Tropical Medicine and International Health doi:10.1111/j.1365-3156.2009.02341.x

VOLUME 14 NO 9 PP 1143–1153 SEPTEMBER 2009

Reducing costs and operational constraints of dengue vector control by targeting productive breeding places: a multi-country non-inferiority cluster randomized trial

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Summary

OBJECTIVES To test the non-inferiority hypothesis that a vector control approach targeting only the most productive water container types gives the same or greater reduction of the vector population as a non-targeted approach in different ecological settings and to analyse whether the targeted intervention is less costly.

METHODS Cluster randomized trial in eight study sites (Venezuela, Mexico, Peru, Kenya, Thailand, Myanmar, Vietnam, Philippines), with each study area divided into 18–20 clusters (sectors or neighbourhoods) of approximately 50–100 households each. Using a baseline pupal-demographic survey, the most productive container types were identified which produced $\geq 55\%$ of all *Ae. aegypti* pupae. Clusters were then paired based on similar pupae per person indices. One cluster from each pair was randomly allocated to receive the targeted vector control intervention; the other received the 'blanket' (non-targeted) intervention attempting to reach all water holding containers.

RESULTS The pupal-demographic baseline survey showed a large variation of productive container types across all study sites. In four sites the vector control interventions in both study arms were insecticidal and in the other four sites, non-insecticidal (environmental management and/or biological control methods). Both approaches were associated with a reduction of outcome indicators in the targeted and non-targeted intervention arm of the six study sites where the follow up study was conducted (PPI, Pupae per Person Index and BI, Breteau Index). Targeted interventions were as effective as non-targeted ones in terms of PPI. The direct costs per house reached were lower in targeted intervention clusters than in non-targeted intervention clusters with only one exception, where the targeted intervention was delivered through staff-intensive social mobilization.

CONCLUSIONS Targeting only the most productive water container types (roughly half of all water holding container types) was as effective in lowering entomological indices as targeting all water holding containers at lower implementation costs. Further research is required to establish the most efficacious method or combination of methods for targeted dengue vector interventions.

keywords dengue, vector control, targeted intervention, efficiency of interventions

Introduction

Dengue is the fastest spreading arboviral disease worldwide with an estimated annual incidence of 50 million cases and 500 000 severe cases (WHO 2006). Over recent decades an almost exponential growth has been observed (Nathan & Dayal-Drager 2006). The severe socio-economic impact of the disease is being increasingly better documented (Suaya *et al.* 2007). In the absence of antiviral drugs and vaccines, vector control is the only way of preventing or reducing dengue transmission. However, the implementation of dengue vector control strategies is resource-intensive.

A recent multi-centre study used the 'pupal/demographic survey technique' (Focks & Chadee 1997; Focks 2003) to identify the container types producing a high proportion of all pupae (as a proxy for adult mosquitoes as long as all relevant water containers are being detected and adequate collection techniques particularly in large containers are being employed) and measured the Pupae per Person Index (the average number of pupae per person in the community, PPI) as potentially one of the important parameters in determining the risk of dengue virus transmission (Focks & Alexander 2006; Nathan *et al.* 2006). The subsequent questions were:

(1) if the reduction in pupal production through interventions targeting only the most productive containers is equivalent or non-inferior to 'blanket' (non-targeted) interventions in all water holding containers and
(2) whether targeted interventions are cheaper.

Study sites and methods

Overall study design

Cluster randomized trial design. In the eight study sites (Venezuela, Mexico, Peru, Kenya, Thailand, Myanmar, Vietnam, Philippines, Table 1) a cluster randomized trial design was used, with each study area divided into 18–20 clusters (sectors or neighbourhoods) of 50–100 households. Care was taken to assure that the sectors/clusters receiving the targeted intervention were at least 200 m (which is beyond the usual flight range of *Aedes* mosquitoes) (Getis *et al.* 2003) from the nearest control sector to avoid any spill-over effects. Using baseline pupal-demographic surveys (see below), the most productive container types that contributed ≥55% of all pupae were identified. Clusters were then paired based on similar PPIs and one cluster from each pair was randomly allocated to receive the targeted intervention aimed at the most productive water containers for pupae and the other cluster acted as an active control, receiving the 'blanket' intervention by the research team or quality controlled local public health staff (Table 1). Every attempt was made that the quality of interventions in both study arms was of a comparable standard and that the effect of the insecticidal or non-insecticidal intervention covered the whole study period. Follow-up surveys were conducted approximately 1 month and 5 months after the start of the intervention.

