

Cost-effectiveness of Insecticide-treated wall liner and indoor residual spraying as additions to insecticide-treated bed nets to prevent malaria: findings from cluster randomized trials in Tanzania

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Abstract

Background: Despite substantial progress and widespread use of insecticidal bed nets, malaria caused 409,000 deaths in 2019. An established supplemental technology, indoor residual spraying (IRS), is moderately expensive and logistically challenging. It must be applied just before the rainy season(s) and potentially requires multiple reapplications per year in endemic areas. A new technology, insecticide treated wall liner (ITWL), might overcome these challenges.

Methods: We conducted a 44-cluster two-arm randomized controlled trial in Muheza, Tanzania from 2015-2016 to evaluate the cost and efficacy of a non-pyrethroid ITWL to supplement long-lasting insecticidal nets (LLINs). We estimated the efficacy (with 95% confidence interval) of IRS as a supplement to LLINs from a published randomized trial in Muleba, Tanzania and the Global Burden of Diseases Study. We obtained per capita financial costs of IRS in mainland Tanzania from published reports and conducted a household survey of a similar IRS program near Muleba to determine household costs. We amortized ITWL costs over four years (its expected lifetime). We converted all costs (products, program operation, and household time) to 2019US\$ using Tanzania's GDP deflator and market exchange rates.

Results. Ninety days after completing the installation of ITWL in 5,666 households, the randomized trial was terminated prematurely. Cone bioassay tests showed that ITWL no longer killed mosquitoes and therefore could not prevent malaria. The ITWL cost \$10.11 per person per year compared to \$5.69 for IRS. With an efficacy of 57% (3%-81%), IRS averted 1,162 (61-1,651) disability-adjusted life years (DALYs) per person per year. Its incremental cost-effectiveness ratio (ICER) per DALY averted was \$490 (45% of Tanzania's per capita gross national income).

Conclusions. These findings provide design specifications for a future ITWL to be useful. It would need to be more effective and/or less costly than IRS so more persons could be protected with a given budget. Results from a previous trial in Kenya, economies of scale and competition, as occurred with insecticide treated bed nets, strengthened community engagement, and more efficient installation and management procedures, all offer promise of achieving these goals. These features suggest that ITWLs merit ongoing study.

Trial first posted: 2015 (NCT02533336)

Background

Vector control is an essential component of the global strategy for malaria control aiming to avert parasite transmission through interventions targeting adult anopheline vectors.[1] Two vector control approaches, long lasting insecticide treated nets (LLINs) and indoor residual spraying (IRS), have substantially reduced malaria morbidity and mortality since 1990.[2, 3] Nevertheless, this disease remains a major health challenge, especially in sub-Saharan Africa.[3, 4] The disease still caused some 409,000 deaths globally in 2019.[5] Increasing mosquito insecticide resistance, especially to pyrethroid products, threatens the long-term effectiveness of both LLINs and IRS.[3, 6-8] IRS is moderately expensive and logistically challenging. As IRS provides only a few months of protection,[9] it must be applied just before the rainy season(s) and potentially requires multiple reapplications per year in endemic areas.

To address these challenges, researchers developed a new technology: the non-pyrethroid insecticide-treated wall liner (ITWL). Early research showed that local nails with a plastic nail cap could affix ITWL to the interior of mud wall.[3] Subsequent research showed that the product was well accepted by users and could serve as a complement to LLINs.[3, 10-12] The ITWL offers several logistical advantages over IRS. The ITWL's expected multi-year efficacy avoids the complexity of repeated rounds of application in the same and successive years.[7] Also, ITWL installation is not time sensitive. As a complement to bed nets, ITWLs were expected to protect household members before going to bed, not using any LLIN, or utilizing a damaged LLIN, and address mounting insecticide resistance to pyrethroids.[3, 7] We are aware of only a single epidemiological efficacy study of ITWLs in Africa as a supplement to LLINs.[13] That trial randomized clusters to 6 control (bed nets only) and 6 intervention (ITWL plus LLIN) conditions involving 1,592 children overall. The trial was conducted near Asembo (Nyanza Province), Kenya before the onset of pyrethroid resistance. This trial found that the pyrethroid ITWL had a 38% overall protective efficacy, with 31% efficacy among children under five years and 42% among those aged 5-11 years.[13] These findings made the pyrethroid ITWL promising and likely cost-effective in this site without resistance.[12] An evaluation of the same product from Balaghat, India, subsequently published, gave comparable results.[14]

As described below, in the face of pyrethroid resistance, a non-pyrethroid ITWL was developed and deployed in a 44-cluster randomized trial in Muheza District, Tanzania, but found to be ineffective.[7] In spite of this deficiency, a future ITWL could potentially be effective against malaria and other vector borne diseases.[10] However, the usefulness of an ITWL also depends on its cost and comparison

with alternative approaches. Thus, this paper first reports the economic cost of installing and removing ITWL in the Muheza trial.[7] Next, it uses the lessons learned to project the cost of a future, efficient installation. Additionally, it examines the cost and effectiveness of IRS from Muleba, Tanzania, another district with endemic malaria. Finally, using IRS as a benchmark, this paper assesses the cost and cost-effectiveness of alternative product profiles of future potential ITWL installations.

