Optimizing Insecticide Allocation Strategies Based on Houses and Livestock Shelters for Visceral Leishmaniasis Control in Bihar, India

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Abstract. Visceral leishmaniasis (VL) is the most deadly form of the leishmaniasis family of diseases, which affects numerous developing countries. The Indian state of Bihar has the highest prevalence and mortality rate of VL in the world. Insecticide spraying is believed to be an effective vector control program for controlling the spread of VL in Bihar; however, it is expensive and less effective if not implemented systematically. This study develops and analyzes a novel optimization model for VL control in Bihar that identifies an optimal (best possible) allocation of chosen insecticide (dichlorodiphenyltrichloroethane [DDT] or deltamethrin) based on the sizes of human and cattle populations in the region. The model maximizes the insecticide-induced sandfly death rate in human and cattle dwellings while staying within the current state budget for VL vector control efforts. The model results suggest that deltamethrin might not be a good replacement for DDT because the insecticide-induced sandfly deaths are 3.72 times more in case of DDT even after 90 days post spray. Different insecticide allocation strategies between the two types of sites (houses and cattle sheds) are suggested based on the state VL-control budget and have a direct implication on VL elimination efforts in a resource-limited region.

INTRODUCTION

In India, visceral leishmaniasis (VL) is a vector-borne infectious disease that is fatal within 2 years in most cases if left untreated.¹ Known as kala-azar in India, it is transmitted to the human population when an infected female sandfly bites a susceptible human and transmits the parasite *Leishmania donovani*. Mammal blood is a crucial source of protein and iron for female sandflies that helps in the development of eggs. *Phlebotomus argentipes* is the primary vector of *L. donovani* in the Indian state of Bihar.² India, an agricultural country, has a sizable cattle population that is frequently visited by sandflies for mating and feeding purposes.

The blood-feeding preferences of different sandfly species have been well documented in the literature. An investigation of the stomach contents of *P. argentipes* from six districts of north Bihar showed that blood-fed female sandflies have a preference for bovine blood (68%), followed by human blood (18%) and avian blood (4%),³ hence showing them to be more zoophilic. Furthermore, an examination of soil samples in Bihar showed that *P. argentipes* has a higher tendency to breed in the alkaline soil of cattle sheds than in soil that has a neutral pH found in human houses.⁴ Cattle sheds, where the soil might have a high content of moisture and organic matter such as cow dung and availability of large cattle blood source, provide an ideal breeding site for *P. argentipes*.⁵ The foregoing discussion verifies the importance of considering cattle sites in insecticide residual spraying (IRS) efforts. Previous studies⁶ showed that spraying cattle sheds in Brazil caused increased sandfly density in unprotected human dwellings. The average number of annual VL

cases in India was reported to be 28,382 cases in 2010⁷ and the provisional number of kala-azar cases in 2011 was 31,000.⁸ However, these reported numbers may be highly underreported. A study on VL transmission dynamics⁹ showed as high as 90% underreporting in some districts of Bihar in 2003–2005. Given the seriousness of infection, the governments of India, Bangladesh, and Nepal launched an initiative in 2005 to reduce annual incidences of VL to lower than 1/10,000 persons by 2015.¹⁰ As an intervention measure, the Bihar government now carries out IRS every year starting in February,¹¹ although reaching the elimination target with current vector control strategies seems to be an unachievable task.

The challenges faced in implementing interventions to control VL by limiting sandfly population are well documented in literature. A study¹² on IRS identified two main issues adversely affecting IRS effectiveness in India: 1) a lack of mass community effect¹³ (reduction in overall sandfly population including in unsprayed houses) because of insecticide sprayed at a few dispersed (targeted) houses and 2) reduced susceptibility (increased resistance) of sandflies to dichlorodiphenyltrichloroethane (DDT). Recently, these two issues (addressed by this model) have been causing lower reduction levels of sandfly densities after the implementation of an IRS campaign. Another study¹⁴ compared the effectiveness of three insecticide intervention measures to control kala-azar via a small sampling of data. Their findings suggest that IRS, when executed properly, is the most long-acting and effective vector control measure, as compared with other measures such as insecticide-treated bed nets and ecological vector management. However, these studies considered only human dwellings and missed the impact of sandfly populations at the livestock sheds.

