

# Suppression of malaria vector densities and human infection prevalence associated with scale-up of mosquito-proofed housing in Dar es Salaam, Tanzania: re-analysis of an observational series of parasitological and entomological surveys



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## Summary

**Background** In the city of Dar es Salaam, Tanzania, rapid and spontaneous scale-up of window screening occurred through purely horizontal commercial distribution systems without any public subsidies or promotion. Scale-up of window screening coincided with a planned evaluation of programmatic, vertically managed scale-up of regular larvicide application as an intervention against malaria vectors and transmission. We aimed to establish whether scale-up of window screening was associated with suppression of mosquito populations, especially for malaria vectors that strongly prefer humans as their source of blood.

**Methods** This study was a re-analysis of a previous observational series of epidemiological data plus new analyses of previously partly reported complementary entomological data, from Dar es Salaam. Between 2004 and 2008, six rounds of cluster-sampled, rolling, cross-sectional parasitological and questionnaire surveys were done in urban Dar es Salaam to assess the effect of larviciding and other determinants of malaria risk, such as use of bed nets and antimalarial drugs, socioeconomic status, age, sex, travel history, mosquito-proofed housing, and spending time outdoors. The effects of scaled-up larvicide application and window screening were estimated by fitting generalised linear mixed models that allowed for both spatial variation between survey locations and temporal autocorrelation within locations. We also conducted continuous longitudinal entomological surveys of outdoor human biting rates by mosquitoes and experimental measurements of mosquito host preferences.

**Findings** Best-fit models of *Plasmodium falciparum* malaria infection prevalence among humans were largely consistent with the results of the previous analyses. Re-analysis of previously reported epidemiological data revealed that most of the empirically fitted downward time trend in *P falciparum* malaria prevalence over the course of the study (odds ratio [OR] 0·04; 95% CI 0·03–0·06;  $p < 0\cdot0001$ ), which was not previously reported numerically or attributed to any explanatory factor, could be plausibly explained by association with an upward trend in city-wide window screening coverage (OR 0·07; 0·05–0·09;  $p < 0\cdot0001$ ) and progressive rollout of larviciding (OR 0·50; 0·41–0·60;  $p < 0\cdot0001$ ). Increasing coverage of complete window screening was also associated with reduced biting densities of all taxonomic groups of mosquitoes (all  $p < 0\cdot0001$ ), especially the *Anopheles gambiae* complex (relative rate [RR] 0·23; 95% CI 0·16–0·33) and *Anopheles funestus* group (RR 0·08; 0·04–0·16), which were confirmed as the most efficient vectors of malaria with strong preferences for humans over cattle. Larviciding was also associated with reduced biting densities of all mosquito taxa ( $p < 0\cdot0001$ ), to an extent that varied consistently with the larvicide targeting scheme and known larval ecology of each taxon.

**Interpretation** Community-wide mosquito proofing of houses might deliver greater impacts on vector populations and malaria transmission than previously thought. The spontaneous nature of the scale-up observed here is also encouraging with regards to practicality, acceptability, and affordability in low-income settings.

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## Introduction

Vector control with insecticide-treated nets (ITNs) and indoor residual spraying (IRS) accounted for most of the 1·3 billion fewer malaria cases and 6·8 million fewer malaria-related deaths that occurred globally between

2000 and 2015.<sup>1,2</sup> Although direct protection of individuals and households by these approaches is obvious, most of their impressive effects on malaria transmission are mediated by area-wide population suppression of mosquitoes that feed and rest indoors,

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### Research in context

#### Evidence before this study

We have proactively and retroactively surveyed the malaria vector control literature for more than 20 years, with a particular focus on larval control and mosquito-proofed housing, through regular active searches on PubMed, weekly publication alerts, advice from colleagues, and following reference trails. Furthermore, we repeated the PubMed searches of the most recent authoritative systematic reviews on larval control and improved housing using exactly the same search terms to capture literature published since these reviews were completed in 2012 (larval control) and 2013 (housing). Most of the enormous reductions in malaria transmission and burden achieved since the turn of the century arose from scale-up of vector control with insecticide-treated nets (ITNs) and indoor residual spraying (IRS). Both of these approaches achieve these reductions by not only protecting indoor sleeping and living spaces, but also by killing mosquitoes that attempt to feed or rest inside houses. Mosquito-proofed housing is one of the oldest methods for protecting against mosquitoes and malaria, and netting screens allow the use of more open, better-ventilated housing designs that reduce exposure to household pollutants. Netting screens have several advantages over bed nets, walls, and ceilings as targets for the insecticides considered essential to achieving the full, community-level effects of ITNs and IRS on vector populations. However, the evidence base remains largely descriptive, and the only fully controlled trial to date was randomised at the level of houses rather than housing clusters large enough to achieve such area-wide mass effects. Between 2004 and 2008, a planned observational assessment of pilot-scale rollout of regular larvicide application fortuitously coincided with unplanned, rapid, and completely spontaneous scale-up of mosquito-proof window screening in the Tanzanian city of Dar es Salaam. Previously reported analyses of data from six rounds of repeated cross-sectional parasite surveys yielded quite modest estimates for the area-wide effects of larvicide application on infection prevalence of *Plasmodium falciparum* malaria (odds ratio [OR] 0.79; 95% CI 0.66–0.93), as well as the

household-level effects of complete netting screens (OR 0.79; 0.66–0.93) and closed ceilings (OR 0.93; 0.85–1.01).

#### Added value of this study

The previously reported findings were obtained with regression models that accounted for the large overall decline in malaria prevalence across Dar es Salaam, from more than 28% in the first survey round to less than 2% by the final round 4 years later, by including an empirical time trend that was not attributed to any intervention or other consistent change occurring in the city during that period. Here, we present a re-analysis of these data, illustrating how this overall downward trend in malaria prevalence might plausibly be attributed to an upward trend in city-wide coverage of complete window screening. Other than larviciding, no other substantial change in malaria control practices occurred over that period. Regression analyses that replaced the unattributed empirical time trend term with the city-wide window screening coverage trend provided an equally plausible model fit with a correspondingly large estimate for the area-wide effect of window screening coverage (OR 0.07; 95% CI 0.05–0.09;  $p < 0.0001$ ) and a much larger effect estimate for larvicide application (OR 0.50; 0.41–0.60;  $p < 0.0001$ ) that is consistent with subsequent assessments of scale-up across the whole city. Similar analyses of complementary entomological data confirmed effects of both interventions on populations of all common mosquito species, with the effects of window screening coverage being greatest for the most important malaria vectors, which prefer to feed indoors on humans.