Methods

Cluster randomized trial of ITWL

The cluster randomized trial of ITWL was planned for Muheza district. Muheza is located 35 km west of Tanga City, the capital of Tanga Region and 364 km north of Dar es Salaam. It had a 2012 population of 204,461 residents (100,843 males and 103,618 females). With an area of 1,498 km², its density was 140 inhabitants per square kilometer.[15]

Malaria is endemic in the district with the main vectors *An. gambiae s. l.* and *An. funestus s.l.* The trial initially planned to use the pyrethroid product that had proved efficacious in Kenya. During the planning phase of the Muheza trial, however, entomological data showed that pyrethroid resistance had been documented, indicating that a pyrethroid product might not be effective.[16] In response, implementation was delayed while the ITWL supplier, Vestergaard (formerly Vestergaard Frandsen) in Switzerland, developed a new ITWL designed to address insect resistance to pyrethroids.

The final ITWL product was composed of a high-density polypropylene non-woven fabric containing a proprietary combination of two nonpyrethroid insecticides (0.25% abamectin and 1% fenpyroximate).[17] The side of this fabric that is attached to house walls is inactive, moisture resistant, dust free, and thermo-stable. The side which faces the house interior is the active one, functioning as a long-lasting insecticidal reservoir containing the insecticidal mixture embedded in a polymer. A pilot found that a prototype of this product (termed PermaNet Lining) was well accepted by rural African households.[3, 9]

The protocol was updated to ensure statistical power as a two-arm 44-cluster randomized trial comparing the existing standard of care (long-lasting insecticide-treated nets, LLINs) against the experimental intervention (ITWL plus LLINs). To ensure the accuracy of this comparison, in August 2015 all enumerated households in both experimental and control arms were given one Interceptor® net (BASF Corporation, Germany) for every two persons and instructed on their use. These nets contained alphacypermethrin (200 mg/m²) coated onto polyester fibers. The primary planned endpoint was the cumulative one-year incidence of parasitemia in children aged 6-59 months assessed through a malaria rapid diagnostic test administered at monthly household visits. The trial protocol has been published.[7] The trial, NCT02533336, was first posted on 26/08/2015.

Implementation in experimental clusters began with recruitment of 140 installers. Next, NIMR professionals and a consultant who had managed the previous Asembo trial conducted a 5-day training session for the installers. The installers needed to be residents of the study villages and most were males. The installers were supposed to be capable of manual labor and have a basic knowledge of carpentry, but had no specific educational requirement. The training provided an overview of the project, and instruction and practice on the installation of ITWL. This entailed measuring the rooms, cutting ITWL (which came on rolls about 2 meters wide), identifying standard intervals for nails, attaching the material to walls while avoiding damage to the houses, household items, and the environment; and documenting the work. As manpower needs grew, additional installers were added and given on-the-job training. Some of the original installers were promoted to team leaders or supervisors. Supervisors were required to be literate to ensure they could complete the necessary forms.

Supervisors visited households in experimental clusters ahead of the planned installation exercise to describe the process and request consent from the household head. They assigned the installation teams to specific houses who consented to have ITWL installed, monitored the installation process, and approved installers' payment on confirmation of the completion of work. The team leaders guided teams, measured the walls, windows and doors of each house, and ensured timely completion of each day's work. Throughout the installation, five full-time NIMR staff oversaw the work, including epidemiology, entomology, sensitization, installation, logistics, and finances.

Updating to current epidemiologic and economic conditions

To facilitate the interpretation of this study, we have adjusted all epidemiologic and economic information to values for 2019, the most recent year with comprehensive data. All economic data are expressed in current 2019 US dollars. We converted monetary amounts to

2019 USD through three steps: (1) We converted costs reported in US dollars to the equivalent in Tanzania shillings in the same year using the applicable exchange rate. The applicable rate for the organization installing the wall liner, the National Institute for Medical Research, was the net rate received by its bank (i.e., 2074.1 in 2015 and 2065.0 in 2016) while the applicable rate for other sources was the official rate of 1572.1 Tanzania shillings (TZS) per US dollar in 2011 [18]; (2) We converted TZS in any year prior to 2019 to 2019 TZS based on the Tanzanian official GDP deflator in that year and in 2019 [19] (i.e. 72.333 in 2011, 100.000 in 2015, 107.472 in 2016, 121.006 in 2019) [19]; (3) We converted 2019 TZS to 2019 USD based on the 2019 exchange rate at US\$1 equals 2288.1 TZS.[20]

For comparative indicators, we used Tanzania's 2019 per capita GNI (\$1080).[21] We adjusted epidemiologic information based on malaria's 2019 burden of 2,038 disability-adjusted life years (DALYS) lost per 100,000 population per year.[22]

ITWL intervention phases

Installation of ITWL in experimental clusters was conducted in three phases totaling 204 days, characterized by distinct modes of sensitization and payment. The first installation phase, August 10, 2015 through December 4, 2015 (117 days), used large community meetings to try to sensitize residents about the desirability of ITWL. This phase involved 352 workers (220 installers, 110 team leaders, and 22 supervisors). Village leaders, community health workers (CHWs), and researchers used these meetings to try to inform residents about ITWL, the installation schedule. These meetings also sought to raise awareness, enhance participation in the trial, and increase the use of bed nets. In this phase, installers and team leaders were each paid 10,000 TZS per day. (\$4.82 in 2015, equivalent to \$5.29 in 2019 USD).

