The Relative Role of Climate Variation and Control Interventions on Malaria Elimination Efforts in El Oro, Ecuador: A Modeling Study.

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Supplementary Material

Statistical analysis in R-INLA

S1.1. Zero-inflated negative binomial models

Zero-inflated models have been developed to account for the high occurrence of zeros observed in overdispersed count data. A standard negative binomial model for the malaria case data in El Oro 1990-2018, would assume monthly malaria cases, y_{st} in each canton (s = 1,…14) for each timestep (t = 1,…,348) follow a negative binomial distribution $y_{st} \sim$ NegBin(μ_{st}, κ), where μ_{st} is the mean number of monthly cases of malaria in each canton, with parameter κ accounting for overdispersion frequently observed with count data. The zero-inflated negative binomial model assumes that each zero j, has a probability π, to arise from the negative binomial distribution and a probability, 1 - π to arise as a result of a non-zero being undetected (excess zero). The zeros in the data are therefore modelled as a mixture of the negative binomial distribution and the logit distribution (Rue, Martino, & Chopin, 2009). The distribution of y_{st} can then be written as:

$$Pr\left(y_{st} = j\right) = \begin{cases} \pi_{\mathrm{i}} + (1 - \pi_{\mathrm{i}})\ \mathrm{NegBin}\left(y_{\mathrm{i}} = 0\right) & \text{when } j = 0 \\ (1 - \pi_{\mathrm{i}})\ \mathrm{NegBin}\ \left(y_{\mathrm{i}}\right) & \text{when } j > 0 \end{cases}$$

S1.2. Prior distribution specifications

Model parameters were estimated in a Bayesian framework using Integrated Nested Laplace Approximation (INLA) and implemented in R-INLA (http://www.r-inla.org/) using R version 3.6.0. Annual parasite incidence was modelled using case counts by multiplying the model offset, population per 1,000, by 12 to align with the monthly case counts. Unstructured random effects were included in the model framework to account for unknown and unobserved confounding factors influencing malaria in El Oro, such as healthcare access and population movements. These random effects introduce an extra source of variability into the model that can assist in modelling overdispersion (Lowe, Cazelles, Paul, & Rodó, 2016). The annual cycle of malaria was accounted for by assigning autocorrelated random effects for each month, m_t. The monthly effect was assigned a random walk prior, in which the effect in one month is derived from the effect in the previous month, $m_t - m_{t-1} \sim N(0, \sigma^2_\beta)$, where β is the parameter estimate for each month January-December. Random effects for each year of the study, y_t (1990-2018) were assigned exchangeable priors, $y_t \sim N(0, \sigma^2_y)$. Hyperparameters for the random effects were assigned the default gamma prior on the precisions, the inverse of the variance $\tau = 1/\sigma^2$ (Lowe *et al*., 2018). The fixed effects in the models were assigned the default prior in R-INLA, $\beta \sim N(0,1000)$. Non-linear relationships for the climate variables (minimum temperature, precipitation) were introduced through the use of a random walk prior of order 1.

References

Lowe, R., Cazelles, B., Paul, R., & Rodó, X. (2016). Quantifying the added value of climate information in a spatio-temporal dengue model. *Stochastic Environmental Research and Risk Assessment*, *30*(8), 2067–2078. https://doi.org/10.1007/s00477-015-1053-1

Lowe, R., Gasparrini, A., Van Meerbeeck, C. J., Lippi, C. A., Mahon, R., Trotman, A. R., … Stewart-Ibarra, A. M. (2018). Nonlinear and delayed impacts of climate on dengue risk in Barbados: A modelling study. *PLOS Medicine*, *15*(7), e1002613. https://doi.org/10.1371/journal.pmed.1002613

Rue, H., Martino, S., & Chopin, N. (2009). Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, *71*(2), 319–392. https://doi.org/10.1111/j.1467-9868.2008.00700.x

S2. Influence of interventions on malaria risk in El Oro

Detailed monthly and district-level data of vector control interventions that were implemented across El Oro were provided by the Ecuadorian Ministry of Health for the period 2001-2015. Monthly estimates per canton for three control measures were available (Figure S1). The first measure was for the number of households that were sprayed using indoor residual spraying (IRS) with different insecticides; deltamethrin 5% concentrated suspension, deltamethrin 2.5%, malathion 50%, alphacypermethrin 10% concentrated suspension and betacipermethrin 2.5%. The number of households that were fogged, using a backpack fogger that creates a fog of insecticide to treat both inside and outside the home, for which 2.5% deltamethrin concentrated emulsion was used. Finally, data were available for ultra-low volume (ULV) fumigation, which is performed by spraying entire neighborhoods, or blocks using 96% malathion. These interventions were all carried out at different times with varying intensity, up until 2015.

