



Evaluation of intensified dengue control measures with interrupted time series analysis in the Panadura Medical Officer of Health division in Sri Lanka: a case study and cost-effectiveness analysis

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Summary

Background Dengue has become a major public health problem in Sri Lanka with a considerable economic burden. As a response, in June, 2014, the Ministry of Health initiated a proactive vector control programme in partnership with military and police forces, known as the Civil-Military Cooperation (CIMIC) programme, that was targeted at high-risk Medical Officer of Health (MOH) divisions in the country. Evaluating the effectiveness and cost-effectiveness of population-level interventions is essential to guide public health planning and resource allocation decisions, particularly in resource-limited health-care settings.

Methods Using an interrupted time series design with a non-linear extension, we evaluated the impact of vector control interventions from June 22, 2014, to Dec 29, 2016, in Panadura, a high-risk MOH division in Western Province, Sri Lanka. We used dengue notification and larval survey data to estimate the reduction in Breteau index and dengue incidence before and after the intervention using two separate models, adjusting for time-varying confounding variables (ie, rainfall, temperature, and the Oceanic Niño Index). We also assessed the cost and cost-effectiveness of the CIMIC programme from the perspective of the National Dengue Control Unit under the scenarios of different levels of hospitalisation of dengue cases (low [25%], medium [50%], and high [75%]) in terms of cost per disability-adjusted life-year averted (DALY).

Findings Vector control interventions had a significant impact on combined Breteau index (relative risk reduction 0·43, 95% CI 0·26 to 0·70) and on dengue incidence (0·43, 0·28 to 0·67), the latter becoming prominent 2 months after the intervention onset. The mean number of averted dengue cases was estimated at 2192 (95% CI 1741 to 2643), and the total cost of the CIMIC programme at 2016 US\$271 615. Personnel costs accounted for about 89% of the total cost. In the base-case scenario of moderate level of hospitalisation, the CIMIC programme was cost-saving with a probability of 70% under both the lowest (\$453) and highest (\$1686) cost-effectiveness thresholds, resulting in a net saving of \$20 247 (95% CI -57 266 to 97 790) and averting 176 DALYs (133 to 226), leading to a cost of -\$98 (-497 to 395) per DALY averted. This was also the case for the scenario with high hospitalisation levels (cost per DALY averted -\$512, 95% CI -872 to -115) but with a higher probability of 99%. In the scenario with low hospitalisation levels (cost per DALY averted \$690, 143 to 1379), although the CIMIC programme was cost-ineffective at the lowest threshold with a probability of 77%, it was cost-effective at the highest threshold with a probability of 99%.

Interpretation This study suggests that communities affected by dengue can benefit from investments in vector control if interventions are implemented rigorously and coordinated well across sectors. By doing so, it is possible to reduce the disease and economic burden of dengue in endemic settings.

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Introduction

Dengue, an arbovirus infection with an explosive epidemic potential, has become a global public health problem, with the number of symptomatic infections estimated to have doubled every 10 years between 1990 and 2013.¹ The disease places a major economic burden on endemic developing countries in tropical and sub-tropical regions, particularly during outbreaks.² Dengue is transmitted by *Aedes* mosquitoes, principally

Aedes aegypti and secondarily *Aedes albopictus*.³ The complex interplay between human hosts, dengue viruses, and *Aedes* mosquitoes shapes dengue transmission, but transmission dynamics are further affected by factors related to climate, natural and human-built environment, human mobility, urbanisation, and global travel and trade.⁴ Current control efforts aim to suppress dengue vector populations through source reduction, environmental management, larviciding and adulticiding, and

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Research in context

Evidence before this study

Evaluation of the effectiveness and cost-effectiveness of large-scale dengue vector control interventions is methodologically challenging, but important in public health research. There are only a few such published studies; however, methods are not standardised and study designs are questioned for their ability to generate rigorous effectiveness evidence to guide public health action and policy making. Objective and comparable measures of effectiveness are crucial to evaluate an intervention's success and its economic value compared with alternatives. Trials with cluster randomisation are considered the gold standard design for providing high-quality evidence on public health interventions introduced at population level. The issue of contamination due to human and vector mobility, however, is a key limitation for vector control programmes where interventions require coordination at large geographical scales to be effective. Furthermore, because of high cost and resource demand, these trials might not be feasible in resource-limited settings where dengue is usually endemic.

Added value of this study

Interrupted time series analysis is a quasi-experimental research design, which allows for an estimation of the counterfactual effect of interventions that are introduced over a clearly defined time period. We used this design to evaluate the public health impact of a rigorously implemented large-scale vector control programme by the National Dengue Control Unit (NDCU) in a highly affected urban area in the Western Province of Sri Lanka. The results of this empirical study provided evidence of a

significant impact of the programme on both dengue vector indices and incidence, as well as its cost-effectiveness. The main advantage of this study design over cluster randomised trials is that it accounts for trends prior to intervention over the entire area and avoids the issue of contamination resulting from vector and human mobility. Our study provides a comprehensive methodological framework to assess the effectiveness and cost-effectiveness of a population-level public health intervention delivered over a well defined intervention period.