The second installation phase, December 5, 2015 through January 15, 2016 (42 days), aimed at raising the number of community members participating in the project. This phase introduced better personal protective equipment (flexible gloves) for installers, added a megaphone so that project staff could better attract residents' attention, and initiated door-to-door visits and sensitization to explain the product and answer questions in detail. It also sought to improve the efficiency of the installation. This phase had only 242 workers (22 supervisors and 220 installers). The payment system was changed from a daily wage to an output-based payment, with each supervisor receiving 1500 TZS (\$0.72 in 2015USD, equivalent to \$0.79 in 2019USD) and each team of installers receiving 7,000 TZS (\$3.37 in 2015, equivalent to \$3.70 in 2019 USD) for each installed house. This piecework mode of payment was implemented after noting that the daily wage system appeared to create a perverse incentive for installers to work slowly so as to maximize their number of work days.

The third installation phase, January 16, 2016 through February 29, 2016 (45 days), involved additional sensitization approaches. It added the distribution of brochures with photographs and simply-worded Swahili explanations of ITWL benefits. Members of the project's socio-economic team continued to make announcements throughout the village with a portable megaphone to increase residents' willingness to have the product installed in their homes. While maintaining the previous phase's piecework payment modality, the third phase sought to further reduce costs per household by lowering the number of personnel to 154 workers (14 supervisors and 140 installers).

At two months after installation, an entomological trial in experimental huts in Zeneti, near Muheza, of the incremental benefit of alternative ITWL products over LLINs alone found no benefit of the pyrethroid product due to insecticide resistance but a small, though not statistically significant incremental benefit of the non-pyrethroid product on mosquito mortality.[23] Noting that results at two months were not necessarily predictive of longer term results, the investigators initiated the cluster randomized epidemiologic trial in Muheza with this non-pyrethroid product in 2015. However, the entomological results from this trial that emerged in May 2016 showed that this wall liner was no longer effective. Cone bioassay tests at 90 days after installation found that ITWL no longer killed mosquitoes in residents' houses in Muheza district, perhaps due to issues with degradation of chemical content and/or bioavailability of the insecticides in the ITWL, such that mosquitoes did not obtain a lethal dose upon contact". Entomological studies on mosquito age confirmed the lack of efficacy.[16]

As a result, the study's data safety monitoring board, investigators and sponsors determined that the study needed to be terminated prematurely. Collection of epidemiologic data was stopped. Since ITWL was no longer beneficial and potentially harmful, they concluded later in 2016 that the ITWL should be removed from residents' houses where possible.[8]

De-installation of ITWL material lasted from September 21, 2016 through October 6, 2016 (16 days). It involved 13 regular NIMR staff. The de-installation phase began by a three-day training by NIMR staff of 220 de-installers and 22 cluster supervisors. Next, community

residents were invited to sensitization sessions, aided by project staff, community leaders and CHWs, to explain why ITWL was being removed prematurely.

Determining economic costs of the ITWL intervention

For analytic purposes, the unit of analysis was a household, defined as a group of people who live together and share food and expenses. In small villages each household generally owned its own house (a building). However, in large villages and small towns, multiple households could share a house. In most cases, the household members were related to one another, so they also constituted a family. The sample for the intervention arm consisted of the 5,666 households in experimental clusters who had received ITWL. The NIMR Office at Muheza provided aggregate financial expenditures for all project activities serving these households. Non-financial data on the other hand, represented the opportunity cost of contributed labor used in the intervention. Specifically, non-financial costs involved the average time and number of household members spent in the following activities: (i) attending sensitization meetings, (ii) consenting, (iii) removing household items before the installation took place, (iv) waiting for the installers to arrive and complete their work, (v) putting household items back after ITWL installation, (vi) removing household items before de-installation, (vii) waiting for the de-installers to arrive and/or assisting them or waiting for them to complete their work, and (viii) putting household items back after ITWL de-installation. Research staff from the project's socio-economic team interviewed 136 households using questionnaires and recorded their observations. The authors obtained qualitative data through regular interactions with residents and community leaders.

We then imputed and valued the aggregate and average time for the 5,666 households. The numbers of households installed were derived from records of payments to installers. While Vestergaard donated ITWL products for this trial, we imputed its cost based on a related product. Vestergaard had previously marketed the pyrethroid ITWL used in the Asembo study under the name ZeroVector.[14] As both products had comparable purposes, settings (rural areas with mostly mud houses), and methods of supply (rolls about 2 meters wide and 100 meters long), we used the average cost per household in Kenya based on that product's latest sales price per roll (\$68.50) as the estimate for this study.[8]

To compute the cost of time households spent during sensitization, installation, and de-installation exercises, we used Tanzania's 2015 daily wage rate of TZS 6,581 for a typical laborer from nearby sisal estates in Muheza district, obtained as part of the interviews in this study. Since none of the resources used in installing and de-installing ITWL involved capital inputs, we considered all costs occurring at the time of installation. We added 15% of the direct expenditure(s) for overhead based on the rate allowed by the main sponsor of this economic assessment for expenses in Tanzania.[24] These overhead costs covered utilities, facilities upkeep, and central administration.

Efficacy and cost of IRS in Tanzania

Information in the efficacy and financial costs of the comparative intervention (IRS) came from existing publications. Tanzania had previously hosted a cluster randomized trial of the incremental efficacy of IRS as an addition to bed nets. That study was conducted near Muleba, Tanzania (in the country's Lake Region). The intervention arm, entailing rounds of spraying conducted prior to the long and short rains, followed the same two-round schedule as another intervention study in the same district.[25] In the randomized trial, IRS added to bed nets reduced malaria incidence by 57% compared to the control arm with only bed nets, a significant change, with a 95% confidence interval of 3%-81%.[26] We multiplied the best estimate of efficacy times the DALY burden in Tanzania to get the best estimate of the DALYs averted and used the confidence interval on efficacy to generate the confidence interval on DALYs averted.