#### Implications of all the available evidence

Mosquito-proofed housing might have greater effects on vector populations and might be more readily scalable in low-income settings than previously thought. Rigorous cluster-randomised trials of mosquito-proofed housing with and without insecticide treatments should be prioritised, along with operational research to develop optimal programmatic systems for installation, maintenance, promotion, and subsidisation.

especially the most efficient malaria vectors that depend heavily on human blood.<sup>3</sup> However, ITNs and IRS both have substantial practical limitations and will need to be superseded in the long term by more sustainable and effective approaches to achieve the same dual functionality, specifically vector population suppression through high coverage of humans with personal protection measures that are lethal to mosquitoes.<sup>3</sup>

IRS has a well established record as an effective malaria vector control tool that allows safe deployment of multiple insecticide classes, so that insecticide resistance can be mitigated using rotations and mosaics of different active ingredients.<sup>4</sup> However, the largest single drawback of IRS is the sheer cost of treating the large inner surface areas of entire domestic structures,

especially because rampant resistance to pyrethroids increasingly necessitates the use of more expensive alternative insecticides.<sup>5–8</sup> Global coverage of IRS has therefore lagged behind that of ITNs and is now less than 5% of the world's at-risk population.<sup>9</sup>

ITNs offer a more selective format for targeting insecticides to human-feeding mosquitoes and provide personal protection through a physical barrier that offers a standardised surface matrix for insecticide application. However, one major limitation of ITNs is their close contact with the end user. Although new active ingredients for ITNs are emerging,<sup>10</sup> most of the insecticides used for IRS are too hazardous for use in ITNs. Furthermore, enclosure of sleeping spaces that occupants must enter and exit repeatedly every night<sup>11,12</sup>

renders ITNs vulnerable to wear and tear, so their cost-effectiveness is primarily limited by their physical durability.<sup>13</sup>

Mosquito-proofed housing is essentially universal in populations that can afford it, even in some of the poorest countries in the world.<sup>14–16</sup> In Africa, the most common forms of mosquito proofing are closed ceilings, closed eave gaps, and netting screens placed over windows, eaves, and other ventilation openings. Mosquito-proofed housing extends the physical protection provided by a bed net beyond sleeping spaces to entire domestic spaces that are much larger and might accommodate a wider range of indoor activities. Indeed, such mosquito-proofed indoor spaces are used more frequently by occupants than unprotected houses.<sup>17,18</sup> Netting screens also allow use of more open, better-ventilated housing designs that reduce exposure to indoor pollutants, such as smoke, insecticides, and other domestic chemical products.<sup>19,20</sup>

The netting materials used to screen windows and other openings also offer opportunities to merge the best features of ITNs and IRS for targeting insecticides to mosquitoes that attack humans indoors. Netting screens offer a standardised target surface for durable insecticide treatments that can include IRS formulations unsuitable for use on bed nets.<sup>7,8,21</sup> It should, therefore, be possible to achieve similar effects to IRS with existing insecticides, but with lower reapplication frequency and cost<sup>8</sup> as well as reduced household exposure and environmental contamination. Although an ITN protects only a single sleeping space, approximately the same amount of netting material is enough to cover all the windows and eave gaps of a typical rural Tanzanian house, so this approach could substantially reduce the quantities of netting and insecticide needed to protect a household.<sup>21</sup> Furthermore, because they are left undisturbed once installed, these netting panels might last far longer than a bed net and a wider range of netting materials could be exploited to maximise durability and minimise cost over the long term. Although insecticide treatment products designed specifically for durable window screen netting materials remain to be developed,<sup>8</sup> perhaps the most important remaining question about mosquito-proofed housing is whether it can be practically and affordably scaled up in low-income settings.<sup>22</sup> It also remains to be seen whether, similar to bed nets,<sup>23</sup> the physical protection provided can deliver vector population suppression effects when insecticide treatments are absent, underused, or rendered ineffective by insecticide resistance.

Dar es Salaam is a typical contemporary African city where rapid scale-up of mosquito-proof window screening occurred spontaneously between 2004 and 2008, through purely horizontal commercial distribution systems without any public subsidies or promotion.<sup>17,24,25</sup> Although this unplanned scale-up of window screening coincided with a planned observational analysis of rolling

out regular larvicide application, previous analyses of these epidemiological data<sup>26</sup> only examined the protective effects of window screening at individual and household levels. Furthermore, these previously reported analyses detected an overall city-wide decline in malaria prevalence of more than an order of magnitude, but accounted for it by fitting it as a simple empirical time trend of unreported magnitude to which no underlying cause was attributed.<sup>26</sup> Here, we present a re-analysis of these longitudinal parasitological survey data to examine whether the large observed decline in malaria infection prevalence across Dar es Salaam over that period could be explained by rapid and spontaneous scale-up of mosquito-proofed housing. Furthermore, we examine complementary entomological data to establish whether scale-up of window screening was associated with suppression of mosquito populations, especially the most important malaria vectors, which strongly prefer humans as their source of blood.

## Methods

### Study design

This re-analysis of a previous observational series of cross-sectional malaria parasite surveys in Dar es Salaam<sup>26</sup> is reported alongside new analyses of complementary entomological data that have previously only been partly reported, from Dar es Salaam, Tanzania.<sup>27</sup>

Dar es Salaam is the biggest city in Tanzania, situated on the shores of the Indian Ocean. Administratively, the city comprised three municipalities that were divided into 73 wards at the time of the study. Each ward is further divided into smaller neighbourhood units called *mitaa*, and then into ten-cell units (TCUs), comprising clusters of about ten to 100 houses. The study area comprised 15 urban and semiurban wards, with 610 000 inhabitants and an area of 55 km<sup>2</sup>.<sup>26,27</sup> More detailed descriptions of the intervention history of the study area with more comprehensive supporting references have been published previously.<sup>25–29</sup> Here, we give a brief summary of relevant malaria control intervention trends between 2004 and 2008.

ITNs were promoted and subsidised nationwide over the course of this study by targeting purchase subsidies towards pregnant women and young children, but little concrete progress towards scale-up of ITNs was achieved in Dar es Salaam until the first local mass distributions in 2010 and 2011, long after completion of this study. Subsidised artemisinin-based combination therapy was initially introduced to public sector health facilities as the first-line antimalarial drug of choice in 2007, after the emergence of sulfadoxine–pyrimethamine resistance. However, this subsidy was only available for young children and pregnant women. Uptake across the population as a whole remained poor because most residents still predominantly relied on private sector health facilities and drug outlets for antimalarials. Microscopy was the only widely available means for

malaria diagnosis at the time, with poor standards of practice and wholesale overdiagnosis common across all facility levels.