Targeted and non-targeted ('blanket') interventions. The interventions in four sites were mainly insecticidal (temephos, pyriproxyfen or *Bacillus thuringiensis var. israelensis*, applied as larvicides, or insecticide-treated water storage container covers) but included in the 'blanket intervention arm' also source reduction through cleaning campaigns and/or community mobilization. In four sites non-insecticidal methods were used [mechanical source reduction, predatory copepods, fish, or dragonflies (Table 1) complemented in the non-targeted intervention arm occasionally by larvicides (Mexico and partially Myanmar)]. The follow up consisted of cross-sectional pupal-demographic surveys, the first 2–4 weeks after the intervention and the second 5 months after the intervention (details in Table 1). Some interventions may not yet have been fully effective at the 2–4 weeks measurement (particularly non-insecticidal interventions) so that the assessment of 'non-inferiority' and pupal/larval reduction were done based on the 5 months measurement. Other interventions needed a repeat application after 3 months (Temephos and Bti) to be efficacious over the whole study period.

Sample size and rationale for pooled analysis. The study was set up as a non-inferiority trial; such a trial intends to show whether a new treatment has at least as much efficacy as the standard or is worse by an amount less than a certain non-inferiority limit. This limit was selected to be an average difference of 1 pupa per person or a difference not more than 10% of baseline values in the Breteau Index (BI) under the assumption that these differences would have little or no impact on virus transmission.

The sample size calculation related to the first objective of the study was based on the methods for the negative binomial distribution modified for non-inferiority testing (Hayes & Bennett 1999). From a previous cluster-randomized trial in Venezuela (Kroeger *et al.* 2006) negative binomial k parameters were obtained as approximately 0.025 for number of pupae per house (for PPI analysis) and 0.25 for positive containers per house (for BI analysis). Further, the between-cluster coefficient of variation from the baseline survey of the trial was estimated as 1.4 for PPI

Table 1 Dengue targeted interventions and non-targeted interventions

		Interventions and implementers	
Country	Study site and location	Targeted	Non-targeted
Venezuela	Trujillo city, 35 000 population, 800 m above sea level, annual average temperature of 23.3°C, two rainfall periods (May and October)	Covering drums with insecticide treated (Permanet 2) water container covers; Research team	Treating drums with temephos plus routine interventions in non-productive containers Research team
Mexico	Merida city, Yucatan, 662 530 pop., annual average temperature of 26.5°C, rainy season (May–October) and dry season (November–April)	Buckets and pot management; Research team	Buckets and pot management plus routine interventions (source reduction) MOH staff/ researchers
Peru	Iquitos city, Amazon forest, 345 000 pop., 120 m above sea level	Source reduction and pyriproxyfen in productive containers; Research team	Source reduction and pyriproxyfen in all containers MOH staff/ research team
Kenya	Malindi city (shore of Indian ocean), 225 791 pop., mean daily minimum and maximum temperatures = 22°C and 30°C, 65% RH., two rainy seasons (April–June and October–December)	Temephos in productive (large) containers; Community and research team	Temephos or BTI in productive (large) containers plus cleaning/elimination of all other containers Community and research team
Thailand	Three provinces of northern, south-east and central Thailand including the capital cities of Chachoengsao, Chiang Mai and Salsabury. Tropical humid climate, rainy season (March–September)	Bti (slow release) and pyriproxyfen every second month in productive containers; Research team	Temephos in productive containers and cleaning/ emptying all other containers every second month; occasionally ULV spraying MoH staff/research team
Myanmar	Yangon city, 4.8 million population, 60 m above sea level, average day time temperature = 31.4°C, R.H. = 67%–91.9%, average annual rainfall = 2833mm, wet season (June–October), dry–cool (November–February), dry–hot (March–May)	Sweep method by supervised local people, Dragon-fly nymphs, fish; Community volunteers and MoH staff	Sweep method by supervised local people, Dragon-fly nymphs, fish plus overall routine interventions (source reduction); temephos in a couple of clusters Community volunteers and MOH staff
Vietnam	Binh Thuan province, 1.16 million population (Ham Phu commune with 7969 population), coastal area of south-central Vietnam, average temperature of 27°C, annual rainfall of 800 mm–1500 mm, rainy season = May–October (tropical monsoon)	*Mesocyclops* in productive containers; Community and research team	Routine control,education, source reduction, household visits Community and health staff
Philippines	Quezon city, 35 000 pop., average annual temperature = 27°C, annual rainfall = 1123 mm, wet season (May–October) and dry season = during the rest of the year	Tire splitting, drum and dish rack cleaning, waste management; Research team/health staff	General clean up, routine awareness campaigns and flyers from project Research team/ health staff