The current policy of the Public Health Department of Bihar considers only the affected human population (and ignores the cattle population) size¹⁵ of each district for computing the amount of insecticide (presently DDT) to be allocated for spraying. Because allocating an amount of insecticide to spraying cattle sheds might control the spread of VL more

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effectively, a novel mathematical framework that identifies a best possible allocation of insecticide based on local human as well as cattle populations would therefore be valuable. For this purpose, the present study develops and analyzes an optimization model to investigate the best possible allocation of insecticide based on both cattle and human population sizes.¹⁵

The second reason for low effectiveness of the current IRS (DDT) program in Bihar is the emergence of *P. argentipes*'s resistance to DDT. Replacing DDT by an alternative insecticide has been suggested.¹⁶ The novel optimization model developed herein can also be used for comparing the impact of different insecticides that can be considered for future use in spray campaigns in Bihar. This work aims to identify optimal insecticide allocation and provides a modeling tool to compare insecticides based on their cost and effectiveness. The maximum achievable insecticide-induced sandfly death rate within the available public health budget is used as a criterion by the presented optimization model.

MATERIALS

Various data sources are used to estimate the model parameters. The 1982 Cattle Census¹⁷ sampling studies and 2011 census from the public health department of Bihar¹⁵ were used to estimate the sizes of the cattle and human populations, respectively, in the 31 VL-affected districts in Bihar. The average number of cattle per cattle shed in Bihar was assumed to be the average livestock herd size (number of cow equivalents per household) from previous studies.¹⁸ We realize that our cattle data are old; however, unlike human census, cattle census in India is not carried out every decade. In spite of this, we carried out extensive literature review to collect data from India to estimate some livestock-related parameters through sampling studies. In the absence of all required recent cattle data, we also performed uncertainty analysis on our model results.

The cost of the insecticide spray campaign was also formulated using data from Bihar state's 2010–2011 public health budget report.¹⁵ The costs related to materials and implementation (including salaries, spray equipment, and miscellaneous expenses) were added to calculate the total cost of the insecticide spray campaign. Both the direct and the indirect costs associated with implementation of IRS were used to derive the cost equation (Supplemental Appendix S3). The number of occupied residential houses was estimated

for 31 VL-affected districts (excluding data for the Arwal district) from the 1991 census of India.¹⁹

Health budget limitations preclude the spraying of all houses in a district. *Decision variables* are quantities whose best possible value needs to be determined to solve an optimization problem. Because the model proposed herein aims to compute the optimal amount of insecticide sprayed per person and per cattle (per capita hereafter), the two decision variables of the model were set as “kilograms of insecticide allocated per person” and “kilograms of insecticide allocated per cattle.” When the available budget cannot procure enough insecticide to cover all sites in the state, it is referred to as a “resource-limited case” and is used to formulate some of the limitations in the model (Supplemental Appendix S4).

The natural sandfly death rate was estimated using 2 years of monthly data representing the daily survival probability of *P. papatasi*.²⁰ Moreover, the appropriate empirical studies were used to estimate *P. argentipes*' insecticide-induced mortality, 24 hours after spraying with DDT¹² and deltamethrin.¹⁶ An insecticide's lethal effect is assumed to decay exponentially over time²¹ as suggested in the literature. The decay rates inside houses¹⁶ and cattle sheds²² were then estimated using data from the literature (the procedure is shown in Supplemental Appendix S1). Previous studies (references in Tables 1 and 2) were also consulted to estimate the epidemiological and demographical parameters for the host (human and cattle) and vector (sandfly) populations.

METHODS

The proposed optimization model comprises three components. *The first component.* The first component is the “objective function,” which captures the insecticide-induced sandfly death rate and which is maximized in the model. The insecticide-induced death rate is achieved by spraying insecticide in both houses and cattle sheds (derivation in Supplemental Appendix S4). The decision (or independent) variables (which are also an output from the model) in the objective function are the amount of insecticide allocated per person and per cattle. The structure of the optimization model is presented as a block diagram in Figure 1A. Figure 1B shows the two different types of sites to which the model allocates insecticide with a given budget. The demographic parameters used in model are described in Table 1.