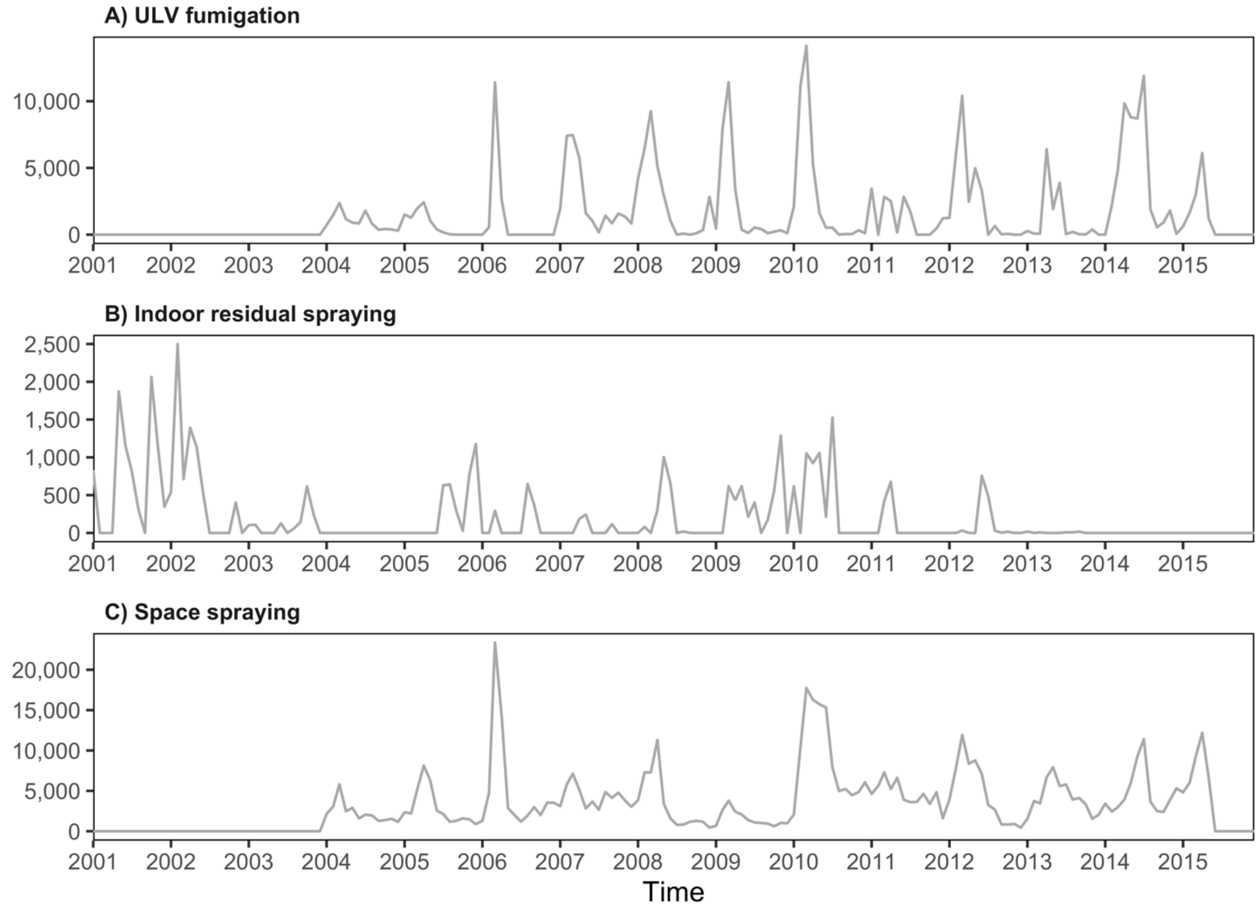

Figure S1. Vector control interventions implemented in El Oro 2001-2015. Total number of A) urban blocks fogged by ULV fumigation, B) houses sprayed by indoor residual spraying and C) houses space sprayed, per year.

Other malaria interventions, such as smaller scale vector control programs and insecticide treated net (ITN) distribution were likely implemented before and after this time period, but no detailed data were available. We wanted to determine how influential the intervention data available for the period 2001-2015 were in the fitted models. We tested if any of the variation in malaria incidence due to the interventions could be captured in the random effects structure in the full model. We wanted to assess the extent to which random effects could account for these variations in the absence of detailed intervention data for a longer time period or another location without such data.

We constructed two Bayesian hierarchical mixed models, for each malaria parasite, one to take advantage of the whole time series of case data for the period 1990-2018, with the assumption that interannual random effects can be used to account for variation caused by the interventions and other unknown and unmeasured factors, such as changes to malaria treatments and diagnostics. This model is referred to as the main model. Another model was formulated for the time period 2001-2015 and included the available data on the control measures implemented. This model is referred to as the intervention model. All other explanatory variables and random effects remained the same. We compared the posterior distributions for *P. falciparum* and *P. vivax* malaria incidence between 2001-2015 from the full models for the whole study period, without the intervention information to distributions from the intervention models. There was a greater amount of uncertainty in the model posterior distributions of the intervention models, especially between 2010-2015 and the posterior distributions from the full models were closer to the actual observed incidence (Figure S2).