Country	Targeted and non-targeted interventions: number of clusters per arm (Households per cluster)	Productive container types (% pupae in productive containers out of all pupae)	Time line (BL = Baseline FU = Follow-up surveys)
Venezuela	9 clusters (80 HH/cluster)	Drums (60% of pupae)	BL = May 07 + intervention, 2-weeks FU = June 07, 5 months FU = October 07
Mexico	9 clusters (100 HH/cluster)	Buckets + pots (55% of pupae)	BL = June 07 + intervention, 2-weeks FU = July 07, 5 months FU = November 07

Table 1 (*Continued*)

Country	Targeted and non-targeted interventions: number of clusters per arm (Households per cluster)	Productive container types (% pupae in productive containers out of all pupae)	Time line (BL = Baseline FU = Follow-up surveys)
Peru	10 Clusters (50 HH/cluster)	unlidded/outdoor/rainfilled + large and medium storage containers, indoor containers associated with roof leaks (92% of pupae)	BL = January/February 07, May/April 07 = intervention, 2-weeks FU = May 07, 6 months FU = September 07
Kenya*	10 clusters (60 HH/cluster)	Metallic + Plastic drums (Jericans) (70% of pupae)	BL = January 07, Feb 07 = intervention, 2-weeks FU = March/April (no long-term follow up)*
Thailand	9 clusters (100 HH/cluster)	Clay jars + toilet tanks (80% of pupae)	BL = July/August 06 September = intervention, 2-weeks FU = October 06, 5 months FU = January/February 07
Myanmar	10 clusters (90–100 HH/cluster)	Drums + Tanks + spirit worship flower vases (73% of pupae)	BL = July 06 + intervention, 2-weeks FU = Aug/Sept. 06, 5 months FU = Jan 07
Vietnam*	9 Clusters (70 HH/cluster)	Large jars (>1000L.), middle Jars (100–1000L.) (88.4% of pupae)	BL = October 06 + intervention, 2-weeks FU = November 06 (long-term follow up only on a small sample)*
Philippines	8 Clusters in targeted arm (90–100 HH/cluster); 9 clusters in non-targeted arm	Tires, drums, dish rack, selected waste(72% pupae)	BL = July 06 August/September 06 = intervention, 4-weeks FU = October/November 06, 7 months FU = April/May 07

*Excluded from long-term assessment.

and 0.8 for BI. We assumed 100 houses per cluster, and using a one-sided 95% confidence limit for assessing non-inferiority. For PPI the needed number of clusters was found to be 62 (31 per arm) requiring 80% power. For BI, 44 clusters (22 per arm) were needed. It was decided that each site should use 9–10 clusters per intervention arm giving in total 72–80 clusters per arm. This approach requires a pooled analysis combining data from a variety of settings using different intervention methods of proven efficacy.

The large range of vector infestation levels at baseline was not seen to be an issue but rather an asset of the study as it reflects the reality which vector control services are facing even in relatively small geographical areas. However, ideally interventions in the productive container types of both the targeted and non-targeted study arms should have been the same, complemented in the non-targeted intervention arm by other intervention methods according to the type of non-productive water containers. As this was not feasible in a number of sites according to negotiations with Ministries of Health (Venezuela, Thailand, Myanmar), the rule was applied that interventions in both study arms should be of proven efficacy for the 5 months study period -requiring in some sites repetitive applications – and that the application was of comparable standard in both arms.

Pupal-demographic surveys. The entomological surveys at baseline, 2–4 and 5 months after intervention (in this paper only the 5 months results will be used in the analysis) investigated all potential *Aedes aegypti* larval/pupal habitats in and around houses in each study area. In cases where immature stages of mosquitoes were present, the presence of larvae was noted and all pupae were counted and collected and taken back to the laboratory where they were allowed to emerge and were identified according to species. Additional information was collected from the head of household, including the number of people who live in the house (to calculate pupae per person) and any other recent mosquito control campaigns in which the household participated (Focks & Alexander 2006; Nathan *et al.* 2006).

Cost estimates and feasibility. Monitoring of costs of the targeted and non-targeted (‘blanket’) interventions was done in Kenya, Mexico, Myanmar, Philippines and

Vietnam. Recurrent costs (staff time – according to employment level –supplies and materials, vehicles and buildings-operation and maintenance – training and social mobilization) as well as capital costs (vehicles, equipment, training and social mobilization) were registered and then compiled in an Excel sheet. Only direct costs to the vector control services were included in the analysis as these are the cost components required by vector control managers. In those sites where the research team had to simulate the targeted and/or non-targeted intervention (to be carried out under programme conditions by vector control staff) staff time was recorded but the salaries of governmental health and control staff were used for the estimate; however, this limits the accuracy of the cost estimates. Local currency was converted into US Dollar using the exchange rate of January 2007.