The insecticide toxicity and entomological parameters used in the model are described in Table 2.

TABLE 1
Demographic parameters for Bihar state

Symbol	Definition	Unit	Estimates: mean (SD) (reference for estimate)
g	Number of PHCs in Bihar	Number of government clinics	354 ¹⁵
N_h	Size of the human population in the 31 VL-affected districts in Bihar	Number of humans	33,898,857 ¹⁵
N_c	Size of the cattle population in the 31 VL-affected districts in Bihar	Number of cattle	21,571,585 ¹⁷
N_v	Size of the sandfly population in Bihar	Number of sandflies	Assumed constant in the optimization model
H	Total number of houses in Bihar	Number of houses	7,933,615 ¹⁹
β	Average herd size per cattle shed	Number of cattle equivalents	4.6 (2.6) ¹⁸
$Z = \frac{N_c}{\beta}$	Number of cattle sheds	Number of cattle sheds	4,689,475 ^{17,18}

PHCs = primary health centers; SD = standard deviation; VL = visceral leishmaniasis.

TABLE 2
Insecticide toxicity and entomological parameters

Symbol	Definition	Unit	Estimates: mean (SD) (95% CI) (reference for estimate)
a_h	Female sandflies' feeding preference for human blood	Dimensionless	179.2×10^{-3} (95% CI, 15.14–20.72) ³
$a_c = 1 - a_h$	Female sandflies' feeding preference for cattle blood	Dimensionless	820.8×10^{-3}
Q	Human visitation proportion of <i>Phlebotomus argentipes</i> based on blood preference	A proportion between 0 and 1	0.2554 (estimated in Supplemental Appendix S1)
τ	Time elapsed after the spray of insecticide	Days	User-defined value
μ_v	Per capita death rate of sandflies	Sandfly deaths/day/sandfly	0.0759 (0.0162) ²⁰
I_h	Amount of DDT consumed per 200 m ² house	kg/house	533×10^{-3} ²⁴
I_h	Amount of deltamethrin consumed per 200 m ² house	kg/house	400×10^{-3} ²⁴
I_z	Amount of DDT consumed per cattle shed	kg/cattle shed	$533 \times 10^{-3}/2 = 266.5 \times 10^{-3}$ ²⁴
I_z	Amount of deltamethrin consumed per cattle shed	kg/cattle shed	$400 \times 10^{-3}/2 = 200 \times 10^{-3}$ ²⁴
C_{i0}	Initial efficacy of DDT (in houses and cattle sheds)	Dimensionless	0.54 (95% CI, 48.7–59.3) ¹²
C_{i0}	Initial efficacy of deltamethrin (in houses and cattle sheds)	Dimensionless	9.75×10^{-1} ¹⁶
b_1	Decay rate of both insecticides' lethal effect inside houses	Fraction per day	0.012 (0.009) (estimated in Supplemental Appendix S1, using data from ¹²)
b_2	Decay rate of both insecticides' lethal effect inside cattle sheds	Fraction per day	0.081 (0.055) (estimated in Supplemental Appendix S1, using data from ²²)

CI = confidence interval; DDT = dichlorodiphenyltrichloroethane.

The notations representing the objective function and variables related to, materials and implementation cost of the spray campaign, available state budget amount, and per capita allocated amount are defined in Table 3.

A parameter, Q , termed as the “human visitation rate” of the vector²³ used in the earlier studies for the malaria transmission dynamics, is used to derive the objective function of our model. Q is defined as the proportion of sandflies visiting human and cattle sites based on the attraction rate of the vector *P. argentipes* toward the blood of each host (Supplemental Appendix S1). The feeding behavior of the vector is thus directly incorporated into the model. In our novel model, we consider insecticide spray at both houses and cattle sheds (Figure 1B).