#### Scale-up of larvicide application and mosquito-proofed housing

Between 2004 and 2008, the Dar es Salaam City Council implemented a pilot operational research programme to develop and assess new systems for implementing regular application of mosquito-specific microbial larvicides (*Bacillus thuringiensis* serotype *israelensis* and *Lysinibacillus sphaericus* [formerly *Bacillus sphaericus*]) to aquatic habitats of local *Anopheles* populations. These systems were developed and established in three urban wards by May, 2006, and then steadily scaled up to encompass all 15 study wards by early 2008.

As more easily installed and affordable construction materials became available on the open market in Dar es Salaam, protection of houses against mosquito entry with window screening and closed ceilings or eaves steadily increased over the same period, despite the absence of any programme to subsidise or promote these measures. Residents cited protection against mosquitoes as their primary motivation for investing in these housing improvements<sup>24</sup> and spent more time indoors in the evenings if both measures were in place.<sup>17</sup>

#### Household surveys of malaria infection prevalence

Six rounds of randomised cluster-sampled, rolling, cross-sectional household surveys were conducted nearly continuously between March, 2004, and December, 2008, in the 15 wards across which larviciding was progressively scaled up.<sup>26,27</sup> All of these wards were in the centre of the city but included several semiurban areas where informal settlements and agriculture occur in flooding river valleys. TCUs were selected randomly, without weighting according to any estimate of their population, so recruitment of the more than 63 000 participants was biased towards residents with low incomes living in high-density, unplanned settlements. Each recruited household was surveyed with a questionnaire to record dwelling occupancy, tenure, and structural features (eg, closed eaves or ceilings and screened or glazed windows), as well as the age, sex, educational status, livelihoods, wealth, perspectives on diseases, intervention use patterns, travel history, and mosquito exposure behaviours of the occupants.<sup>26,27</sup> Peripheral blood samples were collected as thin and thick smears on glass slides from all consenting and assenting household members at each survey visit. These dried blood samples were subsequently tested for the presence of malaria parasites by Giemsa-stained microscopy at a central, quality-controlled laboratory. Although parasite species other than *Plasmodium falciparum* were detected, these were too rare to enable separate analyses and are not considered in our statistical analysis. One fixed set of 131 TCUs were resurveyed in each round, whereas

another set of about 140 TCUs was selected without replacement and surveyed afresh in each subsequent round.<sup>26,27</sup>

#### Entomological surveys of transmission intensity

The surveys of parasitaemia in humans were complemented by parallel surveys of vector biting density with outdoor human landing catches, done once every 4 weeks at 268 sampling locations distributed across the 15-ward study area.<sup>27</sup> To monitor mosquito population densities and infection prevalence, hourly human landing catches were assessed from 1800 h to 0600 h at each location on each occasion by one consenting adult male volunteer sitting outdoors.<sup>27</sup> Although initial data collected from February, 2005, to February, 2007, have been reported previously,<sup>27</sup> these mosquito collections were continued up to the end of the corresponding household surveys<sup>26,30</sup> in December, 2008. All mosquitoes were first identified morphologically as *Culex* spp, other culicines, *Anopheles gambiae* complex, *Anopheles funestus* group, or other *Anopheles* species, after which all *Anopheles* specimens were stored individually over silica. All *Anopheles* were tested in the laboratory for the presence of sporozoites and a subsample of 1993 specimens of the *A gambiae* complex were tested for sibling species identity. Crude estimates of *P falciparum* entomological inoculation rate for each *Anopheles* taxon for each year were calculated by multiplying the mean annual mosquito biting rate on humans by the mean sporozoite prevalence over the course of the study.

#### Entomological surveys of mosquito host preference

Four pairs of C-design Ifakara Tent Traps<sup>31</sup> were randomly assigned to be baited overnight with either an adult male human volunteer or a young calf. The positions of each pair of traps in the Msimbazi River flood plain and their assigned bait host were exchanged each night of trapping, over a total of 120 nights distributed across May to August, 2009, and March to June, 2010. All caught mosquitoes were classified morphologically by genus (*Culicinae*) or species complex or group (*Anopheles*).

#### Outcomes

The primary epidemiological outcome for this study was malaria infection prevalence among humans, as quantified through the cross-sectional household surveys of blood-stage parasitaemia. The explanatory variables assessed as determinants of malaria infection status for individually tested humans were either recorded through the simultaneously administered questionnaire surveys or extracted from programmatic records of where and when larvicide application services were introduced. The secondary outcomes were the outdoor human-biting densities of distinct mosquito taxa, as measured through the continuous, longitudinal human landing catches done all across the study area. The only recorded

explanatory variables for these entomological secondary outcomes were programmatic records of whether larvicide application services had been locally introduced by that time, aggregated estimates of city-wide coverage with complete window screening derived from the household questionnaires, and experimental measurements of blood host preferences for each major mosquito taxon.

### Statistical analysis

We used IBM SPSS and Microsoft Excel for descriptive analysis of the data, after which we used R, version 3.4.3, open-source software augmented with the *lme4*, *nmle*, and *MASS* packages to fit generalised linear mixed models (GLMMs). We obtained all correlation coefficients from the outputs of relevant GLMMs.

All GLMMs fitted to data for *P falciparum* malaria infection prevalence among humans, as recorded through cross-sectional household surveys, specified a logit link function and binomial distribution for this binary dependent outcome. Although we made every attempt to ensure comparability with previous analyses—eg, by using the same age categories—all data exploration and stepwise model building processes were done independently from scratch. For all independent variables collected as continuous numbers or as categorical variables with more than two possible values, initial exploratory analyses of their effect on malaria prevalence were done to establish how best to stratify or combine values for inclusion in more complex models with multiple variables. For example, data on window screening was initially recorded as the following five categories: not screened or glazed; incompletely screened or with large holes, tears, or gaps; completely screened with small holes; completely screened without holes; and glazed with glass windows. Exploratory analysis revealed similar household-level infection risks for the first three and last two categories, and that these two subsets differed from each other, so each of these category subsets was merged to form only two strata. However, for estimating the effect of community-wide window screening coverage on malaria prevalence, combining the last three categories (completely screened, with or without holes, or glazed) yielded the strongest and most consistent effect sizes. This same exploration and simplification approach was also applied to complex interactions between two or more variables such as window screens, eaves, ceilings, and ITNs. In addition to the temporal lag between the onset of larvicide application and impact on adult vector populations, effects on human infection prevalence are also delayed by the development times of both sporogonic-stage parasites in the vector and hepatic stages in the human host. Surveyed humans were therefore only considered to have possibly benefited from larvicide application if this intervention had been implemented in that ward for at least a month before the individual was interviewed and tested. All GLMMs were fitted using the