To estimate the financial cost of IRS, we extracted information from a modeling study of the combination IRS plus LLIN and of LLIN alone in mainland Tanzania (including the vicinity of Muleba), reported in 2011 US dollars.[27] We used the version of their analysis that included the adjustment for increased insecticide resistance (2008-2012). Their analysis generally followed the framework of integrated vector management and incorporated the value of in-kind contributions from government personnel and community leaders.[28] However, their analysis did not include a non-financial component, the economic value of household time for IRS.

As an additional component of the ITWL economic evaluation, we designed and implemented a household survey. After obtaining the appropriate permission from the government and local leaders, we used a cluster sample to select 3 districts in the vicinity of Lake Victoria, Tanzania. From these districts, we randomly selected 29 wards, then randomly chose 5 households from each ward, and invited the chosen households to participate in this costing survey. From the 145 households invited to participate, 135 households (93%) completed the survey. A research team member interviewed a member of each participating household in person between December 2015 and January 2016. The survey collected information about the time household members spent attending

informational meetings with government officials regarding IRS, providing 20 liters of water per household, removing and replacing furniture, awaiting the spraying operator, being present during spraying, waiting for two hours or more after spraying (with windows and doors open), and cleaning up dead insects. We valued their time at the 2015 hourly minimum wage of TZS513 (\$0.2713 in 2019USD).

Cost-effectiveness framework for future ITWL products

The study was approved by the ethics committees of the National Institute for Medical Research, Tanzania, Kilimanjaro Medical College, the London School of Tropical Medicine and Hygiene, and the Committee for the Protection of Human Studies in Research at Brandeis University.

Results

ITWL coverage

The phasing of installation stages provided the opportunity to compare the increasingly stronger approaches to community sensitization and more efficient modalities of payment to installers. Initially, 8,368 households in the district were targeted to receive ITWL, an average of 279 per intervention cluster. In the end, the study completed installation in 5,666 households, 67.7% of the initial target. Figure 1 shows the cumulative coverage across the three installation phases, each phase adding a notable increase in coverage, thanks to better management, enhanced sensitization, and incentives to installers.

In the first phase, many households refused installation because they observed that some of the installers experienced rashes on their arms, hands, and sometimes their private parts. This occurred because they had not been given adequate personal protection equipment (gloves and long-sleeved shirts) and sufficient instruction about removing gloves prior to relieving themselves. These symptoms created fears and initiated rumors that ITWL caused male sterility. Attendance at the community meetings was low, as Tanzania was then in midst of a high-profile presidential election campaign. As a result, phase 1 attained only 35.1% coverage. The door-to-door sensitization and other additions in the second phase rapidly raised coverage to 57.0%. The brochures and other refinements in phase 3 increased coverage further to 67.7% of eligible households. The main barriers in the remaining households were nicely finished walls (where the owners did not want the walls disfigured by nails or covered by ITWL), or occupancy by tenants (who lacked the right to approve installation of ITWL).

ITWL installation costs

In the first phase, during which installers were paid by a daily wage, 2,933 households were installed in 117 days, or 25.1 households per day. This phase resulted in 0.071 households installed per worker per day at an economic cost of \$136.72 per household in 2019 prices (see installation phases columns in Table 1). In the second phase, workers installed 1,835 households in 42 days, or 43.7 households installed per day. The rate was 0.181 households installed per worker per day at an economic cost of US\$135.01 per household. In the third phase, workers installed 898 houses in 45 days, averaging 20.0 households per day or 0.130 households per worker per day at an economic cost of US\$122.25 per household installed. As the most willing houses were installed over successive clusters in phases 1, 2, and 3 and the most reluctant houses were installed last, installation likely faced the greatest challenges in phase 3. Nevertheless, improved management and piecework payment increased the pace of installation and productivity per worker from phase 1 to phase 2. The extra effort in persuading reluctant households and schedule uncertainty likely lowered the pace and productivity from phase 2 to phase 3. However, under the output payment system, personnel and local transport cost per installed house fell compared to phase 2. In summary, the economic cost per house averaged \$136.38 over the installation portion of ITWL, consisting of financial costs of US\$132.19 (97%) and non-financial costs of US\$4.19 (3%).

Table 1: Installation and de-installation costs in 2019 US\$ based on installed households by phase and input