Implications of all the available evidence

It is important to estimate the public health and economic impact of dengue interventions to empower policy makers to deploy the most effective and efficient interventions in resource-limited settings. We provided empirical evidence of the effectiveness of a community-wide dengue vector control programme focused on source reduction, which led to more than 50% reduction in dengue incidence in a highly endemic area in Western Province, Sri Lanka. Moreover, the programme proved to be cost-saving or cost-effective from the perspective of the NDCU under several scenarios. Our findings suggest that the public health sector can greatly benefit from investments in vector control programmes and reduce the disease and economic burden of dengue in endemic settings if the source reduction interventions are rigorously implemented and effectively coordinated. The methodological framework developed in this study can be used to evaluate the impact and economic value of public health response to constantly changing dengue epidemiology.

reducing human–vector contact to levels where dengue transmission is unsustainable. Even if a safe dengue vaccine becomes available in the future, vector control is likely to remain a key complementary strategy to curtail the continued spread and intensification of dengue.⁵

Dengue disproportionately affects countries in south Asia.⁶ In Sri Lanka, dengue was first serologically confirmed in 1962, and the first island-wide outbreak was reported in 1965.⁷ Since the early 2000s, progressively larger epidemics have occurred, but the magnitude of epidemics reached a major turning point in 2009.^{8,9} From 2009 to 2016, Sri Lanka experienced further increase in the prevalence of dengue, with the total number of cases going up from 35 008 to 55 150.⁸ Today, dengue cases are reported from almost all the districts in the country and the infection is hyperendemic with the co-circulation of all four dengue virus serotypes.⁹ Nearly 60% of the total cases are reported from three urban districts in the Western Province—namely, the Colombo, Gampaha, and Kalutara districts.⁸ Although the determinants of dengue transmission vary across the island, climatic conditions, unplanned urbanisation, and inadequate garbage disposal and recycling systems create suitable breeding habitats for vector proliferation.¹⁰ The peak

dengue transmission period is June–July following the southwest monsoon in April–May. A less severe peak occurs in December–January after the northeast monsoon in October–December. The El Niño cycle every 3–4 years is strongly associated with dengue transmission in Sri Lanka, which is further mediated by local rainfall and temperature anomalies.¹⁰

The National Dengue Control Unit (NDCU) is the central body dedicated to providing technical guidance and implementing routine and outbreak response activities, including source reduction through door-to-door inspection and biological and chemical larval and adult control in all provinces of the country. A Presidential Task Force on Dengue Prevention was established in May, 2010, to strengthen intersectoral collaboration and coordinate dengue control activities at national, provincial, and district levels.¹¹ In response to the increasing severity of dengue epidemics, the Task Force introduced a new public health policy in June, 2014, aimed at intensifying source reduction through a large-scale door-to-door premises inspection programme in the highly affected Western Province. Coordinated by public health authorities, the programme was implemented in partnership with military and police

and is known as the Civil-Military Cooperation (CIMIC) programme.^{11,12}

Evaluating the effectiveness of population-wide public health programmes involves conducting counterfactual analysis to estimate health outcomes in the absence of intervention. This is a challenging but important task in public health research. Interrupted time series (ITS) analysis is a rigorous quasi-experimental research design for studying the effectiveness of such large-scale programmes. It is most suited for interventions rolled out at well defined timepoints and when data are routinely collected at multiple timepoints before and after intervention.^{13,14} ITS analysis has also a clear advantage over complex and costly trials with cluster randomisation where changes in viruses and vectors in intervention areas can have an effect on disease transmission in control areas due to human and vector mobility. This so-called contamination effect poses an intrinsic difficulty in studying the effect of interventions that need to be geographically coordinated at larger scales to be effective.¹⁵ Besides the evidence on public health impact, the cost-effectiveness of such programmes is considered key to informing resource allocation decisions in resource-limited health-care settings. In this study, we evaluated the effectiveness of intensified vector control measures through the CIMIC programme on dengue incidence in a highly endemic urban area in the Western Province of Sri Lanka using an ITS design while adjusting for time-varying confounders. We further assessed the costs and cost-effectiveness of the CIMIC programme from the perspective of the NDCU.

Methods

Study setting and dataset

The Panadura Medical Officer of Health (MOH) division is one of the 50 divisions most highly affected by dengue in Sri Lanka. It is situated in the Kalutara district, which is one of the three districts with the greatest burden, accounting for 60% of the total dengue cases every year in Sri Lanka. Panadura MOH is an urban area with a population of 243 984 people distributed over a land area of about 72 km².¹⁶ Weekly dengue surveillance data for the study period Jan 22, 2010, to Dec 29, 2016, were obtained from the National Communicable Disease Surveillance System in which symptomatic patients with dengue were documented according to a standard case definition of dengue.^{8,17} Breteau index data (ie, number of containers positive for larvae or pupae per 100 houses inspected) were extracted from sentinel vector surveillance reports for the same period; we used the combined Breteau index, which comprised containers positive for *A aegypti*, *A albopictus*, or both. We also collected data on time-varying confounding variables during the study period: rainfall and temperature data were extracted from a nearby meteorological monitoring station and the Oceanic Niño Index (ONI) data from the US National Oceanic and Atmospheric Administration's

Centre for Weather and Climate Prediction.¹⁸ A thorough description of the data can be found in the appendix (pp 1–3).

