An. funestus* were the predominant vectors

Outcome	Reference net	Candidate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (72 hours)	PermaNet® 3.0	PermaNet® Dual	1.805	1.654–1.969	Superiority	Superior
	Interceptor® G2	PermaNet® Dual	1.096	1.001–1.199	Non-inferiority	Non-inferior
Secondary: Blood feeding	PermaNet® 3.0	PermaNet® Dual	1.627	1.425–1.856	Superiority	Inferior
	Interceptor® G2	PermaNet® Dual	1.176	1.037–1.334	Non-inferiority	Non-inferior

Independent analysis of data

The independent data analysis (see Annex 4) of the two study datasets considered 24-hour mortality (as per the 2019 study protocol and current WHO ITN testing guidelines), as well as 72-hour mortality, in recognition that this holding period may be more appropriate for assessing mortality with chlorfenapyr, given the insecticide's mode of action. Therefore, this independent analysis used the same analytical model as that used for the other products assessed in the present convening, but with the addition of the 72-hour mosquito mortality end-point for PermaNet® Dual. Assessing this additional end-point aimed at investigating the effect of a prolonged holding time and whether this would affect the conclusions reached.

Kenya

The analysis of mortality after 24 hours showed that PermaNet® Dual was non-inferior to Interceptor® G2, using the pooled (washed and unwashed) data (OR: 1.03; CI: 0.91–1.18). The equivalent 72-hour assessment also supported that PermaNet® Dual was non-inferior (OR: 1.10; CI: 1.00–1.21). In the independent analysis of blood-feeding inhibition, the analysis of pooled (washed and unwashed net) data demonstrated that PermaNet® Dual was non-inferior to Interceptor® G2 (OR: 1.23; CI: 1.07–1.42). However, when unwashed and washed nets were considered separately, PermaNet® Dual was not found to be non-inferior in terms of blood feeding.

With regard to the blood-feeding analysis, it is worth noting that the gravid mosquitoes identified in the mosquito collections were not considered to be blood-fed for the purposes of the analysis (i.e. these mosquitoes were considered to have fed prior to entering the experimental hut).

Benin

The independent analysis of the 24-hour mortality data from the Benin trial using the pooled data from washed and unwashed nets showed that PermaNet® Dual was non-inferior to Interceptor® G2 (OR: 0.887; CI: 0.731–1.077) (see Fig. 6). Analysis showed that the mortality after a 72-hour holding period very closely reflected the mortality after 24 hours. The pooled estimate resulted in an OR of 0.878 (CI: 0.719–1.073). For the secondary end-point of blood feeding, the washed, unwashed and pooled data analyses all demonstrated that PermaNet® Dual was not non-inferior to Interceptor® G2 (see Fig. 7).

Fig. 6. Non-inferiority margins for the primary end-point of mosquito mortality (pooled data for washed and unwashed nets) for the two studies assessing PermaNet® Dual as the candidate net compared to Interceptor® G2 as the active comparator

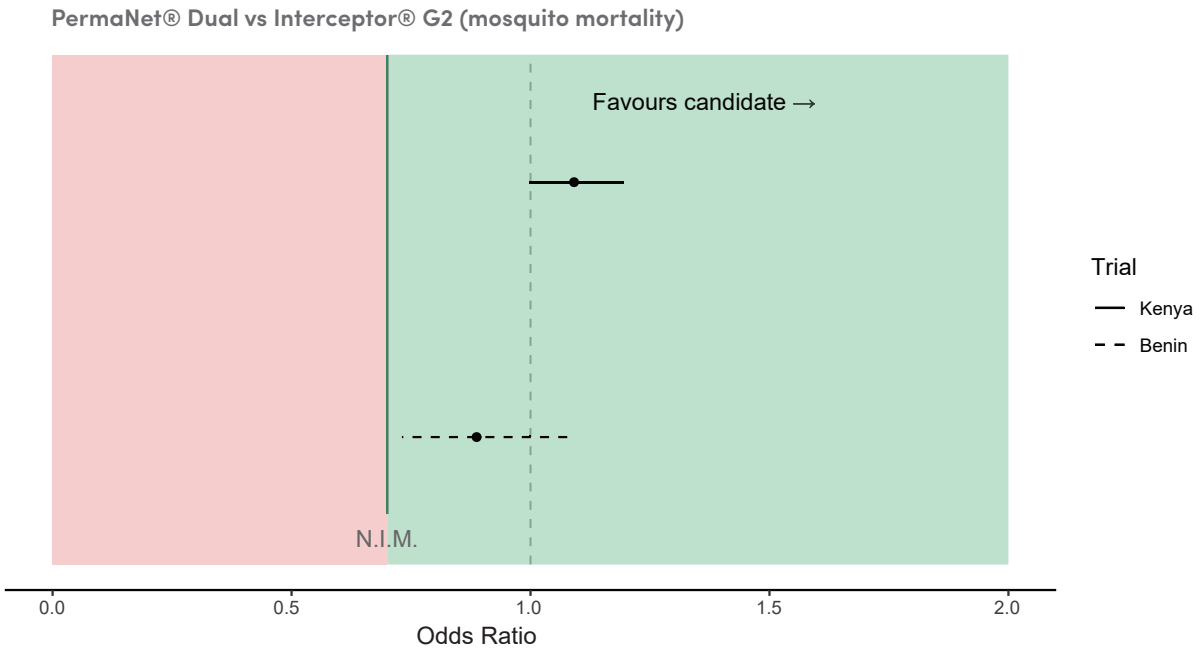
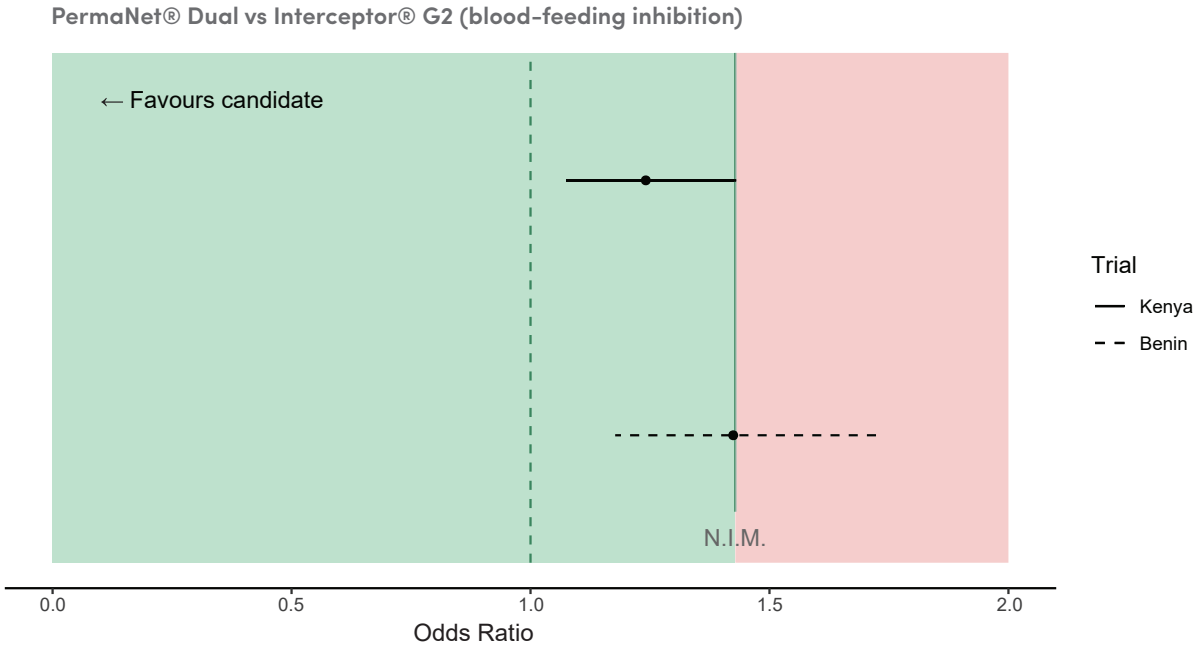


Fig. 7. Non-inferiority margins for the secondary end-point of blood feeding inhibition (pooled data for washed and unwashed nets) for each of the two studies assessing PermaNet® Dual as the candidate net compared to Interceptor® G2 as the active comparator



Discussion

There was substantial discussion during this session on the analytical models used to analyse the data. This was due to an initial discrepancy between the original and independent analyses in terms of the mortality outcomes of one of the trials undertaken for PermaNet® Dual. The former demonstrated non-inferiority, whereas the latter indicated that the lower bound of the 95% CI crossed the non-inferiority margin. Based on the results of the latter analysis, the product would have been considered not non-inferior.

Following an investigation into the specific models used and whether the variables were treated as fixed or random effects, the temporary advisors identified discrepancies between the models used and the WHO statistical guidance *(8)*, which had led to the different outcomes.

Both analyses were therefore re-run with a revised model that incorporated all of the fixed effects recommended in the earlier guidance *(8)*. The results confirmed that PermaNet® Dual was non-inferior to Interceptor® G2 in both trials. Nevertheless, the initial situation in which the CI for a product's OR crossed the non-inferiority margin gave rise to a detailed discussion on the implications of such a finding, in the context of using the OR to compare candidate products to active comparators that induce high mortality. Although adopting the WHO-recommended fixed effects model resolved the situation in the present case, it was recognized that products that perform well (in terms of inducing high mortality) could end up being unable to demonstrate non-inferiority when a fixed OR is used, and that this challenge should be mitigated.