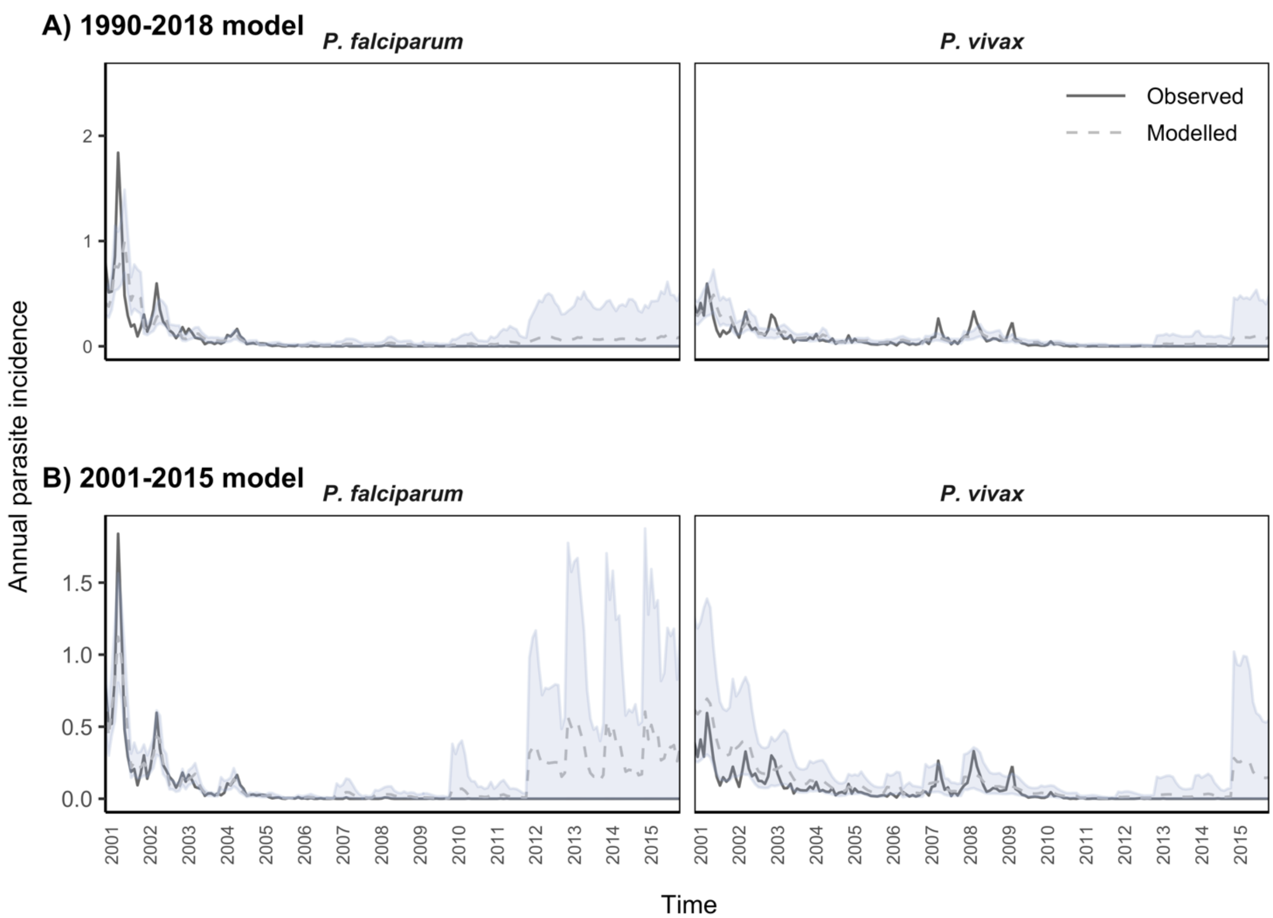

Figure S2. Model posterior distributions with and without intervention information for *P. falciparum* and *P. vivax* malaria in El Oro 2001-2015. Observed (grey solid line), posterior mean (blue dashed line) and 95% credible intervals (blue shading) for annual parasite incidence (API) for a) the full model for the whole time period (1990-2018) without intervention data and b) the intervention model for the period 2001-2015 including intervention data.

Table S1. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI), deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for intervention models of *P. falciparum* and *P. vivax* malaria in El Oro 2001-2015 that include the control measures, indoor residual spraying, ULV fumigation and space spraying, at time lags from 0-3 months. Time lags highlighted in grey are those selected to be used in the final model.

Control measure	Parasite	Lag	Estimate	LCI	UCI	DIC	WAIC
Indoor residual spraying	*P. falciparum*	0	0.01	-0.04	0.06	3752.37	3758.1
		1	0.02	-0.03	0.08	3754.06	3759.12
		2	0.02	-0.03	0.08	3754.22	3759.61
		3	0.03	-0.02	0.09	3746.14	3751.67
	P. vivax	0	0.03	-0.10	0.35	6013.44	6021.71
		1	0.01	-0.05	0.08	6015.79	6023.96
		2	0.02	-0.04	0.08	6015.51	6023.83
		3	-0.04	-0.1	0.02	6013.9	6021.6
ULV fumigation	*P. falciparum*	0	0.02	-0.03	0.08	3754.39	3760.06
		1	0.03	-0.03	0.08	3752.99	3758.44
		2	0.02	-0.03	0.08	3753.63	3759.67
		3	0.02	-0.03	0.07	3753.16	3759.67
	P. vivax	0	0.06	-0.09	0.23	6015.54	6024.27
		1	-0.01	-0.19	0.16	6015.6	6024.75
		2	-0.09	-0.23	0.05	6013.94	6022.75
		3	-0.2	-0.38	-0.01	6011.35	6019.63
Space spraying	*P. falciparum*	0	0.02	-0.03	0.08	3754.35	3760.03
		1	0.02	-0.03	0.08	3752.87	3755.23
		2	0.02	-0.03	0.08	3753.09	3754.8
		3	0.02	-0.03	0.08	3754.69	3757.12
	P. vivax	0	-0.09	-0.17	0	6015.49	6024.29
		1	-0.15	-0.25	-0.05	6012.05	6020.03
		2	-0.11	-0.19	-0.02	6014.26	6022.45
		3	-0.17	-0.28	-0.06	6010.41	6018.38

Table S2. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI), deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for full models of *P. falciparum* and *P. vivax* malaria in El Oro 1990-2018 that include minimum temperature, maximum temperature and precipitation as linear terms at time lags from 0-3 months.