*glmmPQL* function of the *nlme* package, allowing for temporal autocorrelation by nesting a first-order autoregression term with a 1-week time step within a nested random-effect term for all the following geographic and survey round variables. The impacts of larviciding and other ongoing interventions were assessed through cluster sampling at the level of TCU housing clusters, whereas larviciding was allocated and implemented at the ward level. Therefore, both levels of geographic covariance, as well as large fluctuations between survey rounds within each resurveyed TCU, were accounted for with a random effect that nested the survey round within TCU within ward. When some aspects of previous analyses<sup>26</sup> could not be reproduced by our models that included ward as a source of covariance in this nested random-effect term, additional models were fitted that excluded this level of covariance in the same way as the previously reported analyses.<sup>26</sup>

We estimated the effects of routine larvicide application and coverage of complete window screening on densities of common mosquito taxa in Dar es Salaam using the *glmmPQL* function of the *nlme* package by fitting GLMMs with negative binomial distributions to the counts of mosquitoes caught by each catcher by outdoor human landing catch on each night at a given location as the dependent variable. We included the effect of larviciding on adult vector densities as a categorical fixed effect, whereas we treated city-wide mean coverage with complete window screening (holed or unholed) as continuous independent variables. An inevitable temporal lag occurs between larvicide application and effects on adult vector populations, arising from the equilibration periods required for new adults to develop from larvae, emerge, go through general development, and begin feeding on people, as well as the time required for pre-intervention adult populations of mosquitos to die off. Surveyed individuals were therefore only coded as potentially having reduced transmission exposure if larvicide had been applied in that ward for at least 2 weeks before the night of survey.

For all mosquito taxa except *A funestus*, temporal autocorrelation was accounted for by nesting a first-order autoregression term with a 1-week time step within a random-effect term for TCU nested within neighbourhood within ward. Captures of *A funestus* were very sparse, so the model structure for this species had to be simplified slightly by removing the TCU term to enable model convergence and avoid overfitting. In all cases, input values for the  $\theta$  parameter for the negative binomial distribution were first estimated using simpler, non-autoregressive models with no fixed effects and only date and TCU as random effects using the *glmer.nb* function of the *lme4* package.

### Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or



	Proportion (n/N)	Previously reported: <sup>26</sup> empirical time trend without ward clustering		Independently fitted models reported here: empirical time trend without ward clustering		Independently fitted models reported here: empirical time trend with ward clustering		Independently fitted models reported here: window screening coverage trend with ward clustering	
		OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
<b>Age group, years</b>									
<5	13.5% (8506/63 037)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
5–14	28.5% (17 997/63 037)	0.82 (0.76–0.90)	≤0.05	0.81 (0.75–0.88)	<0.0001	0.81 (0.75–0.88)	<0.0001	0.81 (0.75–0.88)	<0.0001
15–29	28.8% (18 165/63 037)	0.67 (0.61–0.73)	≤0.05	0.68 (0.62–0.73)	<0.0001	0.68 (0.62–0.73)	<0.0001	0.68 (0.62–0.73)	<0.0001
30–44	17.3% (10 922/63 037)	0.60 (0.54–0.66)	≤0.05	0.58 (0.53–0.64)	<0.0001	0.58 (0.53–0.64)	<0.0001	0.58 (0.53–0.64)	<0.0001
45–60	7.2% (4561/63 037)	0.55 (0.48–0.63)	≤0.05	0.54 (0.48–0.61)	<0.0001	0.54 (0.48–0.61)	<0.0001	0.54 (0.47–0.61)	<0.0001
≥60	4.6% (2886/63 037)	0.47 (0.40–0.56)	≤0.05	0.44 (0.37–0.51)	<0.0001	0.44 (0.37–0.51)	<0.0001	0.43 (0.37–0.51)	<0.0001
<b>Sex</b>									
Female	63.7% (39 716/62 303)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Male	36.3% (22 587/62 303)	1.08 (1.01–1.15)	≤0.05	1.08 (1.02–1.14)	0.0060	1.08 (1.02–1.14)	0.0050	1.08 (1.02–1.14)	0.0053
<b>Travel in previous 2 weeks</b>									
Had not slept away from home	90.2% (56 211/62 303)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Slept away from home at least once	9.8% (6092/62 303)	0.90 (0.77–1.04)	>0.05	0.89 (0.80–1.00)	0.0412	0.90 (0.81–1.00)	0.0545	0.88 (0.79–0.98)	0.0201
<b>Insecticide-treated net use previous night</b>									
No	75.4% (47 537/63 037)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Yes	24.6% (15 500/63 037)	0.93 (0.86–0.99)	≤0.05	0.93 (0.86–0.99)	0.0308	0.92 (0.86–0.99)	0.0257	0.92 (0.86–0.99)	0.0256
<b>House has screened or glazed windows</b>									
Absent, incomplete, or holed	72.4% (45 470/62 836)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Complete without holes	27.6% (17 366/62 836)	0.90 (0.83–0.98)	≤0.05	0.85 (0.79–0.92)	<0.0001	0.85 (0.79–0.92)	0.0001	0.85 (0.78–0.91)	<0.0001
<b>House has ceilings</b>									
Absent or incomplete	69.4% (43 213/62 303)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Complete	30.6% (19 090/62 303)	0.93 (0.85–1.01)	>0.05	1.00 (0.93–1.09)	0.9129*	1.00 (0.92–1.08)*	0.9828*	NE*	NE*
<b>Usual sleeping location</b>									
Indoors	86.4% (53 811/62 303)	NI	NI	1 (ref)	..	1 (ref)	..	1 (ref)	..
Outdoors	13.6% (8492/62 303)	NI	NI	1.54 (1.32–1.81)	<0.0001	1.52 (1.29–1.78)	<0.0001	1.37 (1.17–1.62)	<0.0001
<b>Participated in a previous survey round of testing and treatment</b>									
Did not participate	56.6% (35 681/63 037)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Participated and treated if infected	43.4% (27 356/63 037)	0.65 (0.56–0.75)	<0.05	0.91 (0.79–1.03)	0.1270	0.91 (0.81–1.03)	0.1504	0.90 (0.79–1.02)	0.1048
<b>Living in a ward with or without active larvicide application</b>									
No larviciding	71.2% (44 901/63 037)	1 (ref)	..	1 (ref)	..	1 (ref)	..	1 (ref)	..
Larviciding	28.8% (18 136/63 037)	0.79 (0.66–0.93)	≤0.05	0.79 (0.66–0.95)	0.0124	0.87 (0.71–1.07)	0.1896	0.50 (0.41–0.60)	<0.0001
<b>Unattributed empirical time trend</b>									
Prevalence in first survey round	28.1% (1206/4288)	NR	NR	1 (ref)	..	1 (ref)	..	1 (ref)	..
Prevalence in final survey round	1.7% (199/11 631)	NR	NR	0.05 (0.04–0.06)	<0.0001	0.04 (0.03–0.06)	<0.0001	NI	NI
<b>Population coverage of screened or glazed windows</b>									
Coverage during first survey round	40.1% (1710/4268)	NI	NI	NI	NI	NI	NI	1 (ref)	..
Coverage during final survey round	85.9% (9975/11 607)	NI	NI	NI	NI	NI	NI	0.07 (0.05–0.09)	<0.0001

Data are for people for whom valid values for all significant variables for malaria, based on 62 303 microscopy tests with complete matching questionnaire data, obtained over the course of 10 070 household visits. NE=not estimable because this model would not converge until this variable was removed. NI=not included. NR=not reported. OR=odds ratio. \*Best estimates before removed from model because clearly and consistently non-significant and caused convergence failure in the window screening coverage model.