To minimize the potential scenario of separate and contradictory conclusions being reached for analyses on the same trial data, a number of recommendations were put forward and some earlier WHO guidance was reiterated, as follows:

- Trials should, where possible, be conducted at good laboratory practice (GLP)-certified (or at least compliant) sites and draw on the expertise of investigators and statisticians who are familiar with the design and analysis of comparative efficacy assessments.
- A standard positive control should be used in trials; in the case of nets, this should be a pyrethroid-only net rather than a pyrethroid-PBO net, as they have different modes of action.
- A blinded interim analysis should be conducted to verify the underlying power calculations so that the study duration may be extended if the study is found to be underpowered. It should be noted that this interim assessment to evaluate the assumptions underlying the power calculations is not an interim assessment of efficacy; the latter is not recommended. A suitable point for such an interim analysis of study power would in general be after one full rotation of products and sleepers *(8)*. Investigators planning to conduct an interim analysis to assess the assumptions underlying the power calculations should include reference to this in their study protocol. To avoid inevitably assessing interim efficacy, such a calculation should be based only on the expected number of mosquitoes that was assumed in the original power calculation.
- WHO should generate analysis code for use in the major statistical analysis packages (namely R and Stata) to enable standardized analysis across all trials, based on WHO guidance, and ideally accompany this with a practical guide on how to use the code for this purpose.

The temporary advisors recognized that, regardless of improvements made to study design, implementation and analysis, well performing products (i.e. ones that induce

high mosquito mortality) may still fail to demonstrate non-inferiority if the mortality induced by the first-in-class comparator is very high. This is characteristic of using a fixed OR for comparative assessment when both products induce high mortality. In an attempt to find a solution to address this issue and thus not prevent market access of well performing products, the technical advisors further discussed potential modified or alternative assessment options:

- In cases where a product that induces high mortality does not demonstrate non-inferiority, the possibility of drawing on an "either/or" solution was considered, according to which the candidate product would need to either meet a specific mortality threshold or demonstrate non-inferiority to the first-in-class product. Given the extensive work involved in running experimental hut studies alongside epidemiological trials in recent years, it was proposed that such a threshold could potentially be informed by the findings of these parallel studies. However, it was noted that if an absolute mortality threshold were to be used as an alternative primary end-point, this would also have to be handled on a non-inferiority basis, specifying a margin below which the 95% CI lower bound of the mortality estimate should not fall. There was uncertainty over how the fixed mortality threshold would be established. Ultimately, this approach was not considered to be a viable solution.
- The use of a weight-of-evidence approach was proposed by colleagues from the WHO Prequalification Team, who use this approach as part of the prequalification assessment. With this approach, additional contextual evidence is drawn on to inform a decision *(17)*. The group of temporary advisors felt that this approach would induce a component of subjectivity that should be avoided to the extent possible.
- Another possibility that was considered would be to use a modified non-inferiority margin (for example, 0.6 or 0.5) in cases where the mortality for the first-in-class product is greater than a given percentage (for example, 90%). Alternatively, in such cases, the non-inferiority margin based on the OR could be abandoned in place of a lower bound based on a maximum difference in mortality of a given percentage (for example, 5%). Ultimately, this approach was explored further, as outlined in the overall recommendations of this report.

Conclusion

The results of the investigators' analyses and the independent analysis were consistent, and there was consensus among the temporary advisors that PermaNet® Dual was non-inferior to Interceptor® G2 in terms of induced mosquito mortality. PermaNet® Dual did not demonstrate non-inferiority to Interceptor® G2 in terms of blood-feeding inhibition (pooled data) in Benin, but did so in Kenya.

PermaNet® Dual was confirmed to be non-inferior to Interceptor® G2, as per the WHO assessment criteria. The existing WHO recommendation for pyrethroid-chlorfenapyr nets is therefore considered to be applicable to this product.

3.2 IRS

One IRS product was evaluated at this meeting: VECTRON™ T500, a new, broflanilide-based product, manufactured by Mitsui Chemicals Crop & Life Solutions, Inc.

As indicated in the WHO consolidated malaria guidelines *(18)*, insecticide formulations currently recommended for use in IRS fall into five major insecticide classes: pyrethroids, organochlorines, organophosphates, carbamates and neonicotinoids. Broflanilide is a meta-diamide, which is not currently covered by the WHO recommendation for IRS. To

be considered covered under this recommendation, WHO therefore requires that this product demonstrate non-inferiority to a first-in-class product.

The mosquito mortality (the primary end-point) induced by the candidate product should be compared to that of the active comparator and reported as an OR with the corresponding 95% CI. The OR should be assessed against the comparator using a non-inferiority margin of 0.7, meaning that the lower bound of the 95% CI for mortality should not cross 0.7 (Fig. 1). The IRS product should be tested on both concrete/cement and mud as the substrate on the wall of the hut.

Following the practice used for the comparative efficacy assessment of ITNs within the present meeting, for each trial, the data were reported by the trial investigators and subjected to a WHO-commissioned independent analysis by a researcher from Imperial College London, acting independently through Imperial Consultants. Dr Challenger presented the results of the independent analysis, which was performed using a logistic regression model in the widely used lme4 package in the statistical software package R *(12)*. Using separate data for each type of substrate, the model employed fixed effects for each treatment arm (the brand of IRS), hut, sleeper and day of collection. Where the data for mud and concrete substrates were pooled, an additional fixed effect was included in the model to account for the substrate type.

3.2.1 VECTRON™ T500

Description of trials and assessment of non-inferiority

Three studies investigating the efficacy of VECTRON™ T500 were submitted to WHO. All of the studies used a negative control (water), Actellic 300CS (currently prequalified product, the active comparator) and VECTRON™ T500 (the candidate product). The presenters were Dr Koama Bayili for the trial in Burkina Faso, Dr Njelembo Mbewe for the trial in the United Republic of Tanzania and Dr Ngufor for the two trials in Benin.

Study aim

- Assess the non-inferiority of VECTRON™ T500 (containing a meta-diamide called broflanilide) to Actellic 300CS (which contains an organophosphate, pirimiphos-methyl).

Trial 1: Burkina Faso

Background

Dr Bayili presented an experimental hut study conducted in Burkina Faso *(19)* that evaluated VECTRON™ T500 against pyrethroid-resistant mosquitoes, compared to Actellic 300CS, with the aim of determining the optimum effective dose and efficacy of VECTRON™ T500 against susceptible and resistant strains of *Anopheles*. *An. coluzzii* was the dominant vector in this area. In the hut study, a total of six huts were sprayed, with the interior wall substrates as detailed in Table 20.

Approach

The design of this trial is presented in Table 20. Residual activity of the different treatments was assessed using cone bioassays at one week and then monthly after spraying up to nine months for the VECTRON™ T500 100 mg/m^2 and Actellic 300CS treatments. For the VECTRON™ T500 150 mg/m^2 treatment, assessments were carried out up to 12 months. Immediate mortality was assessed by counting mosquitoes dead in the hut each morning, while delayed mortality was assessed after 72 hours of

holding. Mosquito strains used in the assays were *An. coluzzii* and *An. gambiae* Kisumu strain.

Table 20. Summary of experimental treatments used in the Burkina Faso study of VECTRON™ T500

Treatment	Concentration (mg/m²)	Walls	Number of huts
VECTRON™ T500	100	Concrete	1
VECTRON™ T500	150	Concrete	1
VECTRON™ T500	100	Mud	1
VECTRON™ T500	150	Mud	1
Actellic 300CS	1000	Concrete	1
Negative control	N/A (distilled water)	Concrete	1

In this study, cows were used as mosquito bait in place of human volunteers because the mosquitoes were zoophilic, and the potential health risk to human participants of the VECTRON™ T500 product had not been fully assessed at the time of study initiation.

Outcome

Point estimates for mortality and blood feeding for the study in Burkina Faso are shown in Table 21. The investigators did not plan for or perform non-inferiority analyses for mortality or blood-feeding inhibition, but provided the data to the independent statistician to conduct the analysis.

Table 21. Point estimates of mosquito mortality and blood feeding for the respective products tested in the trial in Burkina Faso, where *An. coluzzii* was the predominant vector

Outcome	Product	Role in study	Substrate	Concentration (mg/m²)	Point estimate (%)	95% CI
Primary: Mortality (72 hours)	Actellic 300CS	Active comparator	Concrete	1000	100	-
	VECTRON™ T500	Candidate	Concrete	100	60.4	58.78–62.00
	VECTRON™ T500	Candidate	Concrete	150	70.04	68.66–71.39
	VECTRON™ T500	Candidate	Mud	100	55.51	53.95–57.25
	VECTRON™ T500	Candidate	Mud	150	73.22	71.76–74.73
Secondary: Blood feeding	Actellic 300CS	Active comparator	Concrete	1000	94.91	93.70–95.90
	VECTRON™ T500	Candidate	Concrete	100	92.41	91.49–93.24
	VECTRON™ T500	Candidate	Concrete	150	92.51	91.69–93.26
	VECTRON™ T500	Candidate	Mud	100	88.87	87.95–90.02
	VECTRON™ T500	Candidate	Mud	150	95.23	94.43–95.92

The study showed that VECTRON™ T500 had extended residual efficacy against susceptible and resistant mosquitoes for up to six months, on both mud and concrete substrates. The study proposed that a dose of 100 mg/m^2 can be used in community trials.

Discussion

The temporary advisors raised concerns about using the data to inform decision-making on the non-inferiority of the product due to issues with the study design. For example, only six huts were used in the study and the active comparator induced complete mosquito mortality. The lack of experimental repetition was acknowledged as a study limitation by the investigators. Several other concerns were also raised relating to the use of cows as bait, a limited period of mosquito collections due to seasonality of mosquito abundance, the placement of the cones in the cone assay, and the fact that the cone bioassay analysis was performed on cumulative data rather than on individual cones. Given these concerns with the study design, the temporary advisors decided that it was not appropriate to consider the results of this study in the decision-making on the non-inferiority of VECTRON™ T500.

Trial 2: United Republic of Tanzania

Background

This non-inferiority trial was conducted in Lower Moshi, United Republic of Tanzania, and used eight East African-style experimental huts. The main vector at the study site was *An. arabiensis*, which peaked in abundance during the rice-growing season. *An. arabiensis* was found to be resistant to pyrethroids in this area, with resistance driven by over-expression of P450s. The study was conducted over a 12-month period from December 2020 to December 2021.