Temporal exponential functions, Equations 1 and 2, were used to capture the deteriorating lethal effect of the insecticide on vectors, and these include parameters such as decay

rate (b_1 and b_2) and initial efficacy (C_{i0}).²¹ Thus, the proportions of sandflies that die on the τ^{th} day after insecticide application inside houses and cattle sheds, respectively, are given by:

$$h(\tau) = C_{i0}e^{-b_1\tau}, \forall \tau \quad (1)$$

and

$$z(\tau) = C_{i0}e^{-b_2\tau}, \forall \tau \quad (2)$$

The value of initial efficacy (C_{i0}) for both insecticides is assumed to be equal in both houses and cattle sheds. Figure 2 shows the daily distribution of the sandfly population at sprayed and unsprayed sites, which depends on the *blood meal preference* parameter, Q . The objective function is derived using this distribution of the sandfly population (Supplemental Appendix S4) where τ represents days elapsed after spraying. Each day, a sandfly either dies a natural death or dies because of the insecticide's lethal effect. Note that while the repellent effect of the insecticide is ignored in the model derivation, we assume that all sandflies that visit a certain insecticide-treated house or cattle shed are exposed to the insecticide and that a proportion of them die based on the insecticide's lethal effect on that day. The term “spray coverage” is used in this study to capture the number of houses (H_s) and cattle sheds (Z_s) where insecticide is sprayed. Insecticide allocated per person (x) and per cattle (y) can be used to estimate the number of houses (H_s) and cattle sheds (Z_s) that can be sprayed with insecticide, using Equations 3 and 4, respectively.

$$H_s = \left(\frac{N_h x}{I_h} \right) \quad (3)$$

FIGURE 1. Structure of the optimization model. (A) Block diagram of the optimization model. (B) Types of sites (cattle sheds and human dwellings) the model considers for spraying, during an insecticide spray campaign, to achieve the highest possible sandfly death rate.

TABLE 3
Model's objective function, budget constraint, and decision variables

Symbol	Definition	Unit	Description
d_v	Insecticide-induced death rate of sandflies	Sandfly deaths/day/sandfly	Objective function value obtained from the model (equation derived in Supplemental Appendix S4)
$\tilde{C}(x, y)$	Total cost of insecticide materials and spray campaign implementation	Rupees	Budget constraint in the model (equation derived in Supplemental Appendix S3)
$\widetilde{C}_{UB}$	Upper bound on the budget available for the spray campaign	Rupees	User-defined (budget) value in the model
x	Insecticide allocated per capita for a 60-day spray period	kg/person	Decision variable value obtained from the model
y	Insecticide allocated per cattle for a 60-day spray period	kg/cattle	Decision variable value obtained from the model

and

$$Z_s = \left(\frac{N_c y}{I_z} \right) \quad (4)$$

The total sandfly death rate is calculated by adding the natural death rate (μ_v) and the insecticide-induced death rate (d_v) at sprayed sites. The first and second terms of the objective function (Equation 5) are the insecticide-induced death rates in houses and cattle sheds, respectively. In the model, the sandfly population size is assumed to be constant.

The second component. The second component of the optimization model describes the “budget constraint” (limited budget scenario) (Equation 6), which ensures that the total spray campaign cost (materials and implementation in Supplemental Appendix S3) is less than or equal to the available state budget (C_{UB}). Furthermore, insecticide applications are assumed to occur only once per year (derivation of spray campaign cost equation in Supplemental Appendix S3).

The third component. The third component of the optimization model consists of the “remaining constraints” (inequalities 7 and 8) of the model, which are related to insecticide consumption and sites under the insecticide intervention program (Supplemental Appendix S4). It is assumed that the budget is not enough to spray all houses and cattle sheds during the spray campaign (limited budget scenario).