Data management and analysis. After entering and cleaning the data in each site, they were then merged into a single data base and analysed with STATA 10.

Unit of analysis was study-cluster using summary statistics (proportions, mean values) per study-cluster. To adjust for clustering on country level a mixed model with random intercept was used (xtmixed in STATA 10.1) in the pooled analysis.

Baseline data and post-intervention data were analysed both separately and in a longitudinal model. In the latter model an interaction term of being in intervention arm at follow-up was included to estimate the difference in effect between targeted and non-targeted interventions. The difference in intervention effect is then estimated as the difference of the differences and should be zero if there is no difference and negative if a larger reduction in the targeted intervention clusters than in the non-targeted clusters:

$$\text{Effect of intervention} = (\text{B-A})\text{-}(\text{D-C})$$

A = baseline value for the targeted intervention group; B = post-intervention value for the targeted intervention group; C = baseline value for the non-targeted intervention group; D = post-intervention value for the non-targeted intervention group.

Technically the regression model has the structure:

$$\text{Count} = \text{Intercept} + a * \text{Treatment} + b * \text{Time} + c * \text{Interaction} + \text{error}$$

where treatment is one if targeted intervention and zero if non-targeted intervention, time is one if follow up at 5 months after intervention and zero if baseline, and interaction is one if targeted intervention group at follow up.

Significances are stated on 5% level and 95% confidence intervals are reported. Non-inferiority was assessed using two-sided 95% confidence intervals (CI) which corresponds to a 97.5% one-sided CI (Piaggio *et al.* 2006). For simplicity the results are given for original scale. However, significances were compared to results for log-transformed scale due to skewed distributions. Discrepancies were then reported.

Quality assurance throughout the study process. Highly experienced study teams in dengue vector management were selected from a large number of applications by an independent expert panel at TDR/WHO. Meetings of all Principal Investigators at the start and the end of the study took place to develop and follow the study protocol and analyse findings in a coordinated way. In all sites the research teams monitored the interventions by vector control services in a standardized way to ensure a high quality and coverage of the interventions. Double data entry, and data management by an experienced statistician ensured high data quality.

Ethical considerations. The data collected in households did not exceed the information collected by the regular health services in their routine visits of households. However, participants were asked if they wished to participate at the outset of the study and were free to withdraw anytime; they signed a consent form in local language. The study was cleared by the ethical committees in each site and the WHO Ethical Review Committee.

Targeted and non-targeted interventions. The insecticidal interventions targeting productive containers were insecticide treated water container covers in Venezuela (Kroeger *et al.* 2006; Chang *et al.* 2008), pyriproxyfen treatment of water containers in Peru (Morrison *et al.* 2008) and pyriproxyfen with slow release Bti (Mulla *et al.* 2004) and Temephos treatment (Kenya); these were compared in the non-targeted arm with the same or other routine insecticidal interventions of proven efficacy such as temephos or pyriproxyfen or Bti treatment (Table 1) plus interventions in non-productive container types. In the non-insecticidal targeted intervention areas pot management (Mexico), biological control with dragon flies plus sweeping method in Myanmar (Sebastian *et al.* 1990; Tun-Lin *et al.* 1994, 1995a,b) or *Mesocyclops* in Vietnam (Nam *et al.* 1998; Kay et al. 2002, 2005) or health education plus tire splitting (Philippines) was compared with interventions such as source reduction and MoH lead health education, in two sites (Myanmar and Mexico) additionally with larvicidal interventions.

Results

Study sites

All studies were carried out in a tropical humid climate among urban (six sites) or semi-urban/ rural (Thailand, Kenya) populations. At baseline and 2–4 weeks follow-up a total of 149 clusters of households were included, 74 in the targeted intervention arm and 75 in the non-targeted intervention arm. However, two sites (Kenya and Vietnam) could only be included in the baseline assessment and not in the follow-up analysis because for operational reasons full application of the joint protocol in the 5 months evaluation was not feasible. Thus, 111 clusters of 9276 households were assessed for eligibility (Figure 1).

Productive containers: site specific characteristics

'Productive containers' were defined as those container types which, when ranked in descending order of the numbers of *Ae. aegypti* pupae in the study site, cumulatively produced the majority of *Aedes aegypti* pupae (generally >55% out of the total). With few exceptions large water storage containers were the most productive types (Table 1). In Iquitos, Peru, there was a large variety of container types, so that a functional classification was adopted with the unlidded outdoor-rainfilled and occasionally indoor rainfilled containers plus large and medium tanks identified as the most productive ones. In addition to large tanks, in some sites smaller water containers were also identified as being productive such as pots (Mexico), flower vases for religious purposes (Myanmar), tires and dish racks (Philippines) and toilet tanks (Thailand). The proportion of pupae produced by the group of productive containers was between 55%–92%, median 73%. (Table 1).