Input	Installation phases				De-installation phases				Combined	
	Phase 1	Phase 2	Phase 3	Average	Sensi- tization	Pilot	Full scale	Sum	Cost	Col. %
Cost per household										
Personnel	\$35.86	\$28.21	\$24.72	\$31.61	\$0.61	\$0.21	\$5.96	\$6.79	\$38.40	24.4%
Materials	\$13.61	\$13.61	\$13.61	\$13.61	\$0.00	\$0.31	\$2.28	\$2.59	\$16.20	10.3%
Local transport	\$3.49	\$10.23	\$1.66	\$5.37	\$0.31	\$0.00	\$4.21	\$4.52	\$9.89	6.3%
Transfer from port	\$4.07	\$4.07	\$4.07	\$4.07	\$0.00	\$0.00	\$0.00	\$2.33	\$6.40	4.1%
Training	\$1.43	\$1.43	\$1.43	\$1.43	\$0.00	\$0.00	\$0.00	\$0.00	\$1.43	0.9%
Communications	\$0.97	\$0.97	\$0.97	\$0.97	\$0.00	\$0.00	\$0.00	\$0.00	\$0.97	0.6%
Incineration	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$0.00	\$2.33	\$2.33	\$2.33	1.5%
In-country	\$59.42	\$58.52	\$46.45	\$57.06	\$0.92	\$0.53	\$14.78	\$18.56	\$75.62	48.1%
Wall liner	\$75.13	\$75.13	\$75.13	\$75.13	\$0.00	\$0.00	\$0.00	\$0.00	\$75.13	47.8%
Subtotal (financial)	\$134.55	\$133.65	\$121.58	\$132.19	\$0.92	\$0.53	\$14.78	\$18.56	\$150.75	96.0%
Household time	\$2.17	\$1.36	\$0.67	\$4.19	\$0.98	\$0.00	\$1.17	\$2.15	\$6.34	4.0%
TOTAL (economic)	\$136.72	\$135.01	\$122.25	\$136.38	\$1.90	\$0.53	\$15.94	\$20.71	\$157.09	100.0%
Cost per person										
Subtotal (financial)	\$33.64	\$33.41	\$30.40	\$33.05	\$0.23	\$0.13	\$3.69	\$4.64	\$37.69	96.0%
Household time	\$0.54	\$0.34	\$0.17	\$1.05	\$0.25	\$0.00	\$0.29	\$0.54	\$1.58	4.0%
TOTAL (economic)	\$34.18	\$33.75	\$30.56	\$34.10	\$0.48	\$0.13	\$3.99	\$5.18	\$39.27	100.0%
Row %	87.0%	85.9%	77.8%	86.8%	1.2%	0.3%	10.1%	13.2%	100.0%	-

Notes: The 2015 FOB price for the Zero Vector was US\$274 per roll (100m x 2.3m). All calculations are based on the 5,666 installed households.

ITWL de-installation costs

The de-installation phase initially targeted all 5,666 installed households with wall liners installed. However, at the de-installation phase, 165 houses were gone (burned, demolished, or relocated) and 153 had unknown status (locked or information not reported). The ITWLs in the remaining 5,348 households with data were removed by paid installers (90.9%), removed by household members themselves (8.8%), or retained on the walls at the household's request and contrary to program recommendations (0.4%). The de-installation phases columns of Table 1 show that the economic cost per installed household for de-installing ITWL totaled US\$20.71, with financial costs of US\$18.56 (89.6%) and non-financial costs of \$2.15 (10.4%).

The combined economic costs per house of installing and de-installing the wall liner were US\$142.43 per household (see combined columns of Table 1). It comprised installation cost of \$136.38 (86.8%) and de-installation costs of \$20.71 (13.2%). Due to its need for materials and more labor, ITWL installation had an economic cost per house that was almost 7 times that of de-installation.

Of total economic costs for installation and de-installation per household combined, the greatest portion of costs was the imputed cost of ITWL material (47.8% of the total cost), followed by personnel (24.4%), and other materials and supplies (10.3%). Local transport (6.3%), transfer from the port (4.1%), training (0.9%), communications (0.6%), and incineration (1.5%) comprised the remaining 13.4% of the total costs. Field costs, excluding the cost of ITWL itself, were US\$75.62 per household. The cost per person (bottom panel of Table 1) is based on an average of four family members in a typical household in Muheza district.[15] The per-person financial and non-financial costs for installing ITWL were US\$34.10, while those for de-installing the material were US\$5.18, summing to a combined cost of US\$39.27 (\$37.69 financial and \$1.58 household time) per person.

The analysis of installation by project phases provides insights about project management and promising implications for a future adapted model, as shown in Table 2. The change in mode of payment from days worked to households installed and a reduction in the number of installers in the second phase were implemented abruptly. This resulted in some installers going on strike, disrupting the project's timetable. A future project may wish to establish and explain a payment plan based on houses installed and not renege on previous promises. As payment based on the number of households installed creates an incentive to cut corners, regular supervision would be essential.

Table 2: Summary of installation phases and implications for an adapted model

Item	Phase 1	Phase 2	Phase 3	Adapted Model
Dates	10 Aug 2015 - 4 Dec 2015	5 Dec 2015 - 15 Jan 2016	16 Jan 2016 - 29 Feb 2016	Future
Sensitization	Community meetings	Door-to-door	Door-to-door & distribution of brochures	Community meetings, megaphone, door-to-door, radio, posters, involvement of community leaders, NGOs, CBOs, FBOs, political and religious leaders, and district and regional officials
Installers' protective equipment	Non-breathable nylon gloves & inadequate supplies of overalls, safety glasses, & masks.	Adequate supplies of protective equipment	Adequate overalls, safety glasses, masks, & flexible breathable nylon gloves	
Management	Transportation delays, late payments to installers, unclear contracts, procurement shortfalls,& inadequate supervision	Delays in payments to installers	Clear contracts, timely payments to installers, efficient procurement, carefully supervised staff & organizations, including sub-contracting some activities to experienced organizations	

Notes: NGO denotes non-governmental organization; CBO denotes community-based organization; FBO denotes faith-based organization.

The breakdown by phase also highlights the impact of improvements in logistics and personal protective equipment over successive installation phases. During the first two phases of this project, some installers lacked overalls, eye protection, masks, and breathable nylon gloves, resulting in slowed work and skin rashes. Insufficient planning of transportation also caused delays, as staff in disparate locations had to share one vehicle. This situation resulted in some installers waiting at the office for several hours before the scheduled vehicle returned. Late arrivals of installers also kept household members waiting up to four hours for their arrival. Better information, equipment, planning, and management in subsequent phases gradually mitigated these problems.