**Table 1: Minimal, multivariate logistic generalised linear mixed models describing risk factors for malaria in participating households in Dar es Salaam, Tanzania, 2004–08<sup>26,30</sup>**

writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

## Results

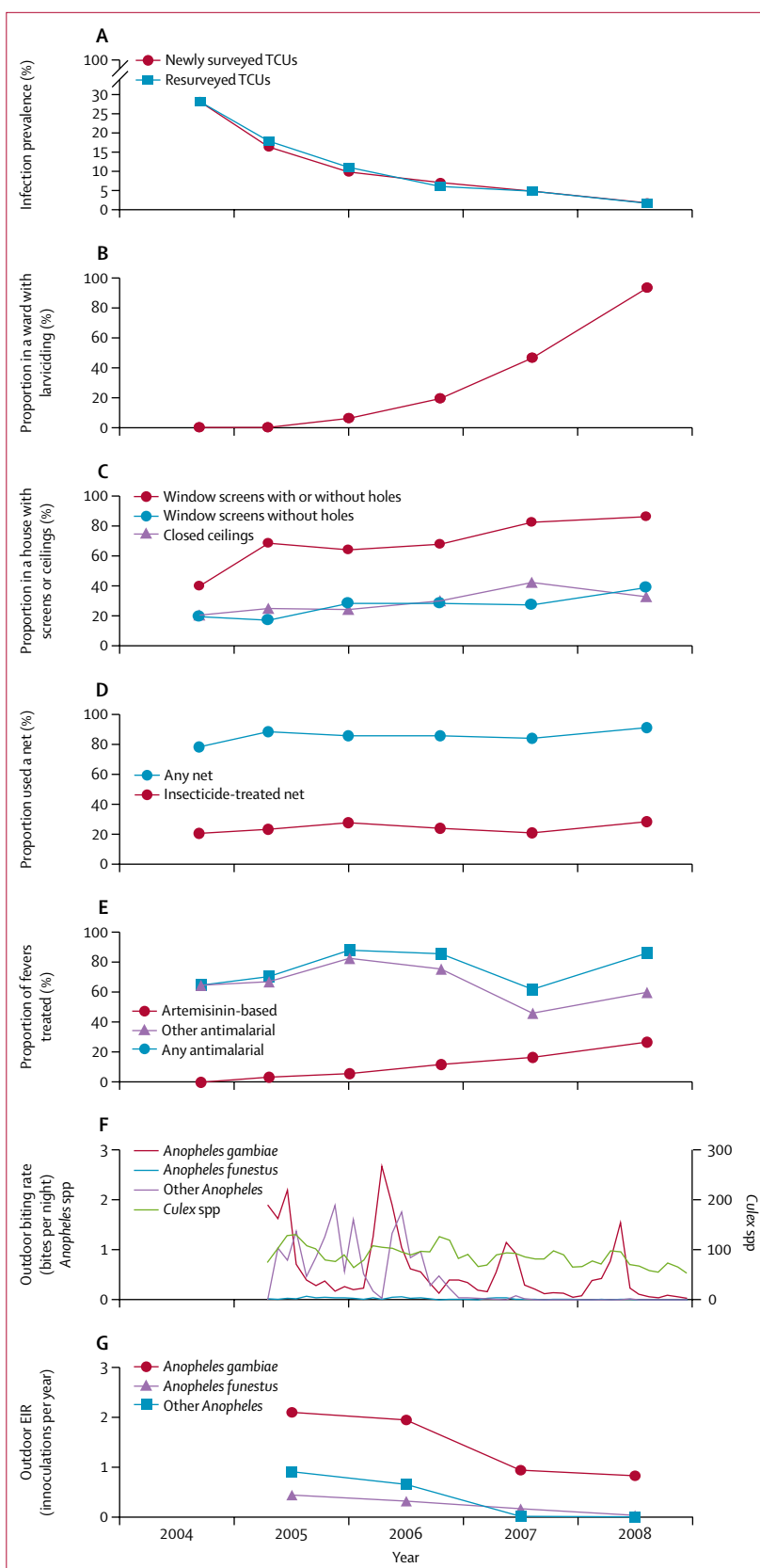
We obtained 63 037 parasitological test results over the course of the cross-sectional household surveys. Of these, 62 303 from 10 070 household visits could also be matched to complete questionnaire data collected during the same household visit (table 1). All age groups were well represented but, as expected, because the surveys were done during working hours of the day, men accounted for only a third of participants.

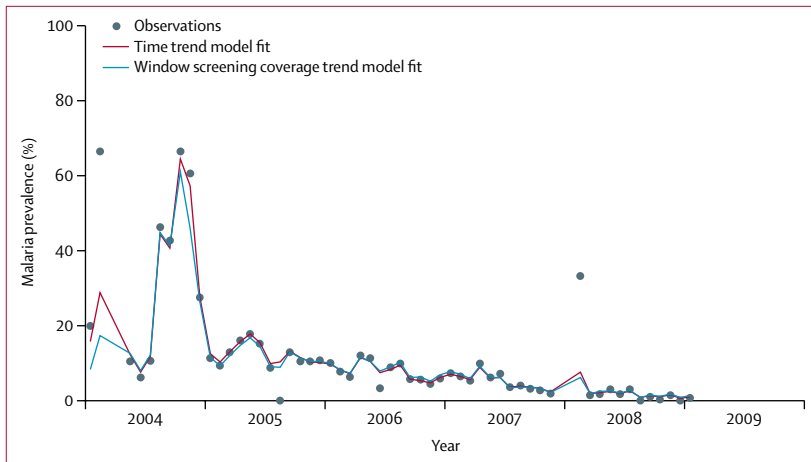
Best-fit models of *P falciparum* malaria infection prevalence among humans were largely consistent with the results of previous analyses<sup>26</sup> (table 1). Similar to previous analyses of the same data, malaria infection risk decreased with age, was slightly higher among men than women, and was lower among occupants of houses with complete and fully intact window screening than among those with absent, incomplete, or holed screening and among users of ITNs than non-users. Counterintuitively, but consistent with previous analyses of this dataset and subsequent analyses of independently collected survey data from the same city,<sup>25</sup> having recently slept away from home was associated with slightly reduced malaria infection risk (table 1). Unlike previous analyses, however, habitually sleeping outdoors was associated with significantly greater probability of malaria infection, whereas neither participation in previous rounds of testing and treatment nor sleeping in a house with a complete ceiling were associated with reduced infection risk (table 1).