See Online for appendix

The CIMIC programme

Dengue high-risk administrative units in Panadura were identified on the basis of past dengue case notifications. Inspection teams were then allocated according to the number of premises to be inspected in each unit. Each team had at least one person from public health authorities, one from the military, and one from police forces. Together with communities, each team inspected at least 50 premises daily to identify and remove vector breeding sites, using standard checklists. These interventions were implemented in an episodic manner in phases. Intervention phases had a baseline duration of 2 days and took place more frequently—extending the phase to a maximum of 9 days—before and during seasonal monsoon rains. A team of experts at the MOH, district, and national levels assured implementation quality through supervision and on-the-job training. A performance summary of programme activities was submitted daily to the NDCU, including number of premises inspected, breeding sites detected, premises where breeding sites were removed, and legal actions taken. At the conclusion of each intervention phase, programme activities were evaluated by all stakeholders, making the approach proactive and adaptive.¹² Overall, Panadura was exposed to 39 intervention phases for a total of 125 days over 31 months, with 35 teams participating in each phase (appendix pp 4–5).

ITS analysis

We made a non-linear extension to the ITS design and estimated the reduction in Breteau index and dengue incidence in Panadura before and after the intervention using two separate ITS models. We assumed a quasi-Poisson distribution and a logarithmic link function in a generalised additive model framework (mgcv package in R) for the analysis.¹⁹ In the models, the estimated Breteau index B_t and number of dengue cases D_t at timepoint t were adjusted flexibly for confounding variables using penalised cubic spline functions, including temporal lag terms. The vector ITS model for the estimated Breteau index was formulated as follows:

$$\log(E[B_t]) = \alpha + s(\text{rain}_{t-1,t-2}) + s(\text{temp}_{t-1}) + s(\text{ONI}_{t-3,t-4}) + \beta_1 \text{time}_t + \beta_2 \text{int}_t$$

and the dengue model for the estimated number of dengue cases as follows:

$$\log(E[D_t]) = \alpha + s(\text{rain}_{t-1,t-2}) + s(\text{temp}_{t-2}) + s(\text{ONI}_{t-5,t-6}) + \beta_1 \text{time}_t + \beta_2 \text{int}_{t-2}$$

where t is time in months from Jan 1, 2010, to Dec 29, 2016; B_t is the monthly combined Breteau index

measured in Panadura at time t ; D_t is the aggregated monthly dengue cases from 2010 to 2016 in Panadura at time t ; and s represents a natural cubic spline function with 4 degrees of freedom. The vector model was specified by a spline function for rainfall lag 1 and 2 months (ie, $\text{rain}_{t-1, t-2}$), temperature lag 1 month (temp_{t-1}), and ONI lag 3 and 4 months ($\text{ONI}_{t-3, t-4}$). The dengue model was specified by a spline function for rainfall lag 1 and 2 months ($\text{rain}_{t-1, t-2}$), temperature lag 2 months (temp_{t-2}), and ONI lag 5 and 6 months ($\text{ONI}_{t-5, t-6}$). The selected lag dimensions for climate variables in the models were based on our findings for the same study area using distributed lag non-linear models in a previous study.¹⁰ We developed the models by a rigorous investigation of all variables and lags using model fit statistics and model residual diagnostics. A time variable, time_t , was introduced to account for general time trends in dengue cases over the 7-year study period. Additionally, the binary variable marking the onset of the intervention, int_t , was set to 0 during the pre-intervention period and to 1 during the intervention period—ie, for any time t from July 1, 2014, onwards. The model of dengue incidence differed from the model of Breteau index in the int_t variable because it was lagged 2 months to account for the lagged effect of interventions on dengue cases. This adjustment was not needed in the Breteau index model as the reduction in vector indices is instantaneous following source reduction intervention. An additional analysis showing the relationship between Breteau index and dengue incidence is described in the appendix (pp 3–4). Estimates for the counterfactual scenario were obtained by setting the variable int_t to 0 during the intervention period.¹³ The difference between estimated dengue cases with and without intervention was considered as averted dengue cases in Panadura. A robustness analysis was done to test if the intervention effect changed when the intervention onset time was modified in the model (appendix pp 6–9). The SEs were computed for averted dengue cases. Relative risk (RR) was calculated by exponentiating the coefficient of the intervention variable.

Health economic evaluation

We first did a retrospective cost analysis of the CIMIC programme in Panadura MOH from June 22, 2014, to Dec 29, 2016. Using financial expenditure records, we extracted and analysed direct costs borne by public health authorities to plan and implement the interventions. The time costs of community members were negligible and thus excluded. We then calculated incremental cost-effectiveness ratios (ICERs) as the ratio of incremental costs to incremental health benefits of the CIMIC programme over the study period. Incremental costs were estimated as intervention costs minus treatment cost savings due to averted dengue cases. We obtained treatment costs of ambulatory and hospitalised dengue cases from a 2012 costing study we did in Sri Lanka.²

Incremental health benefits were expressed in disability-adjusted life-years (DALYs) averted.