Approach

A trial testing the non-inferiority of VECTRON™ T500 was conducted in the United Republic of Tanzania *(20)*. Huts with either concrete or mud-plaster substrate were sprayed with the respective treatments in December 2020, according to random assignment, as summarized in Table 22.

Table 22. Summary of experimental treatments used to evaluate the non-inferiority of VECTRON™ T500 in the United Republic of Tanzania

Treatment	Concentration (mg/m^2)	Walls	Number of huts
Negative control	Distilled water	Concrete	2
VECTRON™ T500	100	Concrete	2
VECTRON™ T500	100	Mud	2
Actellic 300CS	1000	Concrete	1
Actellic 300CS	1000	Mud	1

Wild mosquitoes were collected every morning from each of the experimental huts from January to April and July to October 2021. Monthly cone bioassays were conducted in the experimental huts over a 12-month period after the spraying of VECTRON™ T500 and Actellic 300CS.

As opposed to using humans to attract the mosquitoes, cows were placed inside the huts, with daily rotations between huts. The primary outcome measure was cumulative

mosquito mortality at 72 hours. The secondary outcomes were the percentage of mosquitoes that were blood-fed, blood-feeding inhibition and the percentage of mosquitoes exiting the huts. Analysis was based on a grouped mixed effects multiple regression model, performed in Stata version 16 *(21)*. The power analysis was performed in R, with a 0.05 significance level.

Outcomes

A total of 5740 wild free-flying *An. arabiensis* mosquitoes were collected over 120 days, including 2764 in concrete-plastered huts and 2976 in mud-plastered huts. Point estimates for the primary end-point (mortality) and secondary end-point (blood feeding) are shown in Table 23, while the findings from the comparative efficacy assessment are presented in Table 24. With a 72-hour mortality measurement, VECTRON™ T500 demonstrated higher mortality than Actellic 300CS on both concrete and mud substrates. The data on blood feeding were not presented.

Table 23. Point estimates of mosquito mortality over 120 days for the respective products tested in the trial in the United Republic of Tanzania, where *An. arabiensis* was the predominant vector

Outcome	Product	Role in study	Substrate	Point estimate (%)	95% CI
Primary: Mortality (72 hours)	Water	Negative control	Concrete	2.0	1.0–4.0
	Water	Negative control	Mud	3.0	2.0–4.5
	Actellic 300CS	Active comparator	Concrete	30.5	27.3–33.9
	Actellic 300CS	Active comparator	Mud	34.6	31.5–37.9
	VECTRON™ T500	Candidate	Concrete	62.2	59.8–59.1
	VECTRON™ T500	Candidate	Mud	46.4	43.8–49.1

Table 24. Comparative efficacy assessment of VECTRON™ T500 and Actellic 300CS over 120 days, analysing mosquito mortality after 72 hours in mud and concrete huts in the United Republic of Tanzania, where *An. arabiensis* was the predominant vector

Outcome	Reference	Candidate	Substrate	Adjusted OR	95% CI	Target outcome	Test outcome
Primary: Mortality (72 hours)	Actellic 300CS	VECTRON™ T500	Concrete	3.9	2.9–5.3	Non-inferiority	Non-inferior
	Actellic 300CS	VECTRON™ T500	Mud	1.9	1.4–2.6	Non-inferiority	Non-inferior

The question was raised as to the rationale for using cows in this study, as opposed to humans. The investigators responded that *An. arabiensis* is the predominant vector in the area, and previous studies have shown that this mosquito population has a greater feeding attraction to cows than to humans.

Trial 3: Benin (first trial)

Background

VECTRON™ T500 was compared to Actellic 300CS in Benin, using a West African hut design *(22)*. The vector population consisted of *An. gambiae* s.s. and *An. coluzzii* sibling species – together referred to as *An. gambiae* s.l. These mosquito populations showed high resistance to pyrethroids and dichlorodiphenyltrichloroethane (DDT) but

were susceptible to organophosphates and carbamates. The predominant resistance mechanisms were *kdr* L1014F and P450s. This trial, conducted between September 2018 and March 2019, was the first of two hut trials conducted in Benin; it aimed to identify the ideal dosing and time points for testing, as opposed to the non-inferiority of VECTRON™ T500.

Approach

This study tested two concentrations of VECTRON™ T500 (100 mg/m^2 and 150mg/m^2) and compared them to Actellic 300CS, as described in Table 25. Mosquito mortality was recorded at 24, 48 and 72 hours. At the time of this trial, toxicity against humans had not been cleared. Therefore, cows were used to bait the mosquitoes. A logistic regression model, with the fixed effects of sleeper, hut and day of collection, and all statistics were performed in Stata 17 *(14)*.

Table 25. Summary of experimental treatments used to evaluate VECTRON™ T500 in Benin (first trial, Ngufor et al. 2021).

Treatment	Concentration (mg/m^2)	Walls	Number of huts
VECTRON™ T500	100	Concrete	1
VECTRON™ T500	150	Concrete	1
VECTRON™ T500	100	Mud	1
VECTRON™ T500	150	Mud	1
Actellic 300CS	1000	Concrete	1
Negative control	Distilled water	Concrete	1

Outcomes

The trial lasted six months and demonstrated a delayed mortality effect associated with VECTRON™ T500, from 24 to 72 hours. The trial also showed that acceptable mortality could be achieved with the lower 100 mg/m^2 concentration. VECTRON™ T500 72-hour mortality rates were lower than with Actellic 300CS, as seen in Table 26. As the trial used cows in place of humans to bait the mosquitoes, blood-feeding inhibition was not measured. Non-inferiority estimates were not calculated by the investigators for this trial, but data were shared for independent analysis.

Table 26. Point estimates of mosquito mortality for the respective products tested in the first Benin trial over six months

Outcome	Product	Role in study	Substrate	Concentration (mg/m^2)	Point estimate (%)	95% CI
Primary: Mortality (72 hours)	Actellic 300CS	Active comparator	Concrete	1000	56	50–62
	VECTRON™ T500	Candidate	Concrete	100	57	47–66
	VECTRON™ T500	Candidate	Concrete	150	66	54–78
	VECTRON™ T500	Candidate	Mud	100	63	52–74
	VECTRON™ T500	Candidate	Mud	150	63	52–72

Trial 4: Benin (second trial)

Background

A non-inferiority trial *(23)* was conducted to assess VECTRON™ T500, using the West African hut design. Based on the previous study in Benin by Ngufor et al. *(22)*, it was determined that the lower dose of VECTRON™ T500 was appropriate for use and was thus used to assess the non-inferiority of the product to Actellic 300CS (1000 mg/m^2). The predominant vector in the study area was *An. gambiae* s.l., which was pyrethroid-resistant. The study, which employed eight huts of West African design, began in November 2019 and was concluded after 12 months.

Approach

The trial was designed according to published WHO guidance for non-inferiority assessment and IRS application *(7, 24)*. Performed in a GLP-certified facility with appropriate quality assurance, all huts were confirmed to have been adequately sprayed with the appropriate dosage of the active ingredient; for VECTRON™ T500, a dose of 100 mg/m^2 was applied, while for Actellic 300CS, the dose was 1000 mg/m^2. Table 27 shows the study design. The vector population was confirmed to be susceptible to broflanilide in United States Centers for Disease Control and Prevention bottle bioassays.

Unlike the previous VECTRON™ T500 study conducted in Benin *(22)*, humans occupied the huts, as the study commenced after the toxicity assessment had validated broflanilide as safe for human use. The trial took place over 12 months, with a total of 312 nights of wild mosquito collections. Sleepers rotated daily, and there was one day a week when huts were aired out.

Table 27. Summary of experimental treatments used to evaluate VECTRON™ T500 in the second Benin trial

Treatment	Role in study	Walls	Number of huts
Untreated	Negative control	Concrete	1
Untreated	Negative control	Mud	1
VECTRON™ T500	Candidate	Concrete	2
VECTRON™ T500	Candidate	Mud	2
Actellic 300CS	Active comparator	Concrete	1
Actellic 300CS	Active comparator	Mud	1

Mosquito mortality was measured at 24 and 72 hours post-exposure. Mortality and blood-feeding rates between treatments were compared using logistic regression models with treatment arm, sleeper, hut and day of collection as fixed effects. The ORs and all statistics were run in Stata version 17 *(14)*. End-points included 72-hour mortality, exophily, deterrence, blood-feeding rate and the overall percentage of mosquitoes killed.

As per the previous study conducted in Benin *(22)*, the vector population was susceptible to broflanilide and other classes of insecticides used for vector control. Monthly wall cone bioassays were performed to assess the residual efficacy of the candidate product, using insecticide-susceptible *An. gambiae* Kisumu and pyrethroid-resistant *An. gambiae* s.l. Covè strains.

A total of 23 171 wild free-flying pyrethroid-resistant female *An. gambiae* s.l. mosquitoes were collected in the experimental huts over 12 months.

Outcomes

VECTRON™ T500 induced 62–73% mortality in the first three months of the study and continued to kill > 50% of mosquitoes for a further nine months on both substrate types. By comparison, mortality with Actellic 300CS was very high in the first three months (72–95%), but declined sharply to < 40% after four months. The point estimates for mosquito mortality at six and 12 months are shown in Table 28 and Table 29, respectively.

Six months after spraying, VECTRON™ T500 was found to be non-inferior to Actellic 300CS on mud and superior to Actellic 300CS on concrete (P = 0.042) for the 72-hour mosquito mortality end-point (Table 30). However, at 12 months post-spraying, VECTRON™ T500 was found to be superior to Actellic 300CS for mosquito mortality when tested on both concrete and mud substrates, when assessed for the 72-hour end-point (Table 31).