Initial attempts to reproduce previous estimates for the effect of larviciding<sup>26</sup> using models that included a similar empirical time trend effect were not successful, with no significant effect detected when ward-level covariance was accounted for (table 1). However, the published estimates only accounted for geographic covariance at TCU housing cluster level, without allowing for higher-level covariance associated with this intervention that could arise from the fact that larviciding was allocated and implemented at the ward level.<sup>26</sup> When ward-level covariance was removed from the empirical time trend model, larviciding impact

**Figure 1: Trends in malaria infection prevalence, coverage with malaria control interventions, mosquito biting densities, and entomological inoculation rates in Dar es Salaam, Tanzania, 2004–08<sup>26,27</sup>**

(A) Population-wide prevalence of parasitologically confirmed *Plasmodium falciparum* malaria infection among participants. (B) Proportion who stayed in a ward with larvicide application the previous night. (C) Proportion who stayed in a house with mosquito-proofed windows, ceilings, or eaves. (D) Bed net or insecticide-treated net use the previous night. (E) Proportion of fevers in the previous 2 weeks that were treated with artemisinin-based therapy (including artemisinin-based combination therapies) or any other antimalarial. (F) Rates of outdoor human exposure to mosquito bites. (G) Outdoor *P falciparum* malaria EIRs mediated by *Anopheles* mosquito taxa. EIR=entomological inoculation rate. TCU=ten-cell unit.





**Figure 2: Fitted generalised linear mixed models for malaria prevalence in Dar es Salaam, Tanzania**  
Models included an empirical time trend similar to previous analyses of the same data<sup>26</sup> or a term for city-wide window screening coverage, with both models including ward-level clustering. Predictions of these fitted models are overlaid on the actual observations of malaria prevalence obtained through rolling cross-sectional household surveys, all aggregated by ward and month.

estimates were obtained that were essentially identical to the previously reported analysis,<sup>26</sup> which also excluded this level of clustering (table 1). However, when ward-level covariance was accounted for, the effect of larviciding was estimated to be three times as large with a far lower p value in the model that included city-wide coverage with complete window screening (odds ratio [OR] 0.50; 95% CI 0.41–0.60) rather than an empirical time trend variable (OR 0.87; 0.71–1.07; table 1). Notably, the fitted time trend was highly covariant with larvicide coverage ( $r=0.615$ ), so including both in the same model could have readily caused spurious underestimation of larvicide coverage, exacerbated by regression dilution bias.<sup>32</sup>

As previously described,<sup>26</sup> a strong time trend effect was observed when it was included in models as an empirical variable with no specifically attributed underlying cause (table 1). Although the magnitude of this unattributed empirical time trend was not reported by the previous study,<sup>26</sup> it was estimated here to be the largest single effect in both models that included it (OR 0.05; 95% CI 0.04–0.06 without ward clustering and OR 0.04; 0.03–0.06 with ward clustering; table 1). Indeed, this unattributed empirical time trend was estimated to represent a reduction of about 95% in malaria risk over the course of the study, accounting for most of the steady decline of malaria prevalence, from 28.1% during the first survey round in 2004 to 1.7% by the final round in 2008 (figure 1A, table 1). Apart from the introduction and scale-up of larviciding (figure 1B), the only potential determinant of malaria risk for which a clear time trend was observed over the course of the study was the spontaneous scale-up of complete window screening with or without holes, which rose from 40.1% during the first survey round to 85.9% by the sixth and final round 4 years later (figure 1C, table 1). When the empirical time trend was replaced with a term

for city-wide coverage of window screening (OR 0.07; 0.05–0.09; table 1), the results were very similar to those obtained with the unattributed empirical time trend (figure 2), except that the estimated impact of larviciding was far greater in this model and approximately halved malaria risk. The estimated effect of window screening scale-up was a greater than 90% reduction of malaria prevalence, only slightly smaller than that associated with the empirical time trend to which no underlying cause was previously attributed.<sup>26</sup>

Although terms for city-wide coverage of ITNs or any bed nets were just as readily substituted for the empirical time trend ( $p<0.0001$  for ITNs and  $p=0.0126$  for any bed net) in models with ward-level clustering, both these terms were strongly covariant with coverage of window screening ( $r=0.978$  for ITNs and  $r=0.591$  for any bed net). Furthermore, the absolute magnitudes of these upward trends were far too small (figure 1D) to plausibly explain the large declines in malaria prevalence they were estimated to be associated with (>95%), so we considered these to be spurious artifacts of covariance with window screening that were excluded from the final models (table 1). Formal goodness-of-fit comparisons could not be made between the models associating these city-wide decreases in malaria to either an unattributed empirical time trend or the upward trend in window screening coverage, because these complex models with over a dozen degrees of freedom could only be fitted with the glmmPQL package, using penalised quasi-likelihood methods that invalidate standard goodness-of-fit indicators. Nevertheless, graphical comparison illustrates how the two models are nearly identical and equally plausible as statistical representations of observed malaria prevalence trends (figure 2).

No other potentially relevant factor had an obvious time trend big enough to plausibly explain the collapse of malaria transmission in Dar es Salaam over the 2004–08 study period (figure 1). Although there was a consistent upward trend in usage rates for artemisinin-based antimalarials over the period of assessment, progress was too slow to account for the near-disappearance of malaria, with only 26% of fevers being treated with these new drugs by the end of the study (figure 1E). Overall treatment rates of fevers with antimalarials, including non-artemisinins, varied slightly over the course of the study but with no consistent time trend (figure 1E). Consistent with analyses of similar data from surveys done in 2010–12,<sup>25</sup> socioeconomic status had no effect on malaria risk ( $p=0.321$ ) when factors with direct causal links to malaria prevention (eg, house structure and materials as well as bed net ownership) were excluded from the composite indicator.