We assumed that, on average, 50% of the estimated dengue cases would have been hospitalised and the rest would have been treated in ambulatory settings. This assumption was made because dengue surveillance data used in this analysis were primarily based on hospital-based notifications of cases. The cost-effectiveness results were, however, expected to be sensitive to the changes in this variable because of treatment cost savings associated with averted hospitalisations. In addition to this base-case scenario of moderate level of hospitalisation (50% of cases), we explored the scenarios of low (25%) and high (75%) levels of hospitalisation to assess the cost-effectiveness of the programme. For all scenarios, we then estimated the number of averted cases of dengue fever and dengue haemorrhagic fever among hospitalised paediatric and adult patients using dengue surveillance data from the Kalutara district. We next estimated the number of averted dengue deaths among ambulatory and hospitalised patients with dengue using case fatality rates in the published literature.²⁰ The median DALYs lost during the onset, recovery, and persistent-symptom phase were assumed to be 0·031 for an ambulatory case and 0·035 for a hospitalised case.²¹ To estimate DALYs lost due to premature mortality, we assumed an average life expectancy of 70·6 years for paediatric patients and 46·9 years for adult patients using life tables for Sri Lankan men and women.^{22,23} In our DALY calculations, a yearly discount rate of 3·5% was used.²⁴ Valuing a year of healthy life equally at all ages, age weighting was not applied. In the final step, we combined DALYs averted due to dengue cases and deaths over the study period.

We did probabilistic sensitivity analysis using Monte Carlo simulation ($n=10\,000$) to address uncertainty in key input parameters across all scenarios of hospitalisation levels. We varied all other input parameters over their full range (appendix p 13) to produce 95% CIs. To reflect the opportunity costs of committing resources to a specific intervention as opposed to an alternative under a budget constraint, we used the thresholds estimated by Woods et al²⁵ for Sri Lanka, applying both the lowest (\$453) and highest (\$1686) estimates, given in 2013 US\$. All other costs in our analyses are in 2016 US\$. The CIMIC programme was classified as cost-effective if the cost per DALY averted was less than the threshold. Negative ICER values indicated a cost-saving programme compared with no programme. We used R (version 3.5.1) for the ITS analysis and TreeAge Pro Suite 2018 (TreeAge Software; Williamstown, MA, USA) for the cost-effectiveness analysis. We followed the CHEERS checklist as our reporting guide.²⁶

Role of the funding source

This study was not funded. All data were collected with the administrative approval of the Provincial Director of Health Service, Western Province, Sri Lanka. The first

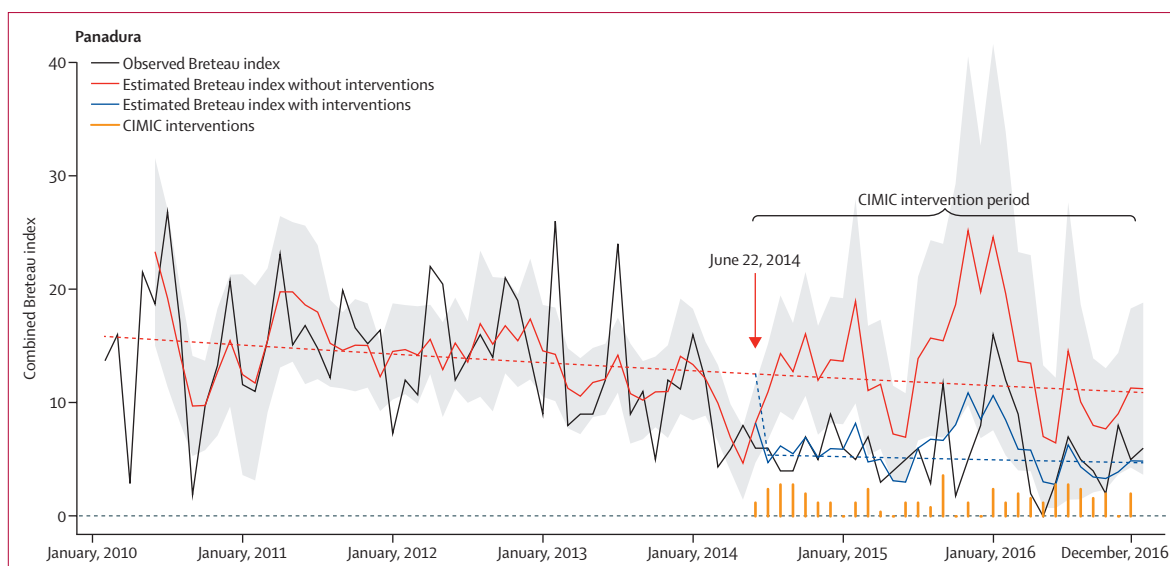


Figure 1: Time series plot of combined Breteau index from 2010 to 2016 in Panadura MOH division, Kalutara district, Sri Lanka

Counterfactual predictions shown are in the absence of intervention. The orange vertical bars show the number of CIMIC intervention days per month, with the highest number (9 days) reached in September, 2015 (see appendix pp 5–6 for breakdown of intervention days). The blue dashed line indicates the trend of and the level of change in combined Breteau index after intervention whereas the red dashed line indicates the trend of predicted combined Breteau index in the absence of intervention. The grey zone represents the 95% CIs for predicted combined Breteau index. MOH=Medical Officer of Health. CIMIC=Civil-Military Cooperation.