Proportion of productive containers out of all containers

The mean percentage of water containers categorized as most productive out of all water containers surveyed was 41.7% (± 21.0 SD) at baseline in the targeted intervention study arm and 54.1% (± 14.4%SD) in the non-targeted arm. This remained consistent with roughly the same values after 5 months (40.1% and 52.5% respectively) indicating that a targeted approach would only require intervention in around half of all available water containers.

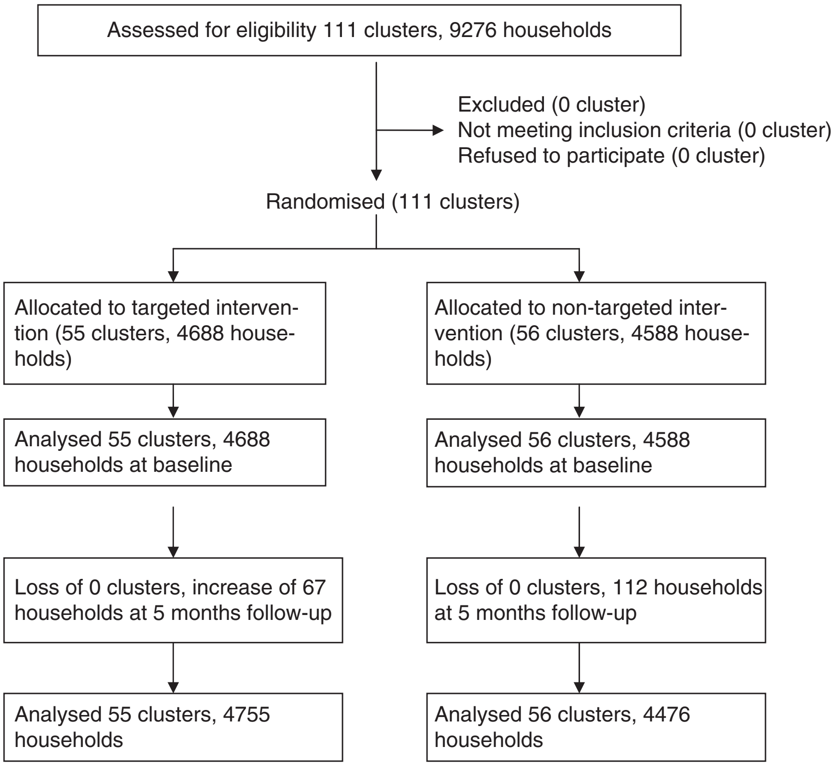

Figure 1 Flow of clusters and households through study (two countries with incomplete date sets at follow up excluded; see text. Slight increase of households at 5 months due to population movement).

Site specific intervention coverage

The proportion of productive containers reached by the intervention was defined as 'coverage' although in the non-targeted intervention a much larger number of water containers was covered.

Coverage in sites with non-insecticidal interventions (Table 1):

- Mexico and Vietnam : 95% (targeted arm) and 98% (non-targeted arm);
- Myanmar : 73.5% (targeted) and 75.0% (non-targeted);
- Philippines: 70% in the targeted and non-targeted arm.

Coverage in sites with insecticidal interventions:

- Peru: 95% in the targeted and non-targeted arm (dropped to 50% at 5 months follow up);
- Thailand: 80% in the targeted and non-targeted arm;
- Kenya: 82% (targeted) 90%(non-targeted);
- Venezuela: 55.0% (targeted) and 43.1% (non-targeted).

Pooled and site specific vector densities estimated by PPI (Pupae per Person Index) and presence of the vector by the larval index BI in targeted and non-targeted intervention arms.

At baseline in the site specific and pooled analysis the PPI and BI were practically the same in targeted and non-targeted intervention clusters ($P > 0.1$) due to the fact that clusters were paired according to entomological indices (Table 2).

The mean PPI in the non-targeted intervention arm was 0.37 (CI 0.19–0.55) and 0.41 (CI 0.21–0.62) in the targeted intervention arm. The mean BI was 39.8 (CI 9.4–70.2) in the non-targeted intervention arm and 41.0 (CI 11.4–70.6) in the targeted intervention arm. Both indices were far above average in Myanmar and far below average in Peru and Mexico (where MOH control activities had been conducted at the time of the study).