Cost-effectiveness of IRS

The cost per person in 2011 prices of the combination of IRS and LLIN was \$7.49 while that of LLIN alone was \$3.41,[27] indicating the net cost of IRS to the public health system of \$4.08 (equivalent to \$4.646 in 2019 prices). Our household survey found that each household spent an average of 7.67 person-hours per round of IRS moving belongings in and out of the area to be sprayed and procuring the required 20 litres of water per household. With four persons per household and two rounds per year, this is 3.835 hours per household member per year. With Tanzania's minimum wage adjusted to 2019 prices of \$0.2713 per hour, the value of the time

spent is \$1.04 per person. The total economic cost of IRS is \$5.686 per person per year in 2019 prices. The insecticides were consistent with WHO recommendations.[30] Table 3 calculates the annual cost of ITWL using national data for Tanzania in the trial for IRS.

Table 3. Annual cost of insecticide-treated wall liner (ITWL) and indoor residual spraying (IRS) in Tanzania (2019 US\$)

Item	ITWL	IRS
Initial economic cost per person (2019 USD)	\$39.27	\$5.69
Years of protection for one round	4.0	1
Annualizing factor at 3% annual discount rate ¹	0.2612	1.000
Cost per person per year (2019 USD)	\$10.26	\$5.69
Cost relative to ITWL	100.0%	55.4%

¹ Assumes that payments are made at the beginning of each year.

The cost of IRS is 55.4% that of ITWL (i.e., \$5.69 / \$10.26). The best estimate of the health impact of IRS was 1,162 DALYs averted per 100,000 population with lower and upper uncertainty estimates of 611 and 1,886, respectively.[26] The best estimate of the ICER is \$490 (i.e., \$5.69 / 1,162 x 100,000) with an uncertainty range of \$344 to \$9,301. As a multiple of Tanzania's per capita 2019 GNI (\$1,080), the best estimate is 0.45 with an uncertainty range of 0.32 to 8.61. The World Health Organization's Commission on Macroeconomics in Health recommended that if an intervention's ICER was below 1.00 times the country's per capita GDP, the intervention should be considered highly cost-effective and recommended.[31] While some researchers acknowledged that other factors also need be considered, many studies used this threshold in cost-effectiveness publications.[32] Actual investment decisions in low- and middle-income countries revealed an actual threshold of 60%-65% of GDP per capita.[33] Under the best estimate, as this multiple is below 1.00, IRS as conducted in this Tanzanian program was highly cost-effective according to both the Commission criterion and consistency with actual investment decisions.

Implications for the target product profile of a future ITWL

As this analysis suggests that IRS was both an effective and cost-effective technology for vector control, IRS serves as a standard for evaluating alternative product profiles of a future ITWL product. Figure 2 provides a framework for this assessment. The key dimensions are the annualized cost, shown on the X-axis relative to the cost of ITWL (range 0%-100%) and the annual effectiveness, shown on the Y-axis, ranging from 0-2,038 DALYs per 100,000 population, corresponding to 0% to 100% of the effectiveness of IRS. The diagonal line, with the slope of \$490 per DALY, corresponds to the best estimate of the ICER of IRS. This framework creates three zones, all above this diagonal line, in which a future ITWL product would be more cost-effective and preferable to IRS, designated by the three shaded blocks.

Rectangular zone A represents situations of pure dominance, where a future ITWL product is both more effective and less costly than IRS. In this case, ITWL would be unequivocally preferable to IRS. Triangular zone B represents situations in which a future ITWL is more costly than IRS, but sufficiently more effective to more than justify the added cost. Triangular zone C depicts scenarios in which a future ITWL saves money compared to IRS. While ITWL is less effective than IRS, the cost savings are sufficient to more than justify the sacrifice in effectiveness. In all three shaded zones, if a country had a limited budget for vector control as a complement to bed nets against malaria, a future ITWL would be preferable to current IRS. Conversely, for all combinations below the diagonal line, shown unshaded, ITWL would be less cost effective than IRS and not recommended.

Discussion

The efficacy of the earlier, pre-resistance version ITWL in Asembo (38%) falls within the wide 95% confidence interval for the effectiveness of IRS in Muleba (3% to 81%).[26] This suggests that a future ITWL has the potential for comparable or superior effectiveness compared to IRS. However, when projected over four years, the cost per person per year of ITWL in Muheza (\$10.26)

would need to be reduced by 44.6% to match of IRS (\$5.69). To guide future planning, it is useful to examine whether and how a future ITWL could meet the dual requirements of an effective and cost-effective product.

Promising efficiencies could lower the cost of the product. The ITWL installed in Muheza was a new product and its installation in 5,666 households was NIMR's largest such activity to date. The 10.6% decline in cost per house from phase 1 to phase 3 suggests that just a few months of experience can generate notable savings in installation costs. The sharp fall in price of a related product, the LLIN, indicates how the price of the ITWL product itself could be reduced. The price per net purchased by a major global charity fell from \$5 in 2005 to \$2 in 2020, a 60% decline, due to economies of scale and competition.[34] A future ITWL product is expected to provide at least four years of protection. Indeed, reports from site visits to Asembo in 2017, where ITWL had been installed in 2010 and 2012, found that ITWL remained installed and in good condition in a number of the houses in that region 5 to 7 years after installation (Maurice Ombok, Kenya Medical Research Institute, personal communication, October, 2017). The favorable experience of residents participating in de-installation suggests that they could easily learn to address minor repairs, such as re-attaching ITWL to a wall if it falls off. If the lifespan could be extended to from four to five years, annualized cost would fall by 19%, i.e., from \$10.26 to \$8.33 per person. Alternatively, further efficiencies might be achieved by combining de-installation with installation of the next cycle of ITWL, possibly avoiding removal and incineration of the old ITWL. Households could be taught safe uses for used ITWL, such as enclosing a latrine, and avoiding contact with food.