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

Results

Our analysis suggests a gradual reduction in the combined Breteau index up until early 2014, followed by a large drop in Breteau index from 13 to 6, concomitant with the onset of intervention in Panadura (figure 1). The climate-based counterfactual predictions showed much higher values for the combined Breteau index compared to what was observed. The coefficient of the intervention variable was significant, with an estimated reduction of 0.43 (95% CI 0.26–0.70) in RR for the intervention period.

By contrast with the downwards trend in observed Breteau index, we observed a gradual increase in the number of dengue cases from January, 2010, to June, 2014 (figure 2). Despite this increasing trend, the interventions led to a reduction in dengue cases of 46 cases per month with a delay of 2 months after the onset of intervention. The model coefficient for the intervention variable was significant, with an estimated reduction of 0.43 (95% CI 0.28–0.67) in RR following 2 months after the start of the intervention (appendix p 7), suggesting that the CIMIC programme was effective. The counterfactual analysis indicated increasing trends (figure 2). Over the entire intervention period of 31 months, the mean number of averted dengue cases was estimated at 2192 (1741–2643). To assess the robustness of the estimated RR, we tested the sensitivity of the estimate by varying the onset time of the intervention in statistical

model fitting. This analysis illustrated that a significant RR reduction was only observed with start dates close in time to the real onset date of the intervention. This supported the robustness of the estimated intervention effect associated with the CIMIC programme (appendix pp 9–10).

The total cost of the CIMIC programme in Panadura between June, 2014, and December, 2016, was estimated at \$271 615 (table 1). The programme relied primarily on workers for identification and removal of vector breeding sites and did not require purchase and use of any consumables (eg, larvicides, insecticides, kerosene oil). The time-limited interventions neither led to any changes in infrastructural facilities at the MOH level nor required use or purchase of any major equipment and machinery. The programme costs were hence recurrent and included personnel time costs (public health, military, police), implementation costs such as transportation costs to and from high-risk administrative units, refreshment costs for inspection teams, stationery costs (paper, printing for data collection), and utilities (telephone, electricity, water), as well as other miscellaneous expenditures. Personnel costs accounted for about 89% of the total cost, highlighting the labour-intensive nature of the interventions (table 1). In 2012, the Panadura MOH division had a population of 243 984 people.¹⁶ The cost per person protected over the intervention period was estimated at \$1.11, which corresponds to an annual per-capita cost of \$0.37 for the public sector.

In our cost-effectiveness analysis, we found that the treatment cost savings from treating fewer dengue cases in ambulatory and hospital settings due to the intervention