Variable	Parasite	Lag	Estimate	LCI	UCI	DIC	WAIC
Minimum temperature	*P. falciparum*	0	-0.24	-0.59	0.11	11944.77	11959.52
		1	0.25	-0.1	0.59	11940.52	11962.85
		2	0.86	0.65	1.07	11945.41	11965.58
		3	1.01	0.79	1.23	11913.6	11938.32
	P. vivax	0	0.08	-0.17	0.33	17824.24	17833.23
		1	0.42	0.17	0.65	17820.76	17829.39
		2	0.52	0.3	0.72	17814.49	17822.85
		3	0.58	0.37	0.79	17804.48	17812.89
Maximum temperature	*P. falciparum*	0	-0.04	-0.31	0.23	11941.4	11965.14
		1	0.34	0.07	0.6	11948.85	11960.76
		2	0.59	0.45	0.74	11924.34	11958.25
		3	0.61	0.47	0.75	11935.02	11950.3
	P. vivax	0	0.18	0.02	0.35	17820.72	17829.23
		1	0.39	0.23	0.53	17814.23	17822.43
		2	0.43	0.31	0.55	17807.16	17815.45
		3	0.34	0.2	0.48	17810.98	17819.87
Precipitation	*P. falciparum*	0	-0.03	-0.18	0.13	11943.82	11960.64
		1	-0.03	-0.19	0.13	11942.01	11958.33
		2	-0.02	-0.16	0.13	11941.66	11958.7
		3	0.18	0.05	0.32	11956.01	11964.58
	P. vivax	0	-0.06	-0.15	0.02	17824.3	17833.28
		1	-0.08	-0.17	0.02	17822.85	17831.3
		2	0.01	-0.09	0.11	17828.14	17837.31
		3	0.1	0.01	0.18	17828.58	17837.32

Table S3. Deviance information criterion (DIC) and Watanabe-Akaike information criterion (WAIC) for full models of *P. falciparum* and *P. vivax* malaria in El Oro 1990-2018 that include minimum temperature, maximum temperature and precipitation as non-linear function at time lags from 0-3 months. Time lags highlighted in grey are those selected to be used in the final model.

Variable	Parasite	Lag	DIC	WAIC
Minimum temperature	*P. falciparum*	0	11948.55	11964.97
		1	11944.32	11960.74
		2	11936.44	11953.48
		3	11921.09	11934.96
	P. vivax	0	17830.35	17836.07
		1	17814.22	17822.74
		2	17800.4	17810.46
		3	17792.98	17801.97
Maximum temperature	*P. falciparum*	0	11924.61	11940.9
		1	11935.75	11952.17
		2	11944.67	11956.47
		3	11934.27	11946.95
	P. vivax	0	17812.66	17831.57
		1	17809.03	17822.45
		2	17802.44	17817.49
		3	17778.01	17806.46
Precipitation	*P. falciparum*	0	11943.34	11961.06
		1	11953.66	11985.54
		2	11949.65	11964.34
		3	11941.54	11961.58
	P. vivax	0	17820.31	17832.98
		1	17820.92	17832.56
		2	17821.94	17830.92
		3	17823.07	17831.76

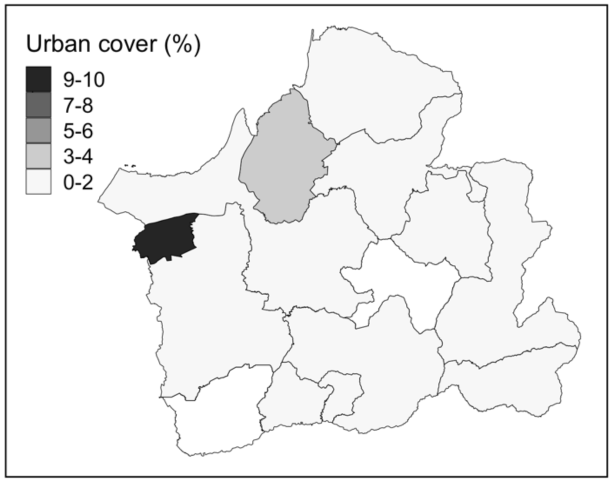

Figure S3. Urbanized areas in El Oro province 1990-2018. Mean percentage of urban cover in each canton between 1990-2018. Percent cover was defined as the proportion of the number of grid cells categorized as urban according to the United Nations Land Cover Classification System (LCCS).