In the model, only two types of sites are sprayed: human dwellings and cattle sheds (note: mixed dwellings do not exist). The other assumptions are cattle are the only non-human hosts that sandflies bite (fact mentioned in empirical studies), all houses are assumed to have an average area of 200 m² based on a previous estimate,²⁴ and the insecticide necessary to spray one cattle shed is assumed to be half that required to cover one house. Using the three above mentioned components and their assumptions, the model can thus be described as follows: maximize

$$d_v(x, y) = \frac{Q[h(\tau)]N_h}{HI_h}x + \frac{(1-Q)[z(\tau)]N_c}{ZI_z}y \quad (5)$$

FIGURE 2. Distribution of the daily sandfly population based on their blood-feeding behavior. N_v = sandfly population size in Bihar; Q = blood meal preference; H and Z = number of houses and cattle sheds, respectively, in Bihar; H_s and Z_s = number of houses and cattle sheds, respectively, where insecticide is sprayed.

subject to

$$\tilde{C}(x, y) = N_h N_1 x + N_c N_1 y + \tilde{C}_{lm} \leq \tilde{C}_{UB} \quad (6)$$

$$0 \leq x \leq \frac{I_h H}{N_h} \quad (7)$$

$$0 \leq y \leq \frac{I_z Z}{N_c} \quad (8)$$

Since we used data from various sources and different periods, we also performed parameter uncertainty and sensitivity analysis on the model results. Uncertainty analysis investigates variations in the model output because of variations observed in the model parameters. It uses Monte Carlo simulation and involves evaluating the model output multiple times by using samples (test instances) of model's input parameters from their respective empirically assumed probability distributions. Sensitivity analysis has been performed to identify model parameters that are critical in quantifying estimates of the model output. The sensitivity of the model output value (insecticide-induced sandfly death rate) because of variation in each of the critical input parameters has been quantified by using partial rank correlation coefficient (PRCC) as the sensitivity index.

The results of these model evaluations are used to obtain 1) an expected value of the insecticide-induced death rate (objective function) and 2) the probability of the model recommending a particular insecticide allocation strategy (from one of the model's four different possible solutions).

ANALYSIS

This section presents the results of the optimization model for computing the per capita insecticide allocation in each of the two sites.

Optimal insecticide allocation strategies from the model. An optimal insecticide allocation strategy recommended by the model represents the amount of insecticide allocated to each of the two sites (x^* and y^*) and optimal insecticide-induced death rate achieved. The model recommends one of the four optimal insecticide allocation strategies depending on the existence of the pair of conditions (Table 4). Supplemental Appendix S2 presents the model's optimal solution in terms of the model parameters. Supplemental Table 8 provides the different abbreviations used in this article.

Each row in this table represents one distinct optimal solution, the existence of which depends on two conditions (conditions I and II). An optimal solution is a function of τ (time since spraying) and $\tilde{C}_{UB}$ (budget available to conduct the vector control program). Observe that the size of the sandfly population is a non-influential factor in the model's threshold conditions and the eventual insecticide allocations as compared with other factors considered in the model. The population of sandflies only impacts their natural death rate.

RESULTS

Evaluation of the effectiveness of the insecticide (DDT and deltamethrin) is performed here using the deterministic optimization model and the uncertainty and sensitivity analysis (UaSA) on optimal insecticide allocation strategies. In the absence of clear data for some of the model parameters for Bihar, the UaSA provides the robustness in optimal allocation strategies (estimates of parameters from available data are shown in Table 2). The estimation of sandfly's *human visitation proportion* (Q) and the insecticide's efficacy decay rates in houses¹⁶ (b_1) and cattle sheds²² (b_2) are described in Supplemental Appendix S1. Using estimated values of Q , b_1 , and b_2 , the quantities lethal effect in houses ($h(\tau)$) and cattle sheds ($z(\tau)$) are computed (Supplemental Figure 1).