Overall, we project that efficiencies in installation through stronger management and greater resident involvement, avoiding the need for de-installation and incineration, less expensive ITWL materials, and extending the product's lifespan could make an ITWL program comparable to or less expensive than IRS.

A feature in Muheza that helped to control cost was the reliance on local, rather than expatriate managers. In Asembo, some personnel came from the U.S. Centers for Disease Control and were paid on international rates. This was a major reason why the overall cost of ITWL per person in Muheza (2019US\$39.27) was about half of that in Asembo (2011US\$64.23).[12] Nevertheless, an economic analysis of the pyrethroid product in Asembo found that even if its lifetime were just 2.2 years, it would be a cost-effective product in areas without pyrethroid resistance.[12] Although one study in India reported a dramatically lower cost per household for ITWL (\$8.06) [11] than ours (\$157.09), it was not clear whether the India study included all the inputs, such as the purchase of the material, full costs of the public health infrastructure, and household time.

Zone B in Figure 2 shows that if a future ITWL product were more effective than IRS, even at a higher cost, it would still be cost-effective. Several factors could increase the effectiveness of a future ITWL compared to IRS. An installer and a supervisor can both see instantly whether ITWL has been installed correctly on a given wall. As IRS dries quickly, it is difficult for a supervisor to determine whether a wall has been fully sprayed and the right dosage has been applied.

High levels of coverage of ITWL would also increase the product's effectiveness by providing additional protection to neighbors. The final ITWL coverage of 67.7% in Muheza was acceptable, but not excellent. As a community vector control effort, ITWL was intended to protect not only the individual household, but also the community overall. The increases in coverage from phase 1 to 3 were both substantial and relatively rapid, showing that the extra sensitization efforts achieved valuable results. The contrast in the percentage of targeted households covered in Muheza (67.7% for ITWL) and Muleba (93% for IRS) reinforces the importance of community engagement.[35] In Muleba, stakeholders from many levels were engaged in promoting IRS: non-governmental organizations (NGOs) and community-based organizations (CBOs), malaria and health education focal persons, environmental managers, and district and regional officials responsible for IRS.[35] By contrast, the Muheza project involved only a few district officials.. Further, their involvement was limited to authorizing the project through issuing letters of introduction, but not actively promoting it.

In summary, several strengths of this study should be noted. Providing a comprehensive measure of resource costs, the study included not only installation costs, but also those of de-installation when the product proved unsuccessful. Second, it used a societal perspective, including both financial costs within the healthcare system and non-financial costs borne by households.

The research also generated qualitative insights. First, a product more like netting (as installed in Asembo) instead of the sheet-like material (used in Muheza) would be less rigid. This would make installation easier and faster, reduce the risk of the product falling off mud walls, allow air flow if the product is used on the eaves, and lower the temptation for households to re-purpose the product it for drying crops. A longer lifespan would also improve the cost-effectiveness. On the other hand, a more effective product could allow a higher cost and still be cost-effective. For example, if ITWL were 100% effective it could allow a cost per person protected of \$9.98, of only 1.3% below the existing amount.

The Muheza experience also highlighted the importance of good communication within a team. In Muheza, all groups' data were stored a single system which was supposed to document each day's progress to plan the next day's activities. However, the process of retrieving data proved cumbersome, with the data manager needing to attend personally to the demands of various groups to determine where to dispatch teams that day. Sometimes the data became available only after mid-day, resulting in a group losing half or all of a work day. With more detailed planning, the appropriate number of installers could have been hired, trained, and kept busy over all three phases. Changing the payment modality from a daily to a per-house modality lowered the wage bill per household installed by 21%. Thus, more robust data, management, and payment systems would have avoided such bottlenecks and inefficiencies, thereby lowering cost and improving coverage.

If a longer entomological pre-test to measure the product's efficacy in killing mosquitoes had been possible, the current product's shortcomings would likely have identified sooner. The manufacturer might then have been able to modify the product, or the epidemiological study deferred until an entomologically sound product was available.

Finally, while the ITWL installed in Muheza was not effective, data from Asembo and Muheza indicate that a future ITWL has the potential to match or possibly exceed IRS on both effectiveness and affordability. Malaria's 409,000 deaths in 2019 highlight the need for multiple control measures. Given ITWL's advantages in implementation, the product merits ongoing investigation starting in the laboratory, and progressing, if results warrant, to experimental huts and African villages.