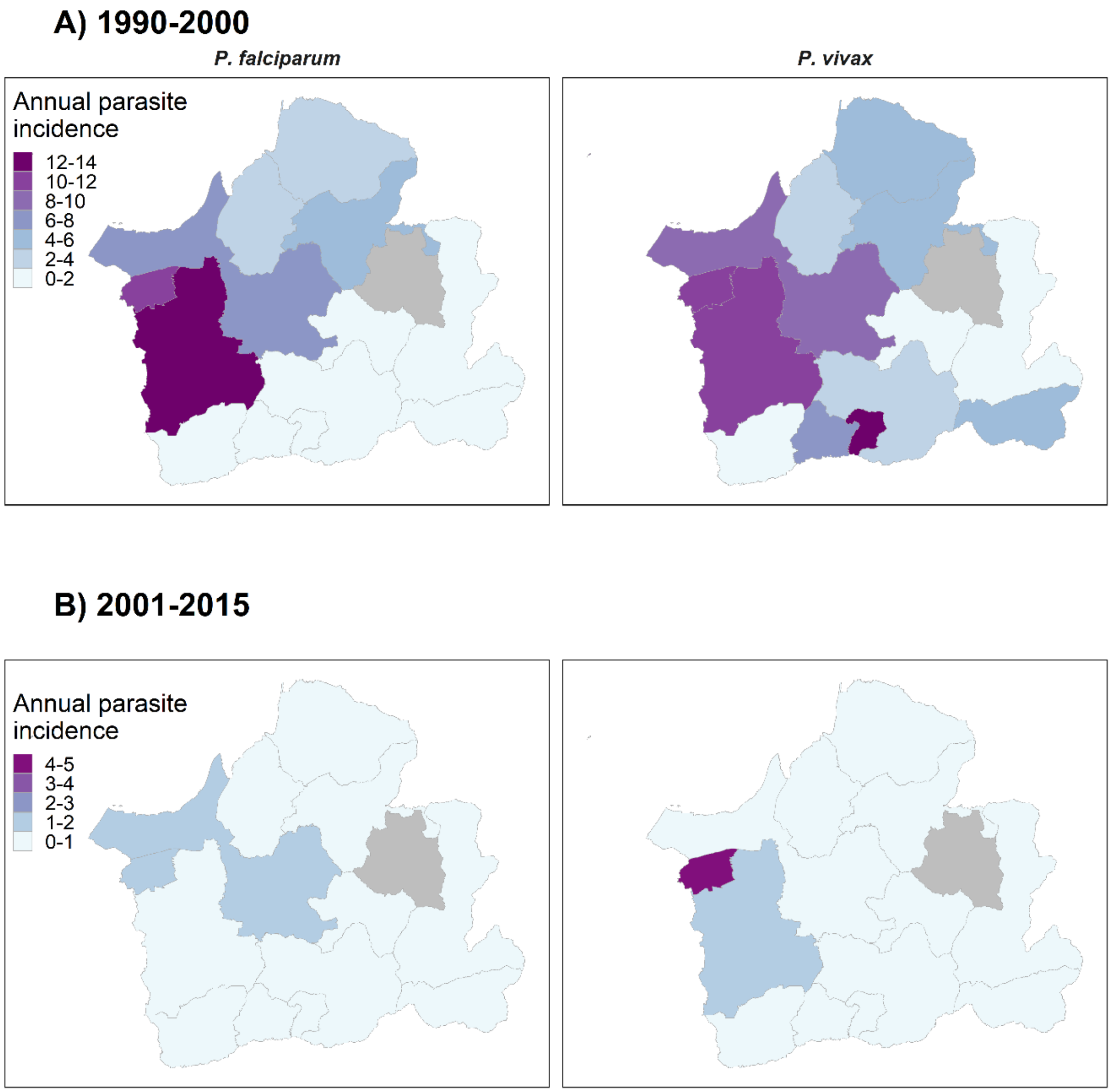

Figure S4. Annual parasite incidence (API) per 1,000 inhabitants in El Oro. Mean API for *P. falciparum* and *P. vivax* malaria for each canton in El Oro a) between 1990-2000 before the period for which intervention data was available and b) 2001-2015 during the 'intervention' period. Grey areas show missing data.