Uncertain parameter estimates. The parameters a_h , C_{i0} , b_1 , b_2 , and $\tilde{C}_{UB}$ are primarily uncertain and are the source of uncertainty in the model output. The female sandfly's feeding preference for human hosts (a_h) in north Bihar³ and insecticide's initial efficacy (C_{i0}) are assumed to follow a truncated (at zero) normal distribution. A discrete uniform distribution is estimated²⁵ for b_1 and b_2 by using various data sources (Supplemental Appendix S1). To capture the different possibilities of the future state budgets for the spray campaign, we assume a uniform distribution for $\tilde{C}_{UB}$, with the minimum and maximum values of the distribution were based on the budget estimates of 2010–2011¹⁵ (Rs. 114 million) and 2012–2013²⁶

TABLE 4

Optimal insecticide allocation strategy recommended by the model, to achieve highest possible sandfly death rate on the τ^{th} day post insecticide spray, with $\tilde{C}_{UB}$ as available budget

Existence		
Condition I: Available budget	Condition II: On the τ^{th} day post insecticide spray, per capita insecticide induced death rate per kilogram of insecticide sprayed	Optimal insecticide allocation strategy
Is not enough to spray in 100% of houses	Is more at houses than at cattle sheds	Spray the maximum possible number of houses with the given budget (FS 1)
Is enough to spray in 100% of houses and is not enough to spray in 100% of both sites	Is more at houses than at cattle sheds	Spray 100% of houses and then the maximum possible number of cattle sheds with the remaining budget (FS 2)
Is not enough to spray in 100% of cattle sheds	Is more at cattle sheds than at houses	Spray the maximum possible number of cattle sheds with the given budget (FS 3)
Is enough to spray in 100% of houses and is not enough to spray in 100% of both sites	Is more at cattle sheds than at houses	Spray 100% of cattle sheds and then the maximum possible number of houses with the remaining budget (FS 4)
Is enough to spray in 100% of both sites	–	Spray 100% of both houses and cattle sheds (FS 5)
Is not enough to cover even the spray campaign's implementation cost	–	Not possible to recommend an insecticide allocation strategy (INFS)

FS = feasible solution; INFS = infeasibility.

Mathematical expression for insecticide allocation strategies FS 1, FS 2, FS 3, FS 4, FS 5, and INFS are in Supplemental Appendix S2 (Supplemental Tables 4 and 5).

(Rs. 497.8 million), respectively (Supplemental Figure 3). The minimum ($\bar{C}_{\min}$ =Rs. 101.4 million) and maximum ($\bar{C}_{\max}$ =Rs. 594.4 million) money (to spray in 100% of houses and cattle sheds in Bihar) required to conduct the spray campaign are estimated in Supplemental Appendix S3. $\bar{C}_{\min}$ and $\bar{C}_{\max}$ represent the worst and best case scenarios, respectively.

Comparison of insecticides. The results from the optimization model provide an optimal insecticide allocation (kilogram per capita): (x^*, y^*) over the maximum insecticide-induced death rate (objective function) for the available state budget. This model requires two inputs, namely decay time (τ) and available budget ($\bar{C}_{UB}$), to yield these results and provides an optimal insecticide allocation strategy by finding the pair of conditions satisfied in Table 4. Figure 3 compares the optimal insecticide-induced death rate for different insecticides (DDT and deltamethrin) τ days after spraying (at $\tau = 30$ and 90 days) by using the estimated model parameters (Table 2 and Supplemental Table 6).

The model results (Figure 3) using the estimated parameters suggest that 90 days after spraying, the maximum possible insecticide-induced death rate achieved by DDT (0.15 E-02 sandflies killed/day/sandfly) in Bihar remains 3.72 times that achieved by deltamethrin (0.41 E-03 sandflies killed/day/sandfly). The model thus suggests that deltamethrin might not be a good replacement for DDT, if insecticide-induced death rate of sandflies is to be maximized.

As DDT is presently used as an insecticide in Bihar, an insecticide allocation strategy can be inferred by comparing model results for DDT at $\tau = 30$ and 90 days (Figure 3). If the aim is to achieve the highest possible sandfly death rate 30 days after spraying, then the model results suggest implementing the campaign in cattle sheds only. However, if the aim is to achieve the highest possible sandfly death rate