Pooled and site specific effect of interventions on entomological indices. The reduction of entomological indices by insecticidal and non-insecticidal interventions both in targeted and non targeted clusters is presented in Table 2 showing a statistically significant reduction of PPI (by 33.7% and 38.6% in the pooled analysis of the targeted and non-targeted intervention arm) and BI (53.7% and 50.0% reduction in the two study arms). In several study sites such a reduction was measured, but not in others (see discussion).

Pooled and site specific analysis: non-inferiority of targeted compared to non-targeted dengue vector interventions

At the 5 months follow-up survey, the PPI and BI values in clusters with targeted and non-targeted interventions remained close to each other (Table 2) and the difference

Table 2 Reduction of entomological indices (BI and PPI) from baseline to 5-month follow up

		BI			PPI		
Country	Study arm	Baseline	5 months	% reduction from baseline* (*P* value†)	Baseline	5 months	% reduction from baseline* (*P* value†)
Myanmar	Targeted	103.0	18.3	−82.2 (<0.001)	0.80	0.19	−76.3 (<0.001)
	Non-targeted	102.4	18.6	−81.8 (<0.001)	0.74	0.16	−78.4 (<0.001)
Philippines	Targeted	28.9	5.7	−80.3 (<0.001)	0.41	0.11	−73.2 (0.007)
	Non-targeted	33.1	8.0	−75.8 (0.009)	0.52	0.14	−73.1 (0.078)
Peru	Targeted	17.1	17.8	4.1 (0.872)	0.11	.37	236.4 (0.071)
	Non-targeted	10.9	12.7	16.5 (0.605)	0.21	0.11	−47.6 (0.478)
Mexico	Targeted	16.6	24.5	47.6 (0.118)	0.27	0.15	−44.4 (0.205)
	Non-targeted	17.6	38.2	117.0 (0.005)	0.17	0.57	235.3 (0.095)
Thailand	Targeted	68.9	33.2	−51.8 (0.013)	0.27	0.23	−14.8 (0.754)
	Non-targeted	68.3	33.5	−51.0 (0.027)	0.35	0.18	−48.6 (0.335)
Venezuela	Targeted	11.2	14.1	25.9 (0.466)	0.61	0.57	−6.6 (0.891)
	Non-targeted	6.6	8.6	30.3 (0.508)	0.23	0.20	−13.0 (0.849)
Pooled‡	Targeted	41.0	19.0	−53.7 (<0.001)	0.412	0.273	−33.7 (0.063)
	Non-targeted	39.8	19.9	−50.0 (<0.001)	0.370	0.227	−38.6 (0.044)

*Reduction in percentage is calculated as 5 months-value minus baseline value divided by baseline value.

†*P* values for individual country tests were calculated using *t*-test for independent observations.

‡*P* values in pooled analysis were calculated based on mixed model analysis.

was not statistically significant (*P* values between 0.14 and 0.8). Non-inferiority was assessed as described in the methods section. Table 3 shows the PPI and BI results from regression analysis estimating the difference in efficacy (reduction of PPI or BI) between targeted and non-targeted interventions from baseline to the 5 month follow-up taking into account baseline values (difference-of-differences approach). A zero estimate indicates no difference between the interventions and a negative estimate indicates that the targeted intervention has a better efficacy in terms of reducing PPI and BI from baseline to last follow up, and the opposite for a positive result.

The aim of the non-inferiority analysis is to test the hypothesis that a targeted vector control approach gives the same or greater reduction of the vector population than a non-targeted approach. The difference in efficacy of the targeted intervention versus the non-targeted intervention is then not allowed to exceed a certain limit. The limit for non-inferiority was set to a difference of +1 in efficacy for PPI, the main outcome indicator. This means that we concluded non-inferiority if the upper limit of the 95% CI of the difference in reduction did not exceed +1, i.e. the reduction in PPI from baseline to follow up was statistically shown not to be more than 1 unit larger for the non-targeted intervention than the reduction for the targeted intervention. This is clearly the case in the pooled as well as in the site specific analysis as there was almost no difference between the two intervention arms (Table 3). Regarding the BI, in the pooled analysis the targeted intervention had a larger reduction in BI than the reduction for the non-targeted intervention. The difference in reduction was estimated to be −2.09 (Table 3). However, due to the large CI indicating a large variation among clusters there is no conclusive answer about inferiority or non-inferiority (limit +4.1, i.e. 10% of baseline BI 41.0) of one or the other intervention.