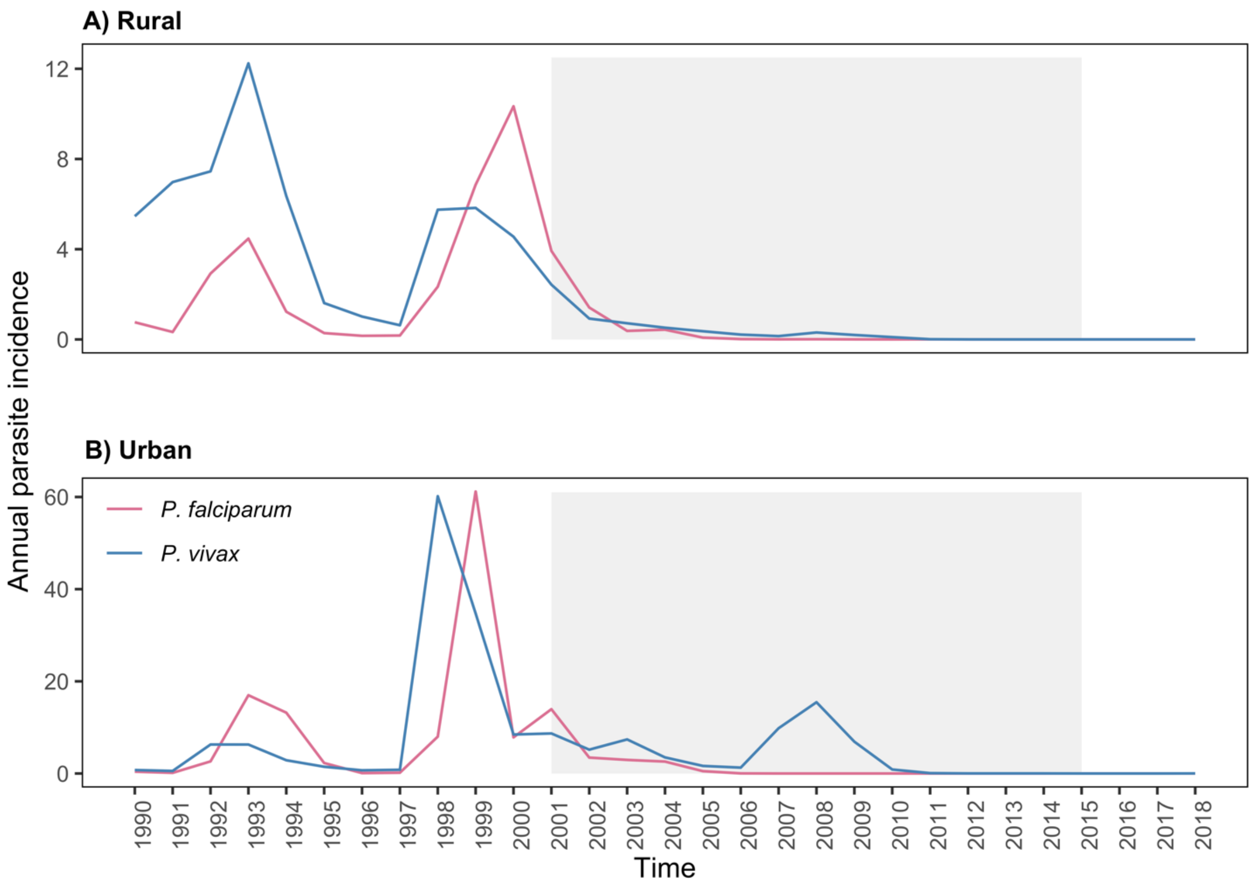

Figure S5. Rural and urban malaria in El Oro 1990-2018. Annual parasite incidence (API) of *P. falciparum* (pink) and *P. vivax* incidence (blue) in A) rural and B) urbanized areas. Grey shading represents the period of intensive vector control in El Oro, 2001-2015. Urban areas were defined as cantons that had urban cover above or equal to 5% of total land cover.

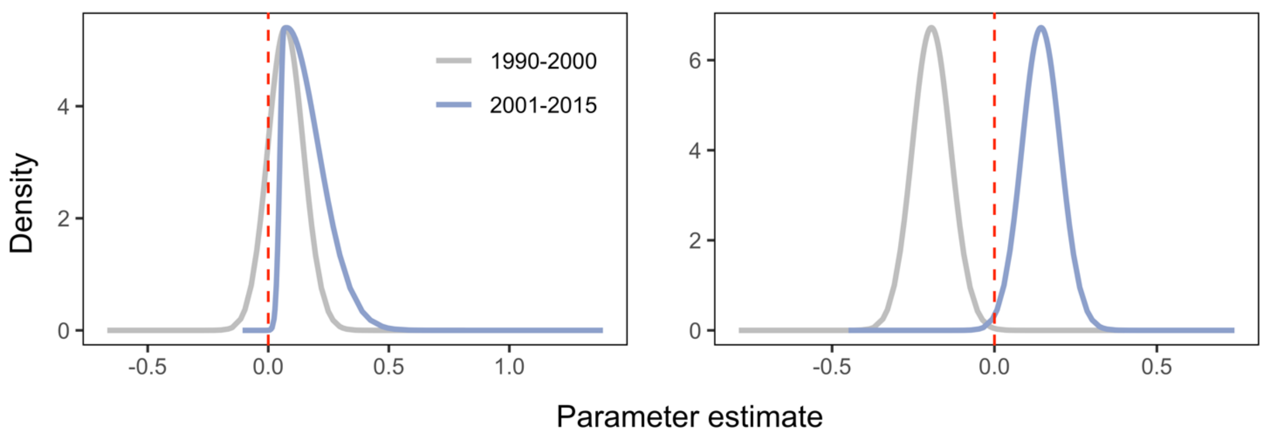

Figure S6. The relationship between urbanized areas and malaria in El Oro before the interventions (1990-2000) (grey curve) and during the elimination period (2001-2015) (blue curve). Posterior mean estimates for the interaction between the period of intensive vector control and urbanized areas for incidence of A) *P. falciparum* and B) *P. vivax* malaria.

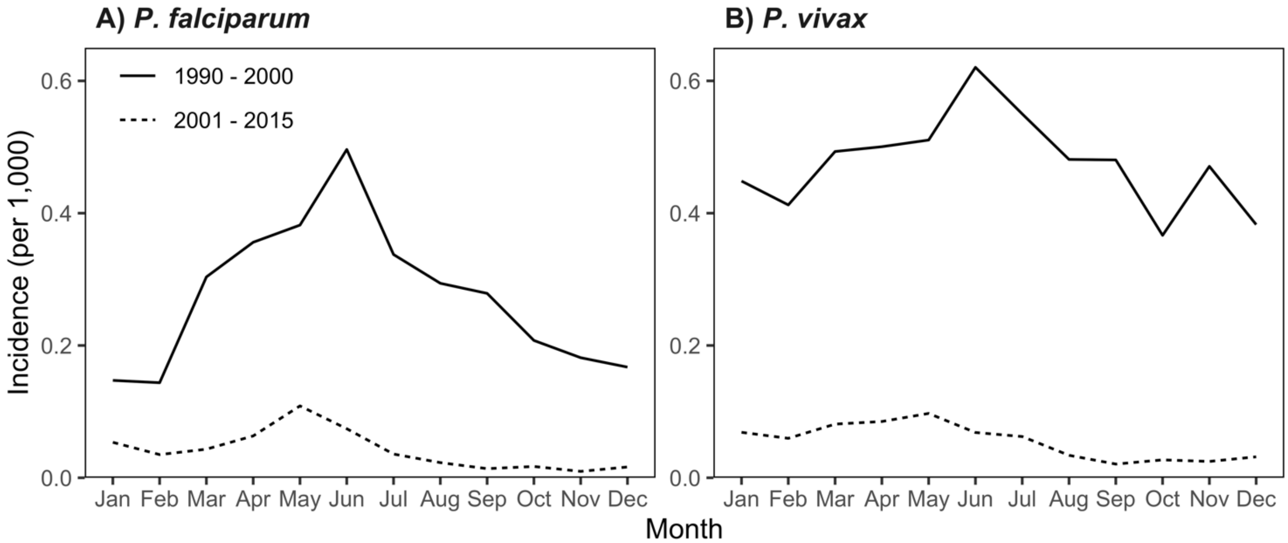

Figure S7. Seasonality of malaria incidence in El Oro. Monthly incidence (per 1,000) of A) *P. falciparum* and B) *P. vivax* malaria in El Oro before the vector control measures were implemented 1990-2000 (solid curve) and during the elimination period 2001-2015 (dashed curve).