Table 28. Point estimates of 72-hour mosquito mortality outcomes for the respective products tested in the second trial in Benin, where *An. gambiae* s.l. was the predominant vector, over six months

Outcome	Product	Role in study	Substrate	Point estimate (%)	95% CI
Primary: Mortality (72 hours)	Actellic 300CS	Active comparator	Concrete	56.5	50.6–62.3
	VECTRON™ T500	Candidate	Concrete	60.7	57.8–63.6
	Actellic 300CS	Active comparator	Mud	58.9	53.2–64.5
	VECTRON™ T500	Candidate	Mud	60.8	57.7–63.8

Table 29. Point estimates of 72-hour mosquito mortality outcomes for the respective products tested in the second trial in Benin, where *An. gambiae* s.l. was the predominant vector, over 12 months

Outcome	Product	Role in study	Substrate	Point estimate (%)	95% CI
Primary: Mortality (72 hours)	Actellic 300CS	Active comparator	Concrete	43.8	39.1–48.5
	VECTRON™ T500	Candidate	Concrete	57	54.2–59.8
	Actellic 300CS	Active comparator	Mud	44.6	33.9–49.2
	VECTRON™ T500	Candidate	Mud	57.9	55.0–60.7

Table 30. Comparative efficacy assessment of VECTRON™ T500 and Actellic 300CS, analysing mosquito mortality after 72 hours in mud and concrete huts in Benin, where *An. gambiae* s.l. was the predominant vector, over six months

Outcome	Reference	Candidate	Substrate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (72 hours)	Actellic 300CS	VECTRON™ T500	Concrete	1.16	1.01–1.35	Non-inferior	Non-inferior
	Actellic 300CS	VECTRON™ T500	Mud	1.01	0.87–1.16	Non-inferior	Non-inferior

Table 31. Comparative efficacy assessment of VECTRON™ T500 and Actellic 300CS, analysing mosquito mortality after 72 hours in mud and concrete huts in Benin, where *An. gambiae* s.l. was the predominant vector, over 12 months

Outcome	Reference	Candidate	Substrate	OR	95% CI	Target outcome	Test outcome
Primary: Mortality (72 hours)	Actellic 300CS	VECTRON™ T500	Concrete	1.49	1.31–1.70	Non-inferior	Non-inferior
	Actellic 300CS	VECTRON™ T500	Mud	1.24	1.09–1.41	Non-inferior	Non-inferior

Independent analysis of data

The independent data analysis (see Annex 4) included fixed effects for hut, sleeper, day of collection and treatment arm. As a standard approach, data were analysed for the three-month time point (as this is considered to be the minimum duration for which any IRS product should remain effective) and the six-month time point, for studies that had been implemented over this longer duration (see Fig. 8). Data from any assessments beyond six months were not considered in the independent analysis.

United Republic of Tanzania

Using data from only the first three months of the study, this analysis demonstrated that VECTRON™ T500 significantly increased the likelihood of mosquito mortality in wild collections of *An. arabiensis* compared to Actellic 300CS. There was no significant difference between the VECTRON™ T500 and Actellic 300CS arms in terms of blood feeding in the wild collection of *An. arabiensis*. These results showed VECTRON™ T500 to be efficacious against pyrethroid-resistant *An. arabiensis* and non-inferior to Actellic 300CS. Pooled data (concrete + mud) for the 24-hour end-point highlighted the superiority of VECTRON™ T500 over Actellic 300CS, with an OR of 2.19 (CI: 1.61–3.00). The equivalent 72-hour end-point also supported this outcome (OR: 3.74; CI: 3.02–4.65).

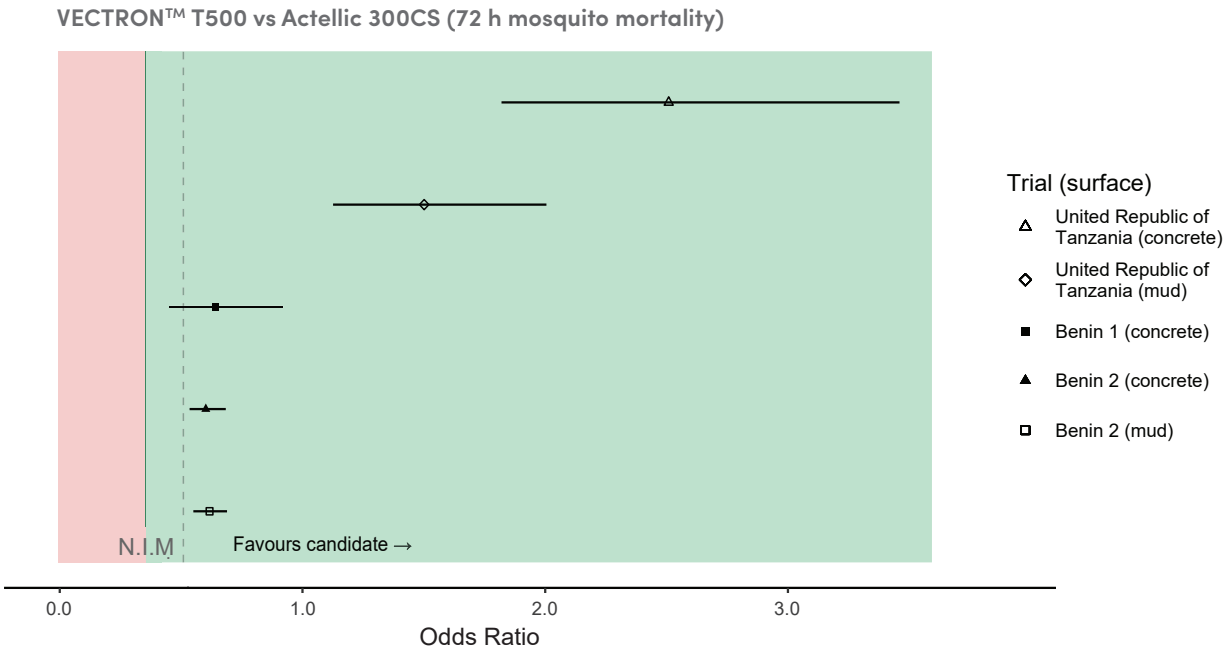
Benin (first trial)

The independent analysis used pooled species data because the number of mosquitoes per hut per night was very low, which had consequences for the power of the study (calculated as possibly as low as 40%). Despite using cows as the mosquito bait and the trial not being designed specifically to assess non-inferiority, the analysis of the first three months (on concrete only) demonstrated that VECTRON™ T500 was not non-inferior to Actellic 300S (a comparison using mud could not be performed because there were no equivalent treatments for Actellic 300CS on mud). Using data from the entire study (which extended to six months in total), VECTRON™ T500 persisted better than Actellic 300CS, showing non-inferiority at 100 mg/m^2 (OR: 1.26; CI: 0.89–1.80) and superiority at 150 mg/m^2 (OR: 1.60; CI: 1.04–2.46) in terms of mortality.

Benin (second trial)

The second study carried out in Benin was specifically designed to enable comparative efficacy assessment. The study compared concrete and mud substrates on the walls of the huts, with the same VECTRON™ T500 dosing in all cases. VECTRON™ T500 was found to be not non-inferior on both substrates at the three-month time point. However, at the six-month time point, VECTRON™ T500 was found to be superior to Actellic 300CS on both concrete (OR: 1.18; CI: 1.05–1.34) and mud (OR: 1.21; CI: 1.08–1.35) substrates. Using pooled data from both substrates, the non-inferiority outcome of superiority was supported (OR: 1.19; CI: 1.10–1.29).

Fig. 8. Non-inferiority margins for the primary end-point of mosquito mortality for the comparison of VECTRON™ T500 (100 mg/m²) as the candidate IRS product and Actellic 300CS (1000 mg/m²) as the active comparator over the first six months



Note: Analyses have been separated by study and by substrate that was applied to the walls of the experimental huts (either mud or concrete). Data represent estimates from the first six months of the respective trials.

Discussion

Guidance issued by WHO indicates that, at a minimum, the non-inferiority of IRS should be assessed at three months, as this is the minimum duration of efficacy required for products used for this intervention. Assessment of efficacy beyond this time point may be warranted depending on the insecticide's mode of action and formulation. Assessment at three months demonstrated that Actellic 300CS had higher efficacy than VECTRON™ T500, but that residual efficacy waned after three months. VECTRON™ T500's longer term efficacy was clearly demonstrated and, in this case, highlighted the importance of measuring IRS beyond the three-month minimum, until 80% efficacy of one of the two products being compared is no longer achieved.

Conclusion

WHO does not currently have guidance on the precise requirements for measuring the duration of IRS efficacy, other than a minimum of three months post-spraying. The temporary advisors suggested that updated non-inferiority testing guidance for IRS products explicitly include additional time points for assessment of residual efficacy (up to and beyond six months), as well as supplementary mortality end-points (i.e. longer holding periods of 48 and 72 hours), consistent with the mode of action and formulation of the insecticide being tested.

The temporary advisors agreed that only the studies conducted in Benin and the United Republic of Tanzania were to be included in the assessment of comparative efficacy, as these studies were designed specifically to generate data for this purpose. Based on the assessment of the three studies judged to meet WHO requirements *(7, 8)*, VECTRON™ T500, the active ingredient of which is broflanilide, demonstrated non-inferiority to Actellic 300CS. The temporary advisors therefore recommended that

WHO's current recommendation for the use of IRS in malaria vector control be extended to include the insecticide broflanilide and that the WHO guidelines for malaria be updated accordingly.

4. Overall discussion and recommendations to WHO

Through the review and evaluation of data from the four candidate products in this technical consultation, the temporary advisors identified numerous points relevant to the approach, protocol and implementation of comparative efficacy assessments that could be improved.

The temporary advisors agreed that while the overall design of the non-inferiority studies and their analysis provided in the original study protocol *(7)* and in the 2021 meeting report *(8)* remains well thought out and valid, WHO should incorporate several updates into the study protocol to ensure that all guidance on studies designed to generate data for comparative efficacy assessment reflects best practices and latest experience, and can be found in one guidance document.