Mosquito densities also decreased over the course of the study. Although *A funestus* and other *Anopheles* (mostly *Anopheles coustani*) almost disappeared, *A gambiae* and *Culex* spp were less affected (figure 1F). Rising coverage of complete window screening



(figure 1C) was associated with substantial declines in the densities of all four mosquito taxa (all  $p < 0.0001$ ), especially *A gambiae* (relative rate [RR] 0.23; 95% CI 0.16–0.33) and *A funestus* (RR 0.08; 0.04–0.16; table 2). Consistent with theoretical analyses,<sup>3,33</sup> the estimated effect of window screening scale-up on each major mosquito taxon was approximately proportional to their preference for human blood (figure 3). Outdoor biting densities of *Culex* spp and other *Anopheles* (mostly members of the *A coustani* group), which clearly but not exclusively preferred cattle over humans, were almost halved (table 2, figure 3). However, outdoor biting densities of clearly anthropophilic *A gambiae* were reduced by almost 80%, and *A funestus*, with an even stronger preference for humans, were reduced by more than 90% (table 2, figure 3). Although no breakdown of species composition was obtained for the *A funestus* sensu lato, the highly anthropophilic behaviour documented for *A gambiae* sensu lato was consistent with the molecular identification results (obtained for 1478 [74%] of 1993 specimens) for this species complex: small proportions of the successfully amplified specimens were accounted for by the more zoophilic *Anopheles arabiensis* (195 [13%] of 1478) and *Anopheles merus* (19 [1%]), but most were identified as nominate *A gambiae* sensu stricto (1264 [86%]), which is notoriously anthropophilic.<sup>3</sup> Increasing coverage with regular larvicide application (figure 1B) was also associated with density reductions for all four mosquito taxa (all  $p < 0.0001$ ), the magnitude of which varied between taxa (table 2) but was approximately consistent with the estimated epidemiological effect (table 1) when the contributions of each taxon to overall transmission was considered (figure 1G).

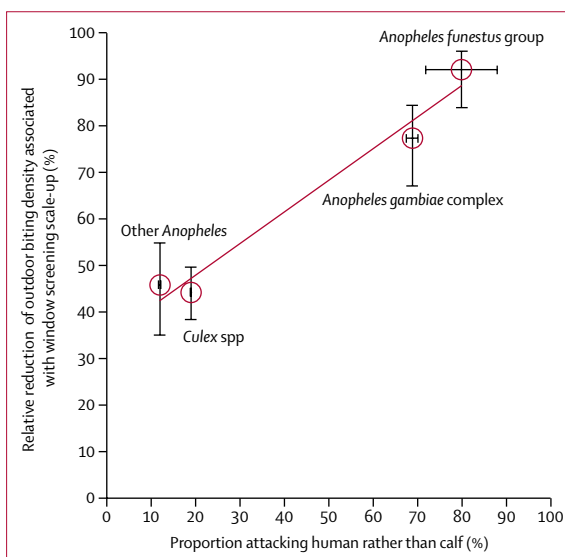
## Discussion

Although some differences exist between our epidemiological modelling results and those previously reported for the same parasitological data,<sup>26</sup> most of the discrepancies probably represent improvements and have little bearing on the most important conclusions. The new analyses presented here consistently found no effect of closed ceilings and suggested that participation in preceding survey rounds of testing and treatment was less important than reported previously.<sup>26</sup> The conclusion on previous participation seems consistent with visual inspection of the data and might arise from the inclusion of habitually sleeping outdoors, a behavioural factor that was negatively associated with mosquito-proofed housing in this setting,<sup>17,18</sup> as an additional, significant variable in these models. Although previous estimates of the effect of larviciding could have been exaggerated by not accounting for within-ward covariance of malaria prevalence and larviciding activity, much greater effects were estimated when the unattributed empirical time trend effect was replaced with a term to reflect rising city-wide coverage of complete window screens.

	Larvicide application		Window screening	
	Relative rate (95% CI)	p value	Relative rate (95% CI)	p value
<i>Anopheles gambiae</i>	0.69 (0.58–0.81)	<0.0001	0.23 (0.16–0.33)	<0.0001
<i>Anopheles funestus</i>	0.39 (0.29–0.53)	<0.0001	0.08 (0.04–0.16)	<0.0001
Other <i>Anopheles</i>	0.40 (0.36–0.44)	<0.0001	0.54 (0.45–0.65)	<0.0001
<i>Culex</i> spp	0.85 (0.81–0.89)	<0.0001	0.56 (0.51–0.62)	<0.0001

Effect sizes were estimated by fitting generalised linear mixed models to nightly counts of mosquitoes from each taxon (5529 *A gambiae* sensu lato, 194 *A funestus* sensu lato, 1955 other *Anopheles* [mostly *Anopheles coustani* sensu lato], and 887274 *Culex* spp) at each survey location, captured over 10 045 nights of all-night human landing catches at 345 sentinel ten-cell units distributed across study site.

**Table 2: Estimated effects of larvicide application and city-wide spontaneous scale-up of complete window screening (with or without holes) on biting densities of common mosquito taxa in Dar es Salaam, Tanzania**



**Figure 3: Estimated effect of spontaneous window screening scale-up on outdoor human biting in Dar es Salaam, Tanzania, 2004–08, plotted against proportion of attacks on a human rather than a calf in an experimental host preference assessment in the same setting in 2009**

Horizontal error bars show 95% CI for proportion attacking human rather than calf and vertical error bars show 95% CI for relative reduction of biting density associated with window screening scale-up. The relative reduction represented by the vertical axis is the complement of the relative rates described in table 2.

When an empirical time trend was included in models, similarly to the preceding analysis, it accounted for most of the large decline in malaria prevalence observed without attributing it to any specific, consistent change in the city. However, most of that rapid downward trend may plausibly be attributed to increasing coverage of window screening, although some part of this reduction might also be caused by covariant but smaller increases in coverage of closed ceilings and bed nets. No other recorded factor exhibited a sufficiently strong, consistent time trend over the course of the study to account for the observed steady reduction of malaria infection prevalence. Furthermore, previous analyses that included an empirical time trend also included rainfall as a predictor, and no consistent trend in rainfall patterns

over the course of the study could explain such a large decrease in malaria infection prevalence.<sup>26</sup>