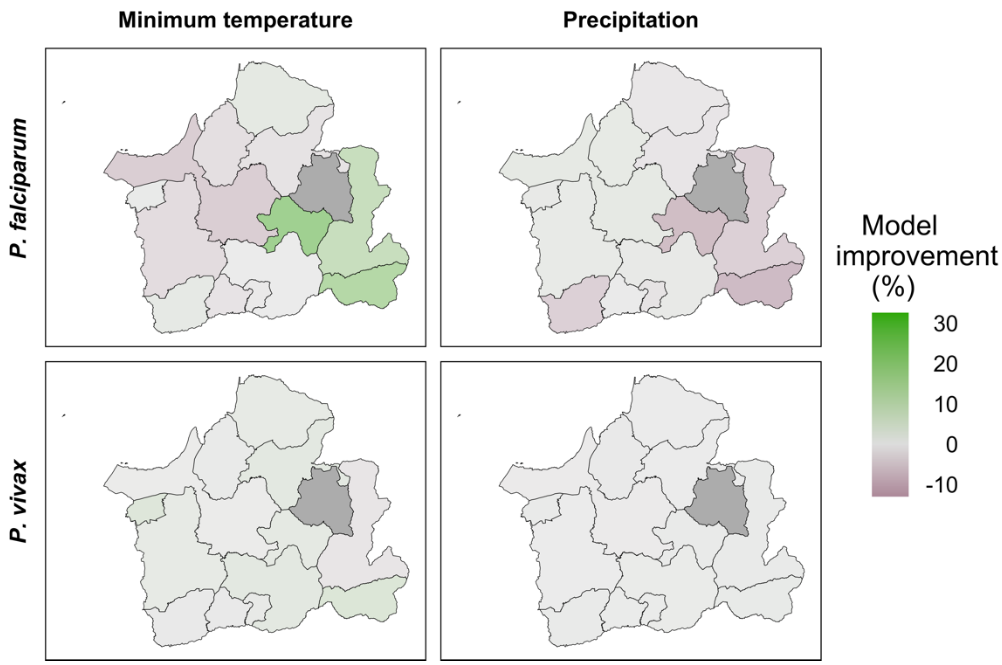

Figure S8. Model improvement for climate variables in El Oro 1990-2018. Model improvement, calculated as percentage change in root mean square error (RMSE) between models of *P. falciparum* and *P. vivax* malaria excluding each climate variable, minimum temperature and precipitation, and models including each variable. Minimum temperature, lagged by three months was included as a linear term for *P. falciparum* models and as a non-linear function for *P. vivax* models. Precipitation, lagged by three months for *P. falciparum* was included as a linear term and for *P. vivax* was lagged one month and included as a non-linear function.