Site specific and overall direct cost s of targeted and non-targeted interventions

The cost analysis (Table 4) showed that the direct 'cost per household reached' was higher in the non-targeted intervention group than in the targeted intervention group. Only in the Philippines (where the targeted intervention included a high level of staff intensive social mobilization effort which were not done in the non-targeted group) the cost estimates were higher for the non-targeted intervention.

Staff salaries made the highest contribution to the recurrent costs; particularly in non-targeted interventions; likewise transport costs were high in most sites (vehicle operation & maintenance) and only negligible in Vietnam where the intervention houses were reached by bicycle. Supplies and material costs were high in Mexico in the non-targeted intervention area (mainly temephos application) and in the Philippines in the targeted intervention area (printing of brochures and flyers). In Vietnam supplies and materials as well as the equipment costs were high in both in the targeted and non-targeted areas mainly due to the costs of the food allowance to staff and collaborators.

Table 3 Difference in reduction (difference-of-differences) for targeted *vs.* non-targeted interventions calculated as BI and PPI from baseline to 5-months follow up

	BI		PPI	
	Reduction controlled for baseline*	95% CI†	Reduction controlled for baseline*	95% CI†
Myanmar	−0.94	−32.20–30.31	−0.029	−0.407–0.348
Philippines	1.95	−18.85–22.76	0.072	−0.402–0.545
Peru	−1.05	−12.64–10.53	0.365	−0.030–0.760
Mexico	−12.65	−28.77–3.47	−0.529	−1.034–−0.024
Thailand	−0.97	−40.14–38.20	0.138	−0.307–0.584
Venezuela	0.84	−8.94–10.62	−0.023	−0.749–0.703
Pooled‡	−2.09	−15.00–10.82	0.008	−0.200–0.216

*The difference in efficacy between targeted and non-targeted interventions from baseline to 5-month follow up was estimated using the difference-of-differences approach. A zero estimate indicates no difference between the interventions and a negative effect estimate indicates that the targeted intervention is more efficacious in terms of reducing PPI and BI from baseline to last follow up; †Confidence intervals for individual countries were calculated given independent observations; ‡Confidence intervals in pooled analysis were calculated based on mixed model analysis. Non-inferiority is stated if the upper limit is below +4.1 for BI and +1 for PPI.

Table 4 Annual cost estimates in US Dollar for targeted (TI) and non-targeted interventions (NTI) by cost category

	Kenya		Mexico		Myanmar		Philippines		Vietnam	
Input	TI	NTI	TI	NTI	TI	NTI	TI	NTI	TI	NTI
A. Recurrent costs										
Personnel	2660	5540	6439	8240	2153	3283	7579	2197	2480	5452
Supplies and materials	748	463		1485	334	2186	1126		2259	1827
Vehicles operation and maintenance	2580	6020	491	1960	2360	2360	478	418		
Buildings operation and maintenance	0	0			434	434				
Training and social mobilization	531	531	450	7500	1360	2040	213	456	717	5547
Other recurrent costs	319	743			1858	1858			540	864
Total recurrent costs	6837	13 297	7381	19 185	8499	12 161	9397	3071	5996	13 690
B. Capital costs										
Vehicles				6551					1048	
Equipment	101	176		2839	50	75			1167	1097
Building	0	0								
Training and social mobilization	967	967					384			
Other capital inputs										
Total capital costs	1068	1143	0	9389	50	75	384	0	2215	1097
Total	7906	14440	7381	28 574	8549	12 236	9781	3071	8212	14 787
Number of HHs covered	570	455	900	900	1912	1896	1049	1399	1226	1270
Cost per HH covered	13.87	31.74	8.20	31.75	4.47	6.45	9.32	2.19	6.70	11.64

TI, targeted intervention; NTI, non-targeted intervention.

Discussion

Variation of productive container types

Our multi-centre study reconfirmed earlier findings (Focks & Alexander 2006; Nathan *et al.* 2006), that the container types with the highest production of *Ae. aegypti* pupae vary from place to place but can be established through cross sectional pupal surveys. Although pupal production is a dynamic process the type of productive containers in a given geographical area remains fairly stable. In most of our study sites the large ground containers were the most productive ones, but important exceptions exist where the small containers were the most productive ones, particularly evident in Peru. An ongoing study in six Asian countries is further investigating this phenomenon (TDR/IDRC study on eco-bio-social dengue research).

Non-inferiority of targeted interventions

The study demonstrated that targeting only the most productive water container types (roughly half of all water holding containers) was as effective in terms of reducing entomological indices (PPI) as targeting all water holding containers. This was particularly evident in the pooled analysis but also in the site specific analyses.

Efficiency ('cost per house reached') and coverage of targeted versus non-targeted interventions.