4.1 Non-inferiority recommendations to WHO

In terms of the final evaluation of the products assessed during this consultation, the temporary advisors recommended that WHO:

- extend the IRS recommendation for malaria to include broflanilide, in turn covering VECTRON™ T500 under this recommendation and thus making VECTRON™ T500 the appropriate active comparator for other broflanilide products in future comparative efficacy assessments;
- consider the DuraNet Plus© and Yorkool® G3 nets to be covered under the current pyrethroid-PBO net recommendation; and
- consider the PermaNet® Dual net to be covered under the current pyrethroid-chlorfenapyr net recommendation.

4.2 Proposed updates to the non-inferiority study protocol

The previous technical consultation in 2021 proposed numerous updates to the study protocol for non-inferiority studies *(8).* In addition to those points, the temporary advisors proposed further protocol updates to ensure that the lessons learned from the present meeting and associated data analyses are captured in the revised protocol.

4.2.1 Statistical analysis

It was noted in the presentations of products that relatively minor variations in the regression model can lead to changes in outcomes. There is therefore a need to ensure that a standardized analysis is performed, with consistency in which fixed effects are included in the model. To address this issue, WHO should – in addition to its guidance – develop a standardized code to enable investigators to perform consistent analyses. The code should be made available in commonly used statistical software packages, such as R and Stata. The code should follow the guidance from the 2021 technical consultation, which stated that the analysis should be based on "a logistic regression model with fixed effects for the brand of net, hut, sleeper, night and number

of washes" *(8)*. Similarly, a template for data collection could be produced to simplify data collection and upload.

4.2.2 Odds ratios

Using a fixed OR of 0.7 as the non-inferiority margin implies that when the mortality of a first-in-class product is 50% then the lower bound of the 95% CI of the observed mortality of the candidate product needs to be above 41.2% to be considered non-inferior; that is, in terms of absolute difference, a non-inferiority margin of 8.8% would be allowed. By contrast, when the observed mortality of a first-in-class product is 95%, then an OR of 0.7 implies that the lower bound of the 95% CI of the observed mortality of the candidate product needs to be above 93% to be considered non-inferior; that is, in terms of absolute difference, a non-inferiority margin of 2% would be allowed. Therefore, at high mortalities, an OR of 0.7 imposes a near impossible condition for the candidate product to demonstrate non-inferiority (and requires very large sample sizes to obtain such narrow 95% CIs).

For this reason, it was decided to recommend to WHO some modifications to the methodology that would preserve the use of non-inferiority as the sole decision-making approach and the use of an OR, but would introduce an OR of the non-inferiority margin that would vary depending on the percent mortality achieved by the first-in-class product. Using this modified approach, a fixed percentage of 7% difference in mortality between the first-in-class product mortality and the lower bound of the candidate product's 95% CI would be used to obtain the applicable OR (see Table 32).

Table 32. Reference table for key mortality estimates of first-in-class products, indicating the corresponding values that would be accepted for a 7% non-inferiority margin

First-in-class product mortality (%)	Lower bound of candidate CI if non-inferiority mortality margin is 7%	Corresponding OR for a 7% non-inferiority margin
95	88	0.39
90	83	0.54
80	73	0.68
70	63	0.73
60	53	0.75
50	43	0.75
40	33	0.74
30	23	0.70

4.2.3 Choice of trial sites

The current 2021 guidance *(8)* indicates that a minimum of two trials should be performed, but it does not prescribe the geographical representation of those sites. The temporary advisors recommended that future guidance be updated to specify that the study sites should not be limited to one geographical/ecological region. Specifically, site selection should include sites from at least two of the following regions: East Africa, and Central Africa or West Africa. It was suggested that comparative efficacy assessments be conducted in the same locations as where the first-in-class product was initially assessed, as this would further enable meaningful comparison of product efficacy.

4.2.4 Choice of bait for the huts

During the course of this review, numerous IRS experimental hut studies that were presented used cows as bait in the huts. While these studies were accepted by the temporary advisors, it was recommended that the protocol update include information about the bait source. Given that these comparative efficacy studies are intended to be used to generate entomological efficacy data as a surrogate end-point to substitute for the clinical end-points in humans used in epidemiological trials, it was considered preferable to draw on human subjects as mosquito bait in future entomological trials. Investigators deviating from this recommendation should provide justification for doing so.

4.2.5 Reporting of study descriptors

The current 2021 guidance states, "For all vector control interventions, the mosquito species composition and its insecticide resistance profile are the minimum requirements to be reported" *(8)*. The temporary advisors recommended that additional information on site location, hut type used, dates of the trial and epidemiology of the site be added to this list, and the study protocol updated accordingly.

4.2.6 Reporting of study outcomes

The pooled assessment of washed and unwashed nets, although it provides a simpler estimate of comparative efficacy, has the potential to mask subtleties and granularity that could be important for understanding impact in terms of both mosquito mortality and blood feeding. The utility of such information could be valuable for country decision-making. It was therefore suggested that both the pooled and individual assessments of washed and unwashed data be included in the standard reporting format. This may provide additional information for programmatic decision-making by WHO Member States, even though WHO would continue to base its decisions on the pooled data *(8)*.

4.2.7 Additional end-points

For insecticide classes other than pyrethroids, preliminary studies should inform the appropriate end-points to be measured in the non-inferiority studies. For both chlorfenapyr and broflanilide, it was clear that assessing mosquito mortality beyond the standing 24-hour time point was important to appropriately measure the impact of these insecticides against mosquitoes. Furthermore, for IRS products, it was recommended that mosquito mortality be assessed at three months and at six months post-application of the product to the huts. The temporary advisors therefore recommended that additional end-points be included in the protocol and related testing guidance for future assessments.

4.2.8 Registry of non-inferiority trials

As proposed in the guidance section of the 2021 meeting report *(8)*, the temporary advisors reiterated the need for non-inferiority trials to be conducted at GLP-compliant sites and to be registered. This is to facilitate standardization and limit the bias introduced if only trials demonstrating non-inferiority are reported. The temporary advisors recommended that WHO work with GLP-compliant and GLP-certified laboratories to set up a registry accordingly, and that the updated study protocol provide clarity on the minimum details to be recorded in the registry.

4.3 Conclusions

The purpose of non-inferiority studies within the WHO vector control evaluation process is to provide reassurance to WHO, as well as to procurers and Member States, that new, second-in-class products perform similarly to products that have demonstrated epidemiological impact in terms of their entomological efficacy. Assessments of comparative efficacy avoid the need to generate epidemiological data for all new vector control products, with the aim of bringing effective products, covered under an existing WHO recommendation, to market sooner.

Following the review of all four products presented at this meeting (DuraNet Plus©, Yorkool® G3, PermaNet® Dual and VECTRON™ T500), there was consensus among the temporary advisors that all products were non-inferior to their first-in-class counterparts or an active comparator. WHO will take steps to update its guidelines to add broflanilide to the insecticides covered under the IRS recommendation for malaria.

Following on from the technical consultation in 2021 *(8)* and the discussions on the studies presented, it was noted that several additional points need to be included in a more prescriptive, updated study protocol. To ensure a high standard of study execution, relevance for understanding the public health value of the product (as is required of epidemiological trials for first-in-class products) and generalizability of results *(1)*, the protocol should articulate the requirements for the location of study sites and species to be used as mosquito bait, as well as the minimum requirements for reporting. It should also encourage investigators and manufacturers to measure additional time points as relevant to the vector control intervention in question.

Further work is also needed in terms of the WHO supporting infrastructure associated with non-inferiority trials. Such support ranges from capacity-building in GLP-certified and GLP-compliant sites, a platform for registering trials, and templates and pre-written analysis code to simplify data collection and standardize analysis output. Finally, the results need to be communicated and shared in the public domain, with the results provided clearly and in context, which will in turn permit informed decision-making for procurement.

The meeting raised the important implications of using a fixed OR for the non-inferiority margin when it comes to assessing candidate products against extremely well performing first-in-class products. The temporary advisors recognized this limitation and, after considerable deliberation, recommended the adoption of a modified approach, as outlined above. WHO will incorporate this recommendation into the ongoing update of the protocol for comparative efficacy studies to be published in the second half of 2023.

5. Concluding remarks

The Director of the Global Malaria Programme, Dr Daniel Ngamije M., thanked the temporary advisors who took part in this technical consultation. Over the past six years, the wider vector control evaluation process has undergone regular evolution to ensure that WHO recommendations for intervention classes are based on solid evidence and that products being prequalified meet strict criteria, with the overall aim of providing the best possible advice and evidence to Member States and informing their prioritization of scarce resources in the area of vector control.

Dr Ngamije noted that this consultation was part of WHO's broader effort to implement comparative efficacy assessments as a routine part of vector control evaluation for malaria, driven by the need to provide Member States with assurance that the second-in-class products in an established intervention class achieve a level of efficacy comparable to the first-in-class products that demonstrated impact against malaria. This process continues to evolve, and updated guidance will be released in due course.

As part of the evolving process, and thanks to the availability of the temporary advisors, WHO was able to quickly review the new data submitted in response to the March 2023 data call. WHO thanks the manufacturers and their research partners for the submission of their data on four products. Bringing everyone together at this technical consultation at quite short notice reflects WHO's commitment to providing market access to new interventions.

Dr Ngamije expressed his thanks:

- to the temporary advisors who participated in this consultation for taking the time to review the data presented;
- to Professor Ghani, who kindly agreed to chair the consultation;
- to the manufacturers and investigators, who kindly shared their data with WHO;
- to Dr Challenger for conducting the series of independent data analyses; and
- to the chair of the Malaria Policy Advisory Group, Professor Dyann Wirth, for participating as an observer during a select number of sessions.