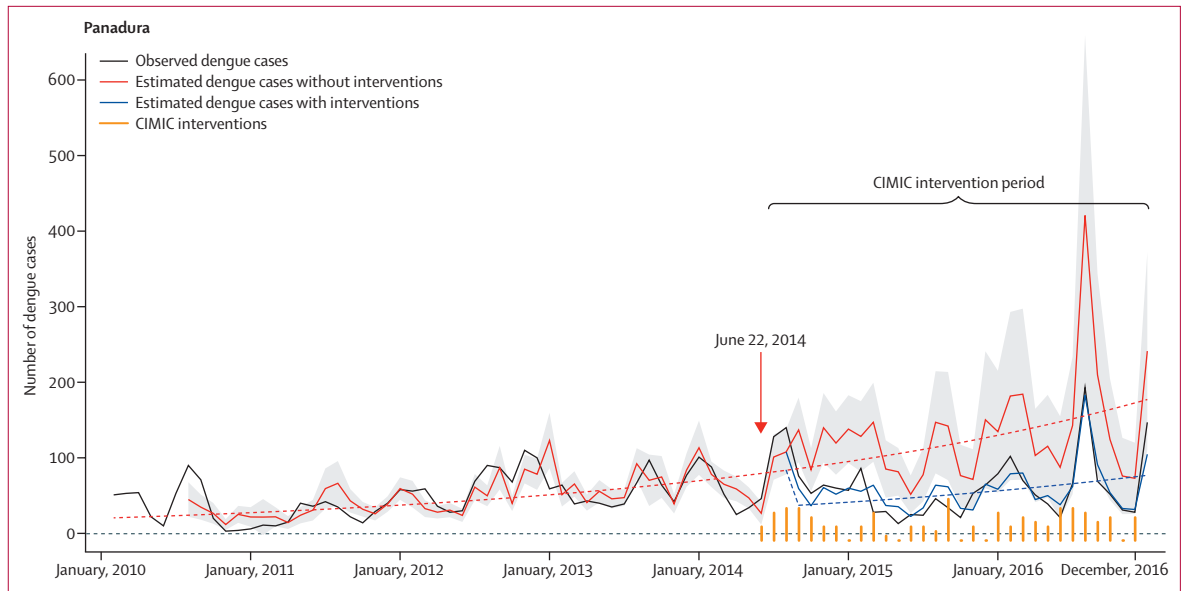


Figure 2: Time series plot of estimated dengue cases from 2010 to 2016 in Panadura MOH division, Kalutara district, Sri Lanka
 Counterfactual predictions shown are in the absence of intervention. The orange vertical bars show number of CIMIC intervention days per month, with the highest number (9 days) reached in September, 2015 (see appendix pp 5–6 for breakdown of intervention days). The blue dashed line indicates the trend of and the level of change in monthly dengue cases after intervention whereas the red dashed line indicates the trend of predicted monthly dengue cases in the absence of intervention. The grey zone represents the 95% CIs for predicted dengue cases each month. MOH=Medical Officer of Health. CIMIC=Civil-Military Cooperation.

	Costs
Personnel	241 475 (88.9%)
Refreshments	17 748 (6.5%)
Transportation	7 839 (2.9%)
Utilities	3 220 (1.2%)
Stationery	629 (0.2%)
Miscellaneous	704 (0.3%)
Total costs	271 615 (100.0%)

Percentages are of total cost. All costs are in 2016 US\$.

Table 1: Costs of the Civil-Military Cooperation programme in Panadura Medical Officer of Health division, Kalutara district, Sri Lanka

were \$291 990 (95% CI 226 560 to 358 234) in the base-case scenario, offsetting the CIMIC programme costs and yielding a net saving of \$20 247 (–57 266 to 97 760). The programme was estimated to avert 176 DALYs (95% CI 133 to 226) over the study period. In our probabilistic sensitivity analysis, the average cost per DALY averted was negative with a probability of 70%, indicating a cost-saving programme under both the lowest (\$453) and the highest (\$1686) cost-effectiveness thresholds. This was also the case for the scenario with a high hospitalisation level (ie, 75% of cases); however, in this case the programme was cost-saving with a higher probability of 99%. In the scenario in which the hospitalisation level is low (25%), although the CIMIC programme proved to be not cost-effective at the lowest threshold with a probability of 77%, it was cost-effective at the highest threshold with a probability of 99% (table 2; appendix pp 10–11).

Discussion

The impact of vector control on dengue incidence has been questioned worldwide.²⁷ Accurate estimates of averted disease burden of dengue following public health interventions are more difficult to obtain compared with other infectious diseases that pose similarly serious public health threats.²⁸ Dengue exhibits complex spatial and temporal dynamics under the effect of biological, human, and environmental factors.^{4,6} In this empirical study, we provided evidence of a significant impact on both vector indices and dengue incidence of a community-wide vector control programme in Sri Lanka. Moreover, the programme proved to be cost-saving or cost-effective from the perspective of the NDCU under several scenarios.

Because the onset of the CIMIC programme was well defined and there were no major changes to public health policies on vector control and disease surveillance during the study period, the ITS analysis was an appropriate research design to assess the public health impact of interventions.^{29,30} A main advantage of this design over others is that it makes full use of the longitudinal nature of the data and accounts for pre-intervention trends through regression modelling.³¹ Other study designs, such as cluster randomised trials, can also evaluate effectiveness but have been challenged by the problem of contamination and spillover effects due to human and vector mobility and its potential impact on disease transmission dynamics, especially in the case of vector-borne disease such as dengue.^{32,33} Furthermore, evaluation of large-scale coordinated interventions, such as

	Low hospitalisation level (25%)	Moderate hospitalisation level (50%)*	High hospitalisation level (75%)
Programme cost	271 893 (229 809 to 313 998)	271 743 (229 789 to 313 951)	271 349 (229 892 to 313 851)
Treatment cost savings	190 968 (150 391 to 234 262)	291 990 (226 560 to 358 234)	391 471 (305 551 to 481 884)
Incremental cost	80 925 (22 465 to 139 384)	-20 247 (-97 760 to 57 266)	-120 122 (-215 520 to -24 723)
DALYs averted	122 (95 to 152)	176 (133 to 226)	231 (172 to 301)
ICER: cost per DALY averted	690 (143 to 1379)	-98 (-497 to 395)†	-512 (-872 to -115)†

Data are mean (95% CI). All costs and thresholds are in 2016 US\$. DALY=disability-adjusted life-year. ICER=incremental cost-effectiveness ratio. *Base case. †Cost saving.

Table 2: Cost-effectiveness analysis of the Civil-Military Cooperation programme in Panadura Medical Officer of Health division, Kalutara district, Sri Lanka

the one evaluated here, requires avoiding contamination, which is by nature difficult to design using cluster randomised trials with reasonably comparable control clusters. We obtained robust estimates of entomological and epidemiological outcomes by addressing the methodological issues related to the ITS design, such as seasonality and climate variability, and by assessing autocorrelation and overdispersion of data^{10,13} (appendix pp 5–9). Furthermore, the non-significant results of sensitivity analysis with modified onset time capturing similar temporally related interventions during previous epidemic years lend support to the observed significant intervention effect in 2014.