List Of Abbreviations

CBO: community-based organization

CHW: community health worker

DALYs: disability-adjusted life years

GNI: gross national income

ICER: incremental cost-effectiveness ratio

IRB: institutional review board

IRS: indoor residual spraying

ITWL: insecticide treated wall liner

LLIN: long lasting insecticide treated net

NIMR: National Institute for Medical Research

TRAction: Translating Research to Action

TZS: Tanzanian shillings

USD: United States dollars

Declarations

Ethics Approval

The overall study received full ethical approval from the Medical Research Coordinating Committee (MRCC) of the NIMR (NIMR/HQ/R.8a/Vol.IX/1613) on 17/7/15, covering both NIMR Muheza and the Kilimanjaro Christian Medical College Research (KCMC) and the Ethics Committee of the London School of Hygiene and Tropical Medicine (LSHTM) (#9898) on 21 July 2015. The protocol for cost and cost-effectiveness was approved by the Brandeis Committee for Protection of Human Subjects (its Institutional Review Board, IRB, as Protocol #12068 Shepard). All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants or, if subjects are under 18, from a parent and/or legal guardian.

Consent for Publication

Not applicable.

Availability of Data and Materials

In responding to surveys and providing documents about time, expenses, and payments, household members and staff were promised confidentiality. Inquiries about other unpublished data should be addressed to Dr. Kisinza.

Competing Interests

All authors declare no competing interests.

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Authors' Contributions

Conception and design (KRM, YAH-R, WNK, LAM, GM, ARK, DSS), data acquisition, analysis or interpretation (KRM, YAH-R, MSM, RCM, KJM, PEM, WNK, JPM, LAM, GM, ARK, DSS), drafting of manuscript (KRM, YAH-R, ARK, DSS), critical review of manuscript (KRM, YAH-R, MSM, RCM, KJM, PEM, WNK, JPM, ARK, DSS), statistical analysis (KRM, YAH-R, ARK, DSS), obtaining funding (WNK, DSS), administrative, technical or material support (MSM, RCM, KJM, WNK, JPM), and supervision (PEM, WNK, JPM, LAM, GM, ARK, DSS).

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Figures

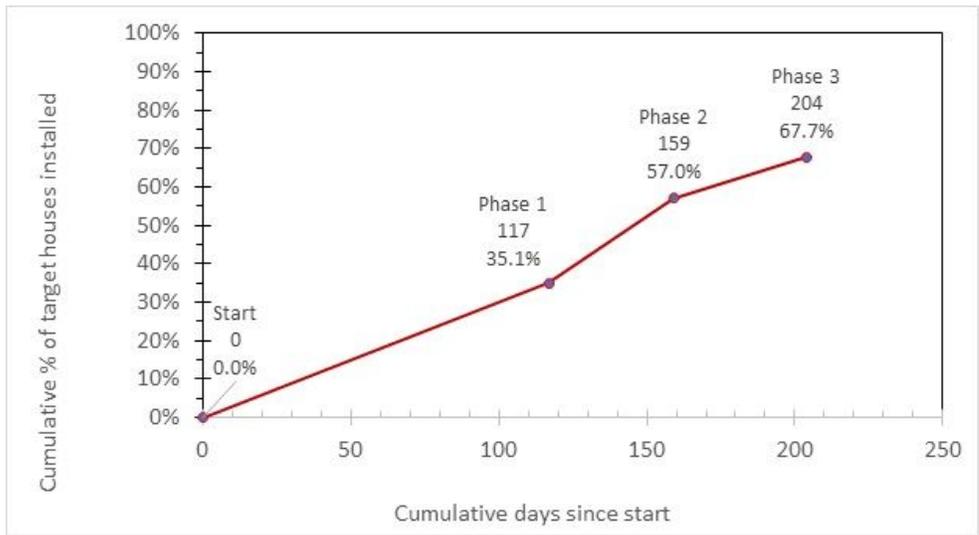


Figure 1

Progress on wall liner installation by phase (labels show cumulative numbers of days since start and cumulative percentage of target households installed)

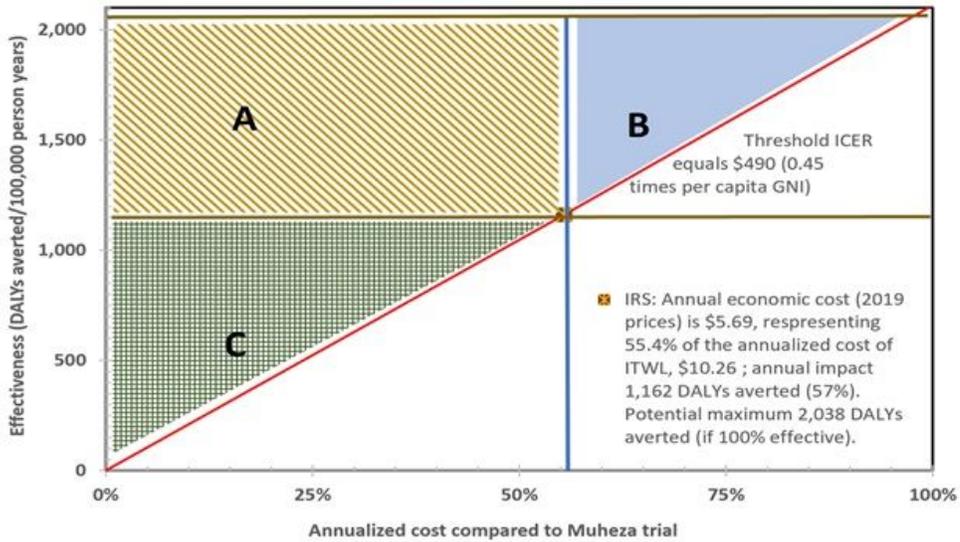


Figure 2

Situations (shown by sharing) in which an insecticide treated wall liner (ITWL) would be more cost-effective than and preferable to IRS