References

1. Norms, standards and processes underpinning development of WHO recommendations on vector control. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/338030, accessed 28 June 2023).
2. Guidelines Review Committee [website]. In: Groups. Geneva: World Health Organization (https://www.who.int/groups/guidelines-review-committee, accessed 28 June 2023).
3. The recommendation development process [website]. In: Global Malaria Programme. Geneva: World Health Organization (https://www.who.int/teams/global-malaria-programme/guideline-development-process/recommendation-pathway, accessed 28 June 2023).
4. WHO guidelines for malaria, 16 February 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/339609, accessed 28 June 2023).
5. WHO malaria policy advisory committee meeting: meeting report, October 2017. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259396, accessed 28 June 2023).
6. Guidelines Review Committee [website]. In: Groups. Geneva: World Health Organization (https://www.who.int/groups/guidelines-review-committee, accessed 28 June 2023).
7. The recommendation development process [website]. In: Global Malaria Programme. Geneva: World Health Organization (https://www.who.int/teams/global-malaria-programme/guideline-development-process/recommendation-pathway, accessed 28 June 2023).
8. WHO guidelines for malaria, 16 February 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/339609, accessed 28 June 2023).
9. WHO malaria policy advisory committee meeting: meeting report, October 2017. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/259396, accessed 28 June 2023).
10. Notice of intent to introduce non-inferiority studies as a component of the vector control evaluation process. Geneva: World Health Organization; 2018 (available upon request).
11. Data requirements and protocol for determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established WHO policy class. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/276039, accessed 28 June 2023).
12. Technical consultation on determining non-inferiority of vector control products within an established class: report of a virtual meeting, 31 August–2 September 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/349446, accessed 28 June 2023).
13. Indoor residual surface treatments for malaria transmission control in areas with insecticide-resistant mosquito populations: preferred product characteristics. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/356901, accessed 28 June 2023).
14. WHO malaria policy advisory group (MPAG) meeting: meeting report, October 2021. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/348220, accessed 28 June 2023).

15. WHO malaria policy advisory group (MPAG) meeting: meeting report, October 2022. Geneva: World Health Organization; 2022 (https://apps.who.int/iris/handle/10665/364715, accessed 28 June 2023).

16. R Core Team. R: a language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2021 (https://www.r-project.org/, accessed 28 June 2023).

17. Schumi J, Wittes JT. Through the looking glass: understanding non-inferiority. Trials. 2011;12:106. doi:10.1186/1745-6215-12-106.

18. Stata statistical software: release 17. College Station: StataCorp LLC; 2021 (https://www.stata.com/, accessed 28 June 2023).

19. Syme T, N'dombidjé B, Gbegbo M, Todjinou D, Ariori V, De Vos P, et al. PermaNet® Dual, a new deltamethrin-chlorfenapyr mixture net, shows improved efficacy against pyrethroid-resistant Anopheles gambiae sensu lato in southern Benin. BioRXiv. 2023 (preprint). doi:10.1101/2023.02.02.526745.

20. EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, Jeger MJ, Knutsen HK, et al. Guidance on the use of the weight of evidence approach in scientific assessments. EFSA J. 2017;15(8):e04971. doi:10.2903/j.efsa.2017.4971.

21. World Health Organization, WHO Pesticide Evaluation Scheme. Guidelines for laboratory and field-testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2013 (https://apps.who.int/iris/handle/10665/80270, accessed 28 June 2023).

22. WHO guidelines for malaria, 14 March 2023. Geneva: World Health Organization; 2023 (https://apps.who.int/iris/handle/10665/366432, accessed 28 June 2023).

23. Bayili K, Ki KD, Bayili B, Sow B, Ouattara A, Small G, et al. Laboratory and experimental hut trial evaluation of VECTRON™ T500 for indoor residual spraying (IRS) against insecticide resistant malaria vectors in Burkina Faso. Gates Open Res. 2022;6:57. doi:10.12688/gatesopenres.13578.2.

24. Mbewe NJ, Kirby MJ, Snetselaar J, Kaaya RD, Small G, Azizi S, et al. A non-inferiority and GLP-compliant study of broflanilide IRS (VECTRON™ T500), a novel meta-diamide insecticide against Anopheles arabiensis. Front Trop Dis. 2023;4:1126869. doi:10.3389/fitd.2023.1126869.

25. Stata statistical software: release 16. College Station: StataCorp LLC; 2019 (https://www.stata.com/, accessed 28 June 2023).

26. Ngufor C, Govoetchan R, Fongnikin A, Vigninou E, Syme T, Akogbeto M, et al. Efficacy of broflanilide (VECTRON™ T500), a new meta-diamide insecticide, for indoor residual spraying against pyrethroid-resistant malaria vectors. Sci Rep. 2021;11(1):7976. doi:10.1038/s41598-021-86935-3.

27. Govoetchan R, Fongnikin A, Syme T, Small G, Gbegbo M, Todjinou D, et al. VECTRON™ T500, a new broflanilide insecticide for indoor residual spraying, provides prolonged control of pyrethroid-resistant malaria vectors. Malar J. 2022;21(1):324. doi:10.1186/s12936-022-04336-x.

28. Guidelines for testing mosquito adulticides for indoor residual spraying and treatment of mosquito nets. Geneva: World Health Organization; 2006 (https://apps.who.int/iris/handle/10665/69296, accessed 28 June 2023).

Annex 1. Declarations of interest

The members of the technical consultation sent in their declaration of interest forms. Of those who declared interests, Professor Azra Ghani declared research and consulting support, but it was determined that none of it constituted a conflict of interest.
Dr Robert Reiner declared research interests, but none that were relevant to the topic of this meeting. Mr Kyeba Swai declared that his research institute contracts with some of the companies submitting products for review, but he had not worked with any of the products involved in this technical consultation. As a result, he was deemed not to have a conflict of interest and was able to participate in all sessions of the meeting.
Mr Olukayode Odufuwa declared receiving remuneration as a consultant from Tianjin Yorkool® International Trading, and so was excluded from Part II of the meeting, when Yorkool® G3 was discussed. None of the other participants declared relevant interests.

Annex 2. Agenda

Day 1 – Monday, 5 June 2023		
Welcome and official opening		Presenters and contributors
8:00–8:10	Opening remarks and welcome	Dr M. Daniel NGAMIJE
8:10–8:15	Declarations of interest	Dr Seth IRISH
8:15–8:25	Background, objectives and expected outcomes	Dr Jan KOLACZINSKI
Part I: Presentation of data and analysis on DuraNet Plus©		Presenters and contributors
8:25–9:25	Presentation of data from Benin, Cameroon and Côte d'Ivoire	Dr Corine NGUFOR
9:25–9:40	Presentation of data and analysis on combined efficacy estimates based on data from Benin, Cameroon and Côte d'Ivoire	Dr Joseph CHALLENGER
9:40–10:00	Discussion and questions	Members, participants, selected observers, WHO staff
Part II: Presentation of data and analysis on Yorkool® G3		Presenters and contributors
10:15–10:45	Presentation of data from Benin	Dr Corine NGUFOR
10:45–11:15	Presentation of data from the United Republic of Tanzania	Dr Sarah MOORE
11:15–11:30	Presentation of data and analysis on combined efficacy estimates based on data from Benin and United Republic of Tanzania	Dr Joseph CHALLENGER
11:30–11:50	Discussion and questions	Members, participants, selected observers, WHO staff
Part III: Conclusions & recommendations		Presenters and contributors
12:00–12:45	Finalization of meeting conclusions & formulation of recommendations to WHO	Chair

Day 2 – Friday, 9 June 2023		
Part IV: Presentation of data and analysis on VECTRON™ T500		Presenters and contributors
12:00–12:10	Background, objectives and expected outcomes	Dr Jan KOLACZINSKI
12:10–12:40	Presentation of data from the United Republic of Tanzania	Dr Njalembo MBEWE
12:40–13:10	Presentation of data from Burkina Faso	Dr Koama BAYILI
13:10–13:40	Presentation of data from Benin	Dr Corine NGUFOR
13:40–13:55	Presentation of data and analysis on combined efficacy estimates based on data from the United Republic of Tanzania, Burkina Faso and Benin	Dr Joseph CHALLENGER
13:55–14:10	Discussion and questions	Members, participants, selected observers, WHO staff
Part V: Presentation of data and analysis on PermaNet® Dual		Presenters and contributors
14:20–14:50	Presentation of data from Benin	Dr Thomas SYME
14:50–15:20	Presentation of data from Kenya	Dr Eric OCHOMO
15:20–15:35	Presentation of data and analysis on combined efficacy estimates based on data from Benin and Kenya	Dr Joseph CHALLENGER
15:35–15:50	Discussion and questions	Members, participants, selected observers, WHO staff
Part VI: Conclusions & recommendations		Presenters and contributors
16:00–16:45	Finalization of meeting conclusions & formulation of recommendations to WHO	Chair

Annex 3. List of participants

Chair

Azra Ghani
Imperial College London
London, United Kingdom of Great Britain and Northern Ireland

Temporary advisors

John Gimnig
United States Centers for Disease Control and Prevention
(Attending in his individual capacity)
Atlanta, United States of America

Immo Kleinschmidt
London School of Hygiene and Tropical Medicine
London, United Kingdom of Great Britain and Northern Ireland

El Hadji Niang
Université Cheick Anta Diop
Dakar, Senegal

Olukayode Odufuwa
Ifakara Health Institute
Bagamoyo, United Republic of Tanzania

Robert Reiner
Institute for Health Metrics and Evaluation
Seattle, United States of America

Peter Smith
London School of Hygiene and Tropical Medicine
London, United Kingdom of Great Britain and Northern Ireland

Kyeba Swai
Ifakara Health Institute
Bagamoyo, United Republic of Tanzania

Participants

Koama Bayili
Institut de Recherche en Sciences de la Santé
Bobo-Dioulasso, Burkina Faso

Joseph Challenger
Imperial College London
London, United Kingdom of Great Britain and Northern Ireland

Tom Churcher
Imperial College London
London, United Kingdom of Great Britain and Northern Ireland

Njelembo Mbewe
London School of Hygiene and Tropical Medicine
Moshi, United Republic of Tanzania

Benjamin Menze
Centre for Research in Infectious Diseases
Yaoundé, Cameroon

Sarah Moore
Ifakara Health Institute/Swiss Tropical and Public Health Institute
Bagamoyo, United Republic of Tanzania

Raphael N'Guessan
London School of Hygiene and Tropical Medicine
Bouaké, Côte d'Ivoire