The cornerstones of the CIMIC programme were door-to-door premises inspection and removal of mosquito breeding places. Therefore, a large proportion (89%) of the total cost was time cost of public health and support staff associated with planning and implementation activities. This highlights the human resource-intensive nature of these interventions, which is similar to other dengue endemic settings.^{34,35} In a costing study done in Colombo, Sri Lanka, the annual per-capita cost of dengue preventive and control activities was estimated at \$0·42 during the epidemic year of 2012.² This cost can be considered as the upper estimate for routine vector control activities in highly affected districts in Sri Lanka. The annual per-capita cost of the CIMIC programme (\$0·37) is similarly high, suggesting that the implementation of such intensified control measures relying on personnel would nearly double the total per-capita cost of dengue vector control. By contrast, the outbreak response in the city of Guantanamo, Cuba, included the intensive use of insecticides for adult vector control and led to a substantial increase in costs by about \$1 per inhabitant per year.³⁴ Few studies have evaluated the costs and cost-effectiveness of dengue vector control interventions in non-epidemic and epidemic years, and recent reviews indicate that there is a lack of consistency in the way costs have been estimated and dengue interventions evaluated across different contexts, making generalisations around costs and cost-effectiveness results difficult.^{34,35}

Our statistical and economic analyses have a number of limitations. First, the CIMIC programme was implemented in a densely populated urban area with high dengue disease burden. Our results are therefore solely

applicable to other urban settings with similar dengue transmission dynamics. Nonetheless, the ITS model can be adjusted using location-specific climate and dengue data to estimate context-specific health effects, and costs should always be informed by the local implementation setting to accurately reflect the local policy context. Although there might not be sufficient readiness to undertake such analyses in endemic countries, a more concerted culture-building and capacity-building effort is often necessary to address institutional and other roadblocks and provide opportunities for more technical uses of existing data. Second, the effectiveness and the sustainability of the programme was challenged by the large outbreak in 2017, demanding programmatic changes with intensified resource mobilisation. Third, since we adopted the perspective of the NDCU in the analysis, the costs of dengue illness incurred by patients and the broader society was not included. Our findings, however, suggest that the CIMIC programme would be economically worthwhile even with a narrow focus on provider costs. We made assumptions when estimating the proportion of dengue cases requiring hospitalisation, which might have influenced the cost-effectiveness results because of substantially higher costs of hospitalisation compared with ambulatory care; however, we did an extensive sensitivity analysis, which was complemented by a scenario analysis targeted at this parameter.

The CIMIC programme was rigorously implemented and achieved effective coordination among many different stakeholders in the society, which could potentially explain its success compared with other vector control programmes in similar endemic settings.³⁵ High-level political commitment, dedicated public health staff along with police and military, and high community acceptability ensured its rigour and sustainability. We provided empirical evidence of the effectiveness of a community-wide dengue vector control programme focused on source reduction, which led to more than 50% reduction in dengue incidence in a highly endemic area in the Western Province of Sri Lanka. It is likely that the effectiveness and sustainability of the programme could be further improved in the presence of highly targeted vaccination with medium efficacy.⁵ The methodological framework developed in this study can be used to evaluate the impact and economic value of public health response to constantly changing dengue epidemiology.

Contributors

PL, JR, and YT conceived and designed the study. PL did statistical and economic analyses. PL and YT drafted the manuscript. JR provided statistical input on interrupted time series analysis and YT provided input on health economic evaluation. All authors contributed to the interpretation of findings, provided revisions to the manuscript, and approved the final manuscript.

Declaration of interests

We declare no competing interests.