The cost analysis showed that targeting productive container types was cheaper and required less work than intervening in all existing water containers. In the case of the Philippines, where a strong component of social interventions was delivered, the costs at the outset of the targeted programme were higher than in the non-targeted programme, but they would likely decrease after having invested in the initial mass campaigns and basic equipment. One major reason for the greater efficiency (cost per household reached) of the targeted intervention arm was the lower staff cost as the job was completed faster than in the non-targeted intervention arm. This increased efficiency in targeted interventions was also reflected in the higher transport costs reported in the non-targeted groups in Kenya and Mexico, with Myanmar and Philippines being the exceptions as the research teams simulated the non-targeted intervention.

Level of reduction of vector densities

With both insecticidal and non-insecticidal interventions, both targeted and non-targeted, the reduction of entomological indices was significant (Tables 2 and 3).

However, the efficacy data has to be interpreted with caution as there was no untreated control group (because non-inferiority testing was the core objective of this study) and confounding factors such as climate and additional interventions by control services may have played a role in reducing vector densities. In Peru at baseline insecticide fogging was carried out by control services explaining the increase of vectors in the follow up period when this intervention was abandoned. In Thailand occasional fogging was done in the non-targeted areas close to the 5-months follow up explaining the vector depletion in these areas. In Venezuela both targeted and untargeted interventions achieved a low household coverage due to acceptance issues explaining the limited effect of insecticidal interventions.

Acceptance of interventions

Myanmar, Kenya, Philippines and Vietnam reported a high level of acceptance (expressed also in the high intervention coverage achieved), particularly in the targeted intervention areas. In contrast in Venezuela, directly observed use of water container covers during follow-up surveys showed that only 55% of targeted containers were correctly covered. While overall the acceptance and initial coverage of the targeted intervention was high, the long-term sustainability of this measure remains to be investigated.

Limitations of the study

Tools for estimating dengue vector densities are controversial as there is no way of directly measuring the number of *Aedes* mosquitoes in a premise. Landing catches are seen to be unethical as there is no drug for treating dengue disease; backpack aspirators for collecting indoor adult mosquitoes (Clark *et al.* 1994) even with skilled laborers catch less than 50% of the existing vectors (Morrison *et al.* 2008). Hence pupal counts are supposed to better reflect vector densities as around 80% of pupae develop to adult mosquitoes (Focks & Chadee 1997; Focks 2003). It has, however, to be ensured that no ‘cryptic’ containers are missed (Barrera *et al.* 2008) and that large containers are either emptied or assessed using the funnel technique (Kay *et al.* 1992) or similar devices. In our study only Vietnam had large containers where a correction factor could be used (Knox *et al.* 2007) and no sites had water containers which were difficult to reach. This is why we are confident that our estimate of vector densities using the Pupae per Person Index (PPI) was fairly robust. However, we do not know with which frequency pupal demographic surveys have to be repeated (once per year or less or more often?) and for how long after the 5 months observation period the effect will be sustainable.

Policy implications

As dengue increases as a public health problem, the status quo of dengue vector control needs to be re-considered. In resource limited settings, vector control must maximize both efficacy and efficiency. This multi-country study provides evidence that targeting only the containers responsible for producing the greatest number of *Ae. aegypti* pupae presents tangible benefits in terms of reducing dengue vector control costs. However, this study was not intended to show the vector control tool with the highest impact on the vector population. Further research is required to identify the most efficacious methods to be used in a targeted dengue vector intervention packages designed according to local conditions. The ultimate goal is to maintain vector densities below threshold levels for epidemic transmission (Focks *et al.* 2000) and there is still a long way ahead to validate acceptable and cost-effective vector control tools which are easy to apply even when targeting only the most productive water container types.

Acknowledgements

The research was supported by the Special Programme for Research and Training in Tropical Diseases (TDR/WHO). Permanet water container covers in Venezuela were donated by Vestergaard-Frandsen company in Lausanne, Switzerland. Without a large number of dedicated researchers and field staff this study would not have been possible. In their representation we would like to mention: Myanmar:Pe Than Htun, Tin Oo, Than Win; Venezuela: Milagros Oviedo, Elci Villegas; México: Alejandra González-Moreno, Adán Zapata-Peniche, Laura Buenfil-Silva; Peru: Greg Devine, Helvio Astete, David Florin; Kenya: Charles Mbogo, Joseph Mwangangi, Rosemary Sang; Vietnam: Nguyen Thi Yen, Vu Bich Diep, Le Trung Nghia; Philippines: Grace Encelan-Brizuela, Ephraim M. Brizuela, Ferdinand V. Salazar. We also thank the many families who accepted to be part of the study and contributed to its success.

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