Corine Ngufor
London School of Hygiene and Tropical Medicine/Centre de Recherche Entomologique
de Cotonou
Cotonou, Benin

Eric Ochomo
Kenya Medical Research Institute
Kisumu, Kenya

Thomas Syme
London School of Hygiene and Tropical Medicine/Centre de Recherche Entomologique
de Cotonou
Cotonou, Benin

Charles Wondji
Liverpool School of Tropical Medicine
Yaoundé, Cameroon

Observers

Duncan Athinya
Vestergaard
Nairobi, Kenya

Marlize Coleman
Innovative Vector Control Consortium
Liverpool, United Kingdom of Great Britain and Northern Ireland

Melinda Hadi
Vestergaard
Lausanne, Switzerland

Takeo Maezawa
Mitsui Chemical Crop & Life Solutions
Tokyo, Japan

Derric Nimmo
Innovative Vector Control Consortium
Liverpool, United Kingdom of Great Britain and Northern Ireland

Kunizo Mori
Mitsui Chemical Crop & Life Solutions
Tokyo, Japan

Graham Small
Innovative Vector Control Consortium
Liverpool, United Kingdom of Great Britain and Northern Ireland

Katsutoshi Tsuchiya
Mitsui Chemical Crop & Life Solutions
Tokyo, Japan

Dyann Wirth
Harvard University
Cambridge, United States of America

Qing Yin
Tianjin Yorkool Technology Group Co., Ltd.
Tianjin, China

WHO

Global Malaria Programme

Daniel Ngamije M.
Director

Jan Kolaczinski
Unit Head
Vector Control and Insecticide Resistance

Isabelle Abello
Team Assistant
Vector Control and Insecticide Resistance

Lauren Carrington
Technical Officer
Vector Control and Insecticide Resistance

Seth Irish
Technical Officer
Vector Control and Insecticide Resistance

Department of Control of Neglected Tropical Diseases

Raman Velayudhan
Unit Head
Veterinary Public Health, Vector Control and Environment

Regulation and Prequalification

Deusdedit Mubangizi
Coordinator
Prequalification, Vector Control Products

Geraldine Foster
Technical Officer
Prequalification, Vector Control Products

Dominic Schuler
Technical Officer
Prequalification, Vector Control Products

Annex 4. Independent data analyses

This annex contains the summary results of each trial following independent analysis of the data, as commissioned by WHO. Point estimates for the mosquito mortality and blood-feeding end-points are shown, along with the calculated blood-feeding inhibition for each net type. ORs and the comparative efficacy results for the non-inferiority analysis of the candidate net against the active comparator are shown thereafter for the indicated time points and end-points.

DuraNet Plus©

Benin

Point estimates

Arm	Total mosquitoes	Mosquitoes / hut / night	Mortality [95% CI]	Blood feeding [95% CI]	Blood-feeding inhibition (%)
Control	723	13.4	1.0% [0.5–1.8]	48.0% [32.9–63.5]	-
DuraNet© (unwashed)	814	15.1	16.9% [7.6–33.5]	20.5% [12.0–33.0]	57.29
DuraNet© (washed)	866	16.0	17.6% [10.1–28.7]	24.0% [14.1–37.8]	50.00
DuraNet Plus© (unwashed)	599	11.1	28.8% [17.6–43.4]	8.0% [4.2–14.6]	83.33
DuraNet Plus© (washed)	674	12.5	25.6% [15.5–39.2]	12.6% [7.0–21.7]	73.75
Olyset™ Plus (unwashed)	1139	21.1	13.3% [7.6–22.3]	23.8% [14.2–37.2]	50.42
Olyset™ Plus (washed)	1200	22.2	10.3% [5.8–17.7]	42.8% [28.2–58.7]	10.83

Analyses

24-hour mortalit		
Unwashed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 2.64; CI: 2.03–3.43)
Washed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 3.00; CI: 2.31–3.89)
Pooled data: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 2.81; CI: 2.34–3.38)

Blood feeding		
Unwashed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.28; CI: 0.20–0.38)
Washed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.19; CI: 0.14–0.26)
Pooled data: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.23; CI: 0.18–0.28)

Cameroon

Point estimates

Arm	Total mosquitoes	Mosquitoes / hut / night	Mortality [95% CI]	Blood feeding [95% CI]	Blood-feeding inhibition (%)
Control	618	11.4	3.6% [0.7–16.9]	63.5% [32.3–86.3]	-
DuraNet© (unwashed)	286	5.3	10.3% [2.1–38.2]	33.3% [12.2–64.2]	47.56
DuraNet© (washed)	342	6.3	8.3% [1.6–32.8]	32.3% [11.8–63.0]	49.13
DuraNet Plus© (unwashed)	283	5.2	34.2% [8.7–73.8]	25.7% [8.7–55.9]	59.53
DuraNet Plus© (washed)	297	5.5	23.1% [5.1–62.7]	29.0% [10.0–59.9]	54.33
Olyset™ Plus (unwashed)	306	5.7	25.5% [5.8–65.3]	35.3% [12.9–66.9]	44.41
Olyset™ Plus (washed)	363	6.7	12.0% [2.4–42.8]	37.4% [13.9–68.8]	41.10

Analyses

24-hour mortality		
Unwashed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 1.52; CI: 0.98–2.35)
Washed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 2.19; CI: 1.38–3.48)
Pooled data: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 1.81; CI: 1.32–2.49)

Blood feeding		
Unwashed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.63; CI: 0.42–0.96)
Washed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.68; CI: 0.47–0.99)
Pooled data: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.66; CI: 0.50–0.87)

Côte d'Ivoire

Point estimates

Arm	Total mosquitoes	Mosquitoes / hut / night	Mortality [95% CI]	Blood feeding [95% CI]	Blood-feeding inhibition (%)
Control	1366	25.3	3.8% [1.3–11.1]	32.3% [16.0–54.5]	-
DuraNet Plus© (unwashed)	785	14.5	26.0% [9.9–52.9]	11.6% [5.0–24.9]	64.09
DuraNet Plus© (washed)	854	15.8	14.2% [4.9–34.5]	13.1% [5.7–27.2]	59.44
DuraNet© (unwashed)	725	13.4	10.8% [3.8–27.3]	19.1% [8.6–37.3]	40.87
DuraNet© (washed)	1017	18.8	7.1% [2.4–19.4]	24.7% [11.5–45.3]	23.53
Olyset™ Plus (unwashed)	908	16.8	12.5% [4.4–31.0]	9.2% [3.9–20.3]	71.52
Olyset™ Plus (washed)	1036	19.2	7.5% [2.5–20.5]	30.9% [15.0–53.3]	4.33

Analyses

24-hour mortality		
Unwashed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 2.46; CI: 1.87–3.23)
Washed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 2.04; CI: 1.49–2.81)
Pooled data: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 2.28; CI: 1.85–2.80)

Blood feeding		
Unwashed nets: DuraNet Plus© vs Olyset™ Plus	NOT non-inferior	(OR: 1.30; CI: 0.98–1.74)
Washed nets: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.34; CI: 0.26–0.43)
Pooled data: DuraNet Plus© vs Olyset™ Plus	non-inferior	(OR: 0.58; CI: 0.48–0.69)

Yorkool® G3

United Republic of Tanzania (pooled species)

Point estimates

Arm	Total mosquitoes	Mosquitoes / hut / night	Mortality [95% CI]	Blood feeding [95% CI]	Blood-feeding inhibition (%)
Control	1349	13.8	11.0% [8.9–13.6]	11.2% [5.7–20.9]	-
Olyset™ Plus (unwashed)	3209	32.7	46.2% [40.2–52.3]	1.3% [0.6–2.8]	88.39
Olyset™ Plus (washed)	4267	43.5	34.5% [29.1–40.3]	1.9% [0.9–4.0]	83.04
PermaNet® 2.0 (unwashed)	2808	28.7	28.5% [23.7–33.9]	5.5% [2.7–10.9]	50.89
PermaNet® 2.0 (washed)	4350	44.4	28.3% [23.6–33.5]	4.3% [2.1–8.6]	61.61
Yorkool® G3 (unwashed)	2783	28.4	59.0% [53.1–64.7]	3.0% [1.5–6.2]	73.21
Yorkool® G3 (washed)	3622	37.0	49.4% [42.1–56.7]	2.5% [1.2–5.1]	77.68

Analyses

24-hour mortality		
Unwashed nets: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 1.67; CI: 1.50–1.87)
Washed nets: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 1.85; CI: 1.68–2.04)
Pooled data: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 1.77; CI: 1.64–1.90)

Blood feeding		
Unwashed nets: Yorkool® G3 vs Olyset™ Plus	NOT non-inferior	(OR: 2.39; CI: 1.65–3.46)
Washed nets: Yorkool® G3 vs Olyset™ Plus	NOT non-inferior	(OR: 1.31; CI: 0.97–1.77)
Pooled data: Yorkool® G3 vs Olyset™ Plus	NOT non-inferior	(OR: 1.68; CI: 1.33–2.12)

Benin

Point estimates

Arm	Total mosquitoes	Mosquitoes / hut / night	Mortality [95% CI]	Blood feeding [95% CI]	Blood-feeding inhibition (%)
Control	518	12.3	0.9% [0.3–2.7]	62.2% [40.7–79.7]	-
Olyset™ Plus (unwashed)	216	5.1	10.7% [3.8–26.5]	10.8% [4.4–24.3]	82.64
Olyset™ Plus (washed)	473	11.3	6.6% [2.2–17.6]	60.1% [38.8–78.2]	3.38
PermaNet® 2.0 (unwashed)	377	9.0	8.9% [2.5–26.7]	56.4% [34.9–75.8]	9.32
PermaNet® 2.0 (washed)	604	14.4	5.4% [1.8–15.3]	63.8% [41.5–81.4]	< 0
Yorkool® G3 (unwashed)	209	5.0	18.8% [6.7–42.7]	22.9% [10.3–43.5]	63.18
Yorkool® G3 (washed)	296	7.0	14.7% [5.3–34.4]	22.4% [10.4–42.0]	63.99