References

- WHO. Dengue and severe dengue. Geneva: World Health Organization, 2017.
- Thalagala N, Tissera H, Palihawadana P, et al. Costs of dengue control activities and hospitalizations in the public health sector during an epidemic year in urban Sri Lanka. *PLoS Negl Trop Dis* 2016; **10**: e0004466.
- WHO, Special Programme for Research and Training in Tropical Diseases. Dengue guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization, 2009.
- Banu S, Hu W, Hurst C, Tong S. Dengue transmission in the Asia-Pacific region: impact of climate change and socio-environmental factors. *Trop Med Int Health* 2011; **16**: 598–607.
- Fitzpatrick C, Haines A, Bangert M, Farlow A, Hemingway J, Velayudhan R. An economic evaluation of vector control in the age of a dengue vaccine. *PLoS Negl Trop Dis* 2017; **11**: e0005785.
- Ooi EE, Gubler DJ. Dengue in Southeast Asia: epidemiological characteristics and strategic challenges in disease prevention. *Cad Saude Publica* 2009; **25** (suppl 1): S115–24.
- Messer WB, Vitarana UT, Sivananthan K, et al. Epidemiology of dengue in Sri Lanka before and after the emergence of epidemic dengue hemorrhagic fever. *Am J Trop Med Hyg* 2002; **66**: 765–73.
- Epidemiology Unit, Ministry of Health Sri Lanka. Disease surveillance and trends. http://www.epid.gov.lk/web/index.php?option=com_casesanddeaths&Itemid=448&lang=en (accessed April 30, 2018).
- Tam CC, Tissera H, De Silva AM, De Silva AD, Margolis HS, Amarasinghe A. Estimates of dengue force of infection in children in Colombo, Sri Lanka. *PLoS Negl Trop Dis* 2013; **7**: e2259.
- Liyanage P, Tissera H, Sewe M, et al. A spatial hierarchical analysis of the temporal influences of the El Niño-Southern Oscillation and weather on dengue in Kalutara District, Sri Lanka. *Int J Environ Res Public Health* 2016; **13**: 1087.
- Tissera H, Pannila-Hetti N, Samaraweera P, Weeraman J, Palihawadana P, Amarasinghe A. Sustainable dengue prevention and control through a comprehensive integrated approach: the Sri Lankan perspective. *WHO South East Asia J Public Health* 2016; **5**: 106–12.
- Tissera HA, Samaraweera PC, Jayamanne BDW, et al. Civil-military cooperation (CIMIC) for an emergency operation against a dengue outbreak in the western province, Sri Lanka. *Dengue Bull* 2014; **38**: 64–77.
- Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2016; **46**: 348–55.
- Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. *Acad Pediatr* 2013; **13** (suppl 6): S38–44.
- Wilson AL, Boelaert M, Kleinschmidt I, et al. Evidence-based vector control? Improving the quality of vector control trials. *Trends Parasitol* 2015; **31**: 380
- Department of Census and Statistics. Census of population and housing 2012—final report. Colombo, Sri Lanka: Department of Census and Statistics Sri Lanka, 2012.
- Tissera H, Amarasinghe A, Weeraman J, Wijewickrama A, Palihawadana P, Fernando L. Expediency of dengue illness classification: the Sri Lankan perspective. *WHO South East Asia J Public Health* 2014; **3**: 5–7.
- NOAA. Cold and warm episodes by season. NOAA/National Weather Service. https://origin.cpc.ncep.noaa.gov/products/analysis_monitoring/ensostuff/ONL_v5.php (accessed May 5, 2018).
- Wood S. mgcv: mixed GAM computation vehicle with automatic smoothness estimation. <https://cran.r-project.org/web/packages/mgcv/index.html> (accessed Jan 15, 2018).
- Tissera H, Amarasinghe A, Gunasena S, et al. Laboratory-enhanced dengue sentinel surveillance in Colombo District, Sri Lanka: 2012–2014. *PLoS Negl Trop Dis* 2016; **10**: e0004477.
- Zeng W, Halasa-Rappel YA, Durand L, Coudeville L, Shepard DS. Impact of a nonfatal dengue episode on disability-adjusted life years: a systematic analysis. *Am J Trop Med Hyg* 2018; **99**: 1458–65.
- Department of Census and Statistics. Life tables for Sri Lanka 2011–2013 by district and sex. Colombo, Sri Lanka: Department of Census and Statistics, 2014.
- WHO. WHO Global Health Observatory data repository. Geneva: World Health Organization, 2018.
- NICE. The guidelines manual. London: National Institute for Health and Clinical Excellence, 2012.
- Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016; **19**: 929–35.
- Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. *Int J Technol Assess Health Care* 2013; **29**: 117–22.
- Bowman LR, Donegan S, McCall PJ. Is dengue vector control deficient in effectiveness or evidence?: systematic review and meta-analysis. *PLoS Negl Trop Dis* 2016; **10**: e0004551.
- Beatty ME, Beutels P, Meltzer MI, et al. Health economics of dengue: a systematic literature review and expert panel's assessment. *Am J Trop Med Hyg* 2011; **84**: 473–88.
- Biglan A, Ary D, Wagenaar AC. The value of interrupted time-series experiments for community intervention research. *Prev Sci* 2000; **1**: 31–49.
- Kontopantelis E, Doran T, Springate DA, Buchan I, Reeves D. Regression based quasi-experimental approach when randomisation is not an option: interrupted time series analysis. *BMJ* 2015; **350**: h2750.
- Soumerai SB, Starr D, Majumdar SR. How do you know which health care effectiveness research you can trust? A guide to study design for the perplexed. *Prev Chronic Dis* 2015; **12**: E101.
- Shepard DS, Undurraga EA, Betancourt-Cravioto M, et al. Approaches to refining estimates of global burden and economics of dengue. *PLoS Negl Trop Dis* 2014; **8**: e3306.
- Ramadana AL, Tozan Y, Lazuardi L, Rocklöv J. A combination of incidence data and mobility proxies from social media predicts the intra-urban spread of dengue in Yogyakarta, Indonesia. *PLoS Negl Trop Dis* 2019; **13**: e0007298.
- Baly A, Toledo ME, Rodriguez K, et al. Costs of dengue prevention and incremental cost of dengue outbreak control in Guantanamo, Cuba. *Trop Med Int Health* 2012; **17**: 123–32.
- Constenla D, Garcia C, Lefcourt N. Assessing the economics of dengue: results from a systematic review of the literature and expert survey. *Pharmacoeconomics* 2015; **33**: 1107–35.