The larger estimates obtained for the effect of larviciding when the empirical time trend was replaced with window screening coverage suggest that the models including the empirical time trend might have spuriously assimilated much of the variance associated with larviciding because these two covariates are so highly covariant. These revised estimates of effect on malaria prevalence are consistent with the results of subsequent assessments of larviciding when it was later scaled up across the entire city,<sup>25</sup> and with estimated simultaneous effects on vector population densities. Reassuringly, these entomological effect sizes were consistent with expectations based on the known larval ecology of each major mosquito taxon and the habitat targeting criteria of this intervention scheme.<sup>25,28,29</sup> Estimated reductions of *Culex* spp by larviciding were marginal, presumably because these were mostly *Culex quinquefasciatus* that breed in the closed, highly contaminated aquatic habitats like pit latrines, septic tanks, soakage pits, and sewers, which were deliberately ignored by this malaria-oriented programme.<sup>27,28</sup> Although *A gambiae* sensu lato was the primary target of this larviciding campaign, larviciding appears to have reduced densities of this species complex by less than 30%. This disappointing outcome probably arises from the fact that this species complex is rather haphazardly distributed across Dar es Salaam<sup>34</sup> because it exploits diverse, ephemeral, often small aquatic habitats that can occur sporadically, unpredictably, and cryptically.<sup>35,36</sup> By contrast, both *A funestus* and *A coustani* (which accounted for most of the other *Anopheles* category) were reduced by approximately 60% and both taxa are known to prefer breeding in much more permanent water bodies<sup>35</sup> that are larger, more obvious, and more predictably distributed. Larval control is laborious and logistically challenging and takes time to optimise through hands-on programmatic learning,<sup>29,37,38</sup> so full effects probably took considerable time to achieve. It therefore seems plausible that fitting an empirical, unattributed time trend might well have exacerbated the risk of regression dilution bias,<sup>32</sup> so that much of the variance associated with progressive scale-up of larviciding over time was assimilated into the empirically fitted time trend with which it was highly covariant.

Probably the greatest limitation of this study is that the scale-up and effects of window screening were unplanned and purely observational in nature, so these results represent evidence of plausibility rather than probability. Nevertheless, these observations make intuitive sense, and no other explanation is obvious for the dramatic decline of malaria in Dar es Salaam over only 5 years. Furthermore, the results obtained for the entomological secondary outcomes and explanatory metrics support the conclusion that scale-up of window screening was probably responsible for most of the steep decline in malaria prevalence. First, biting rates of mosquitoes were

exclusively measured outdoors by completely unprotected human volunteers, so these will vary in direct proportion to population densities per se, regardless of coverage with bed nets, mosquito-proofed housing or any other personal protection measure. Second, the estimated effects on each mosquito population were consistent with theoretical expectations<sup>3,33</sup> based on direct measurement of their host preferences in this setting: strongly anthropophilic *A gambiae* and *A funestus* were reduced to a far greater extent than were zoophilic taxa, specifically *Culex* spp and other *Anopheles* (mostly *A coustani*).

The observational nature of this study also has some advantages in that it provides evidence of practical effectiveness, affordability, and acceptability under programmatically relevant conditions, rather than merely evidence of efficacy under experimentally controlled conditions. Notably, this scale-up process was primarily motivated by protection against mosquito bites, rather than malaria infection per se,<sup>24</sup> and occurred rapidly and spontaneously through pre-existing horizontal distribution mechanisms. Essentially all the mosquito-proofing of houses at that time was implemented and paid for by householders accessing construction materials through private-sector retail outlets, without any public-sector promotion, subsidisation, or facilitation.<sup>24</sup> The rapid, unsubsidised scale-up observed here not only helps to address concerns about affordability, but also some important limitations of previous observational studies in which housing quality was confounded by associated differences in socioeconomic status.<sup>15</sup> No clear macroeconomic changes occurred in Dar es Salaam over the course of this study that could have so rapidly improved the purchasing power of so many residents. Our own observations, while attempting to conduct experiments requiring unscreened houses at that time,<sup>17,31,39</sup> were that this sudden wave of housing improvement was triggered by market entry of affordable, flexible, and readily installed plastic netting materials that accounted for 81% of screens installed over the study period.<sup>24</sup> These were quite new to the market at the time but, consistent with the findings of subsequent qualitative studies,<sup>18</sup> they then grew in popularity as end-users shared their experiences with neighbours by word-of-mouth.

Such large estimates for the effects on malaria infection burden and population densities of two widely important African vector species merit attention, especially given that these window screens did not have any insecticide. Also, given that a substantial proportion of exposure to malaria vectors occurs outdoors in Dar es Salaam,<sup>17,39</sup> it is particularly encouraging that such dramatic effects were nevertheless achieved. Greater impacts on malaria vector populations and parasite transmission might therefore be possible with untreated netting materials than previously thought. Untreated mosquito screens presumably act by simply denying

mosquitoes access to human blood, even in settings like Dar es Salaam where vectors commonly feed outdoors in the evenings or mornings.<sup>17,39</sup> However, the magnitude of effect achieved in this urban setting might be greater than in rural areas, where more abundant livestock provide mosquitoes with alternative blood sources.<sup>33</sup> Insecticide treatments might therefore be required to maximise the effect of mosquito-proofed houses by killing malaria vectors when they attempt to enter rather than merely diverting them to unprotected humans or animals nearby.<sup>21,40</sup>

Even without any insecticide, mosquito-proofed housing might deliver far greater effects on vector populations and malaria transmission than previously thought. Mounting observational evidence for the benefits of improved housing is encouraging,<sup>14–16</sup> and one carefully controlled epidemiological analysis of netting screens with randomisation applied at the level of individual houses rigorously supported the personal protection they grant against malaria risk.<sup>41</sup> However, to our knowledge, no experimentally controlled, adequately replicated, cluster-randomised controlled trial of mosquito-proofed housing has ever been done.<sup>14</sup> Such large-scale trials should now be made a priority to establish rigorous evidence of efficacy under experimentally controlled conditions.<sup>42</sup>

Durable insecticide treatments for mosquito-proofed houses could achieve even greater effects than those reported here, potentially allowing ITNs and IRS to be eventually superseded as front-line personal protection and vector population suppression measures.<sup>3</sup> Even if insecticide treatments are required for mosquito screens to achieve full effect,<sup>21,40</sup> the greatly reduced treatment areas and frequencies required should allow far lower insecticide consumption rates than with IRS,<sup>7,8</sup> which is thus far the only format that allows rotations and mosaics of different insecticide classes.<sup>4</sup> Phase 3 cluster-randomised controlled trials should be done across multiple tropical settings,<sup>42</sup> including two intervention groups with insecticide-treated and untreated netting alongside a third placebo group without mosquito-proofed houses, so that the contributions of physical protection and lethal insecticides can be separately quantified. Alongside these observations of spontaneous, effective scale-up in Dar es Salaam, similar reports from more rural settings elsewhere in east Africa<sup>16,43</sup> are particularly encouraging. Evaluations of alternative housing materials and designs<sup>9</sup> also provide grounds for optimism over the long term, so operational research to develop cost-effective models for promoting and subsidising effective scale-up will also be important.

#### Contributors

GFK, NJG, and PPC conceived the study. NJG, YPM, and PPC collected all the entomological field data. GFK analysed the data and drafted the manuscript. All authors contributed to editing the manuscript and agree with the final submitted version.

#### Declaration of interests

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