Analyses

24-hour mortality		
Unwashed nets: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 1.92; CI: 1.06–3.50)
Washed nets: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 2.45; CI: 1.52–3.97)
Pooled data: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 2.22; CI: 1.54–3.22)

Blood feeding		
Unwashed nets: Yorkool® G3 vs Olyset™ Plus	NOT non-inferior	(OR: 2.45; CI: 1.40–4.29)
Washed nets: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 0.19; CI: 0.13–0.28)
Pooled data: Yorkool® G3 vs Olyset™ Plus	non-inferior	(OR: 0.40; CI: 0.30–0.54)

PermaNet® Dual

Kenya

Point estimates

Arm	Total mosquitoes	Mosquitoes / hut / night	Mortality [95% CI]	Blood feeding [95% CI]	Blood-feeding inhibition (%)
Control	2207	45.0	27.9% [22.7–33.7]	13.1% [8.6–19.3]	-
Interceptor® G2 (unwashed)	2055	41.9	54.3% [47.5–61.0]	10.5% [6.7–15.9]	19.85
Interceptor® G2 (washed)	1981	40.4	56.2% [49.5–62.6]	8.9% [5.8–13.6]	32.06
PermaNet® Dual (unwashed)	2287	46.7	57.8% [51.1–64.2]	13.1% [8.6–19.4]	0
PermaNet® Dual (unwashed)	2194	44.8	57.0% [50.2–63.5]	10.4% [6.7–15.8]	20.61

PermaNet® 3.0 (unwashed)	2430	49.6	44.1% [37.6–50.7]	7.3% [4.7–11.2]	44.27
PermaNet® 3.0 (washed)	1960	40.0	43.0% [36.5–49.8]	5.4% [3.4–8.6]	58.78

Analyses

24-hour mortality		
Unwashed nets: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 1.15; CI: 1.01–1.31)
Washed nets: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 1.03; CI: 0.91–1.18)
Pooled data: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 1.09; CI: 1.00–1.19)

72-hour mortality		
Unwashed nets: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 1.21; CI: 1.06–1.38)
Washed nets: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 1.00; CI: 0.88–1.15)
Pooled data: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 1.10; CI: 1.00–1.21)

Blood feeding		
Unwashed nets: PermaNet® Dual vs Interceptor® G2	NOT non-inferior	(OR: 1.29; CI: 1.06–1.56)
Washed nets: PermaNet® Dual vs Interceptor® G2	NOT non-inferior	(OR: 1.19; CI: 0.96–1.47)
Pooled data: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 1.24; CI: 1.08–1.43)

Benin

Point estimates

Arm	Total mosquitoes	Mosquitoes / hut / night	Mortality [95% CI]	Blood feeding [95% CI]	Blood-feeding inhibition (%)
Control	541	10.4	1.4% [0.5–4.0]	59.2% [34.3–80.2]	-
Interceptor® G2 (unwashed)	623	12.0	80.1% [57.4–92.3]	24.6% [10.4–47.8]	58.45
Interceptor® G2 (washed)	669	12.9	74.0% [48.7–89.5]	33.4% [15.1–58.7]	43.58
PermaNet® 2.0 (unwashed)	490	9.4	17.5% [6.6–38.8]	46.2% [23.4–70.7]	21.96
PermaNet® 2.0 (washed)	903	17.4	11.1% [4.0–27.1]	60.9% [36.0–81.2]	<0
PermaNet® 3.0 (unwashed)	591	11.4	52.1% [26.7–76.4]	14.3% [5.5–32.2]	75.84
PermaNet® 3.0 (washed)	895	17.2	23.7% [9.5–47.9]	38.0% [18.0–63.0]	35.81

Analyses

24-hour mortality		
Unwashed nets: PermaNet® Dual vs Interceptor® G2	NOT non-inferior	(OR: 0.75; CI: 0.55–1.03)
Washed nets: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 0.93; CI: 0.73–1.20)
Pooled data: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 0.89; CI: 0.73–1.08)

72-hour mortality		
Unwashed nets: PermaNet® Dual vs Interceptor® G2	NOT non-inferior	(OR: 0.71; CI: 0.51–0.98)
Washed nets: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 0.96; CI: 0.75–1.24)
Pooled data: PermaNet® Dual vs Interceptor® G2	non-inferior	(OR: 0.88; CI: 0.72–1.07)

Blood feeding		
Unwashed nets: PermaNet® Dual vs Interceptor® G2	NOT non-inferior	(OR: 1.33; CI: 0.98–1.81)
Washed nets: PermaNet® Dual vs Interceptor® G2	NOT non-inferior	(OR: 1.52; CI: 1.19–1.93)
Pooled data: PermaNet® Dual vs Interceptor® G2	NOT non-inferior	(OR: 1.42; CI: 1.18–1.72)

VECTRON™ T500

United Republic of Tanzania

Point estimates

First three months, mosquito mortality

Arm	Substrate	Total mosquitoes	Mosquitoes per hut per night	24-hour mortality [95% CI]	72-hour mortality [95% CI]
Control	Concrete	107	1.7	0% [0–100]	2.7% [0.8–8.2]
Control	Mud	324	5.1	0.3% [0–1.8]	3.4% [1.9–6.0]
Actellic 300CS	Concrete	297	4.6	17.4% [12.6–23.4]	22.7% [17.3–29.2]
Actellic 300CS	Mud	363	5.7	19.5% [14.6–25.6]	25.7% [20.2–32.1]
VECTRON™ T500	Concrete	670	5.2	44.8% [37.9–51.8]	59.0% [52.5–65.1]
VECTRON™ T500	Mud	728	5.7	34.7% [28.7–41.3]	50.3% [44.0–56.6]

Analyses

First three months, 24-hour mosquito mortality			
Concrete:	VECTRON™ T500 vs Actellic 300CS	NOT non-inferior	(OR: 0.56; CI: 0.47–0.68)
Mud:	VECTRON™ T500 vs Actellic 300CS	NOT non-inferior	(OR: 0.47; CI: 0.40–0.56)
Pooled data:	VECTRON™ T500 vs Actellic 300CS	NOT non-inferior	(OR: 0.51; CI: 0.45–0.58)

First three months, 72-hour mosquito mortality			
Concrete:	VECTRON™ T500 vs Actellic 300CS	non-inferior	(OR: 1.18; CI: 1.05–1.34)
Mud:	VECTRON™ T500 vs Actellic 300CS	non-inferior	(OR: 1.06; CI: 0.92–1.21)
Pooled data:	VECTRON™ T500 vs Actellic 300CS	non-inferior	(OR: 1.19; CI: 1.10–1.29)

Benin (first trial)

Point estimates

Arm	Substrate	Total mosquitoes	Mosquitoes per hut per night	72-hour mortality [95% CI]
Control	Concrete	248	1.6	1.7% [0.7–3.9]
Actellic 300CS 1000 mg/m^2	Concrete	434	2.9	62.7% [56.0–69.0]
VECTRON™ T500 vs Actellic 300CS	Concrete	288	1.9	68.0% [60.5–74.7]
VECTRON™ T500 vs Actellic 300CS	Concrete	179	1.2	72.9% [64.3–80.2]
VECTRON™ T500 vs Actellic 300CS	Mud	137	0.9	67.7% [57.7–76.4]
VECTRON™ T500 vs Actellic 300CS	Mud	220	1.5	76.9% [69.3–83.0]

Analyses

First three months, 72-hour mosquito mortality			
Concrete:	VECTRON™ T500 (100 mg/m^2) vs Actellic 300CS	NOT non-inferior	(OR: 0.61; CI: 0.39–0.96)
Concrete:	VECTRON™ T500 (150 mg/m^2) vs Actellic 300CS	NOT non-inferior	(OR: 0.64; CI: 0.36–1.12)

Whole study, 72-hour mosquito mortality			
Concrete:	VECTRON™ T500 (100 mg/m^2) vs Actellic 300CS	non-inferior	(OR: 1.26; CI: 0.89–1.80)
Concrete:	VECTRON™ T500 (150 mg/m^2) vs Actellic 300CS	non-inferior	(OR: 1.60; CI: 1.04–2.46)

Benin (second trial)

Point estimates

All six months

Arm	Substrate	Total mosquitoes	Mosquitoes per hut per night	72-hour mortality [95% CI]
Control	Concrete	3517	24.3	0.8% [0.4–1.6]
Control	Mud	3216	22.2	0.7% [0.3–1.5]
Actellic 300CS	Concrete	1984	13.7	56.8% [38.9–73.1]
Actellic 300CS	Mud	2690	18.6	58.6% [40.4–74.6]
VECTRON™ T500	Concrete	3028	10.5	60.6% [41.0–77.3]
VECTRON™ T500	Mud	3121	10.8	58.7% [40.6–74.7]

Analyses

First three months, 72-hour mosquito mortality			
Concrete:	VECTRON™ T500 vs Actellic 300CS	NOT non-inferior	(OR: 0.49; CI: 0.39–0.61)
Mud:	VECTRON™ T500 vs Actellic 300CS	NOT non-inferior	(OR: 0.34; CI: 0.27–0.43)
Pooled data:	VECTRON™ T500 vs Actellic 300CS	NOT non-inferior	(OR: 0.49; CI: 0.39–0.61)

All six months, 72-hour mosquito mortality			
Concrete:	VECTRON™ T500 vs Actellic 300CS	non-inferior	(OR: 1.17; CI: 1.01–1.35)
Mud:	VECTRON™ T500 vs Actellic 300CS	non-inferior	(OR: 1.01; CI: 0.87–1.16)
Pooled data:	VECTRON™ T500 vs Actellic 300CS	non-inferior	(OR: 1.17; CI: 1.01–1.35)

For further information please contact:

Global Malaria Programme
World Health Organization
20 avenue Appia
1211 Geneva 27
Switzerland
Email: GMPinfo@who.int

9789240078659