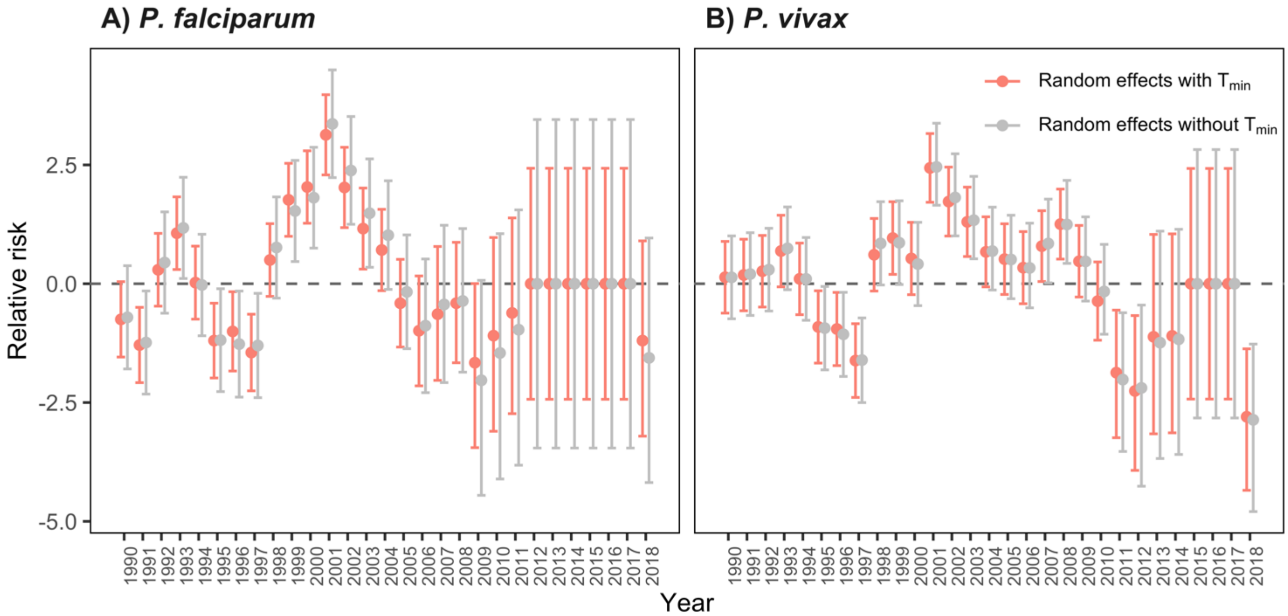

Figure S9. Effect of minimum temperature (T_{min}) on the interannual variation of malaria in El Oro 1990-2018. Difference in the interannual random effect marginal posterior distributions for models of A) *P. falciparum* and B) *P. vivax* malaria that include minimum temperature (orange), lagged by three months, and exclude minimum temperature (grey). Relative risk, on the log scale, is defined as the annual parasite incidence (API), $\log(\rho_{st})$.

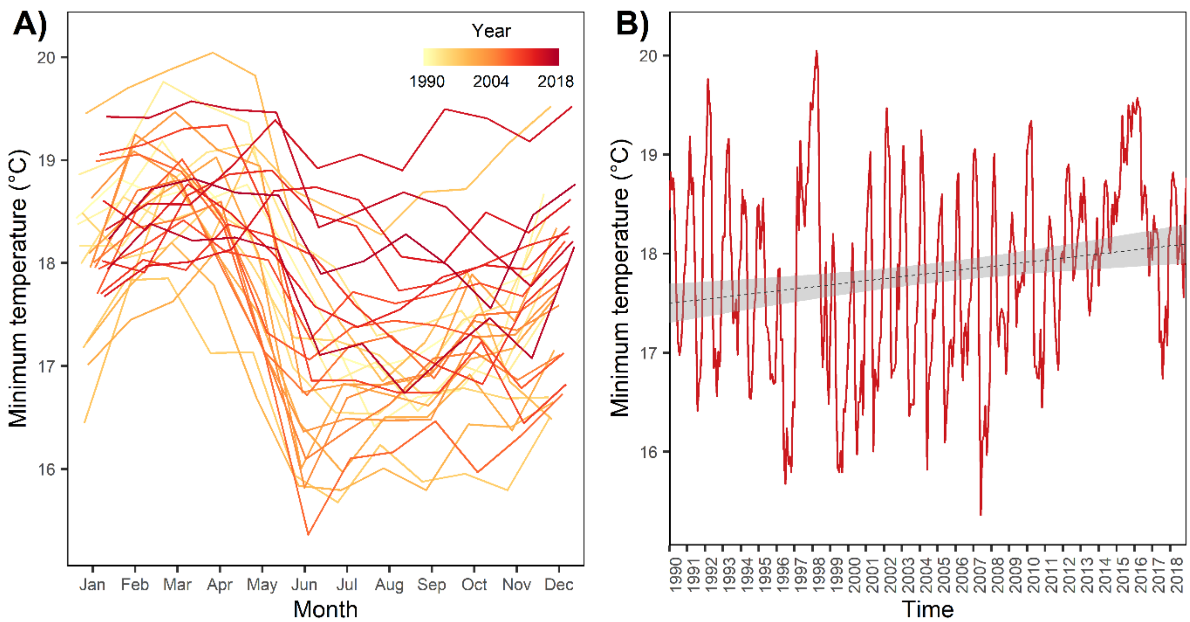

Figure S10. Minimum temperature trends in El Oro 1990-2018. A) Mean monthly minimum temperatures for each year 1990-2018 and B) mean minimum temperature 1990-2018 (red curve), logistic regression line (dashed curve) and 95% confidence intervals (grey shading).

Table S4. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI) for explanatory variables for main models of *P. falciparum* and *P. vivax* malaria in El Oro between 1990-2018 (without intervention data) and for intervention models between 2001-2015 (including intervention data).

Variable	Parasite	Model	Estimate	LCI	UCI
Minimum temperature	*P. falciparum*	1990-2018	0.86	0.6	1.13
		2001-2015	1.31	0.84	1.79
	P. vivax	1990-2018	0.57	0.35	0.79
		2001-2015	0.75	0.36	1.12
Precipitation	*P. falciparum*	1990-2018	0.08	-0.03	0.2
		2001-2015	-0.12	-0.32	0.09
	P. vivax	1990-2018	-0.05	-0.14	0.04
		2001-2015	0.03	-0.14	0.2
Level of urbanization	*P. falciparum*	1990-2018	0.22	0.08	0.37
		2001-2015	0	-0.16	0.16
	P. vivax	1990-2018	0.02	-0.1	0.14
		2001-2015	0.04	-0.12	0.2
Poverty	*P. falciparum*	1990-2018	0.51	-0.22	1.24
		2001-2015	0.15	-0.45	0.76
	P. vivax	1990-2018	-0.03	-0.71	0.63
		2001-2015	0.82	0.12	1.46

Table S5. Posterior mean estimates, lower (2.5%) and upper (97.5%) credible intervals (CI) for vector control measures from intervention models of *P. falciparum* and *P. vivax* malaria in El Oro between 2001-2015.

Control measure	Parasite	Estimate	LCI	UCI
Indoor residual spraying	*P. falciparum*	-0.08	-0.14	-0.02
	P. vivax	-0.04	-0.10	0.02
ULV fumigation	*P. falciparum*	-0.25	-0.78	0.22
	P. vivax	-0.18	-0.36	0.00
Space spraying	*P. falciparum*	-0.15	-0.35	0.07
	P. vivax	-0.17	-0.27	-0.06