90 days after the spray campaign (e.g., because a second round of spraying will be implemented, as per the present policy in Bihar), then the model results suggest that implementing the campaign in houses only, would be a better option. Moreover, Bihar presently allocates 0.375 E-01 kg of DDT per person and 0 kg of DDT per cattle.¹¹ Since insecticide is currently sprayed twice a year with a 90-day gap, we use $\tau = 90$ days, $(x, y) = (0.0375, 0)$ and the other parameter values from Table 2. These estimates are substituted in Equation S4 in Supplemental Appendix S4, which results in the maximum achievable increase in the natural sandfly death rate of 18% ($P = 0.18$). This calculation might be a fair estimate of the percentage increase in the natural sandfly death rate effective in Bihar when the second round of spraying starts. However, by substituting $(x = 0.0375)$ into constraint 7, we further estimate that the number of residential houses that can be sprayed with DDT is 2,385,004 (i.e., 30% of all residential houses). Finally, if the number of houses and cattle sheds that can be covered within the available budget is substituted into the left-hand side of Equation S4 in Supplemental Appendix S4, the percentage increase in the sandfly death rate that can be achieved a certain number of days after spraying insecticide can be estimated.

Uncertainty analysis of the optimal amount of insecticide allocated (x^*, y^*) as a function of uncertainty in a_h, C_{10}, b_1, b_2 , and $\bar{C}_{UB}$. Since the parameter estimates used in the model are derived from different sources and not all relate to the transmission dynamics of VL in Bihar, the resulting variations in the input parameter estimates can be modeled by treating them as random variables.²⁷ Mathematical models used for recommending optimal intervention strategies must account for such parameter uncertainty.²⁸ Uncertainty analyses were performed in this study to investigate the uncertainty

FIGURE 3. Optimal insecticide allocation amount: (x^*, y^*) and insecticide-induced death rate achieved: d_v^* (when $\bar{C}_{UB}$ = Rs. 114 million and τ is varied). Units: x^* is kg/person, y^* is kg/cattle, and d_v^* is sandfly deaths/day/sandfly.

FIGURE 4. Expected optimal value of the insecticide-induced death rate for each of the 10^5 Monte Carlo samples, $\tau = 90$ days. The four uncertain parameters (a_h , C_{t0} , b_1 , and b_2) have the assumed distributions. The value of $\widetilde{C}_{UB}$ varies. $\widetilde{C}_{lm}$ is the implementation cost. The increase in insecticide-induced death rate is negligible beyond $\widetilde{C}_{UB} = \text{Rs. } 594.4$ million (*threshold budget value*).

in the model outputs caused by the assumed distributions in the input parameters. The model outputs studied were the occurrences of the five insecticide allocation strategies (Supplemental Appendix S5: FS 1–FS 5) and the distribution of the objective function value (insecticide-induced death rate: d_v^*).

Global multivariate sensitivity analysis was then performed by sampling repeatedly from the probability distributions assigned to the uncertain parameter estimates and simulating the model with each parameter value set to identify the input parameters that were most statistically influential in determining the magnitude of the output parameters. PRCCs were used in this study as a sensitivity index to estimate the strength of the linear association between the input parameters (a_h , b_1 , and b_2) and output parameter (d_v^*).²⁵

Parameter distributions. Independent samples were drawn 10^5 times from the probability distributions assigned to the five uncertain parameters (a_h , C_{t0} , b_1 , b_2 , and $\widetilde{C}_{UB}$) using a Monte Carlo simulation. The percentage occurrences of each of the four possible insecticide allocation strategies and the statistics of optimal “per capita insecticide allocation amounts (x^* , y^*)” are plotted in Supplemental Figure 4 (Supplemental Appendix S5).

On the basis of the test instance values of the input parameters, insecticide allocation strategy FS 1 occurs most often (76.46%), followed by FS 4 (14.97%), FS 3 (5.27%), and FS 2 (3.3%). Hence, in conjunction with the optimal insecticide allocation strategies expressed in words in Table 4, spraying the required percentage of houses only (allocation strategy FS 1) is recommended the most number of times.

Uncertainty analysis of the optimal insecticide-induced death rate value (d_v^*). The distributions of the optimal insecticide-induced death rate for $\tau = 30$ and 90 days are shown in Supplemental Figure 5 (Supplemental Appendix S5). This distribution is obtained by varying the uncertain input parameters (a_h , C_{t0} , b_1 , b_2 , $\widetilde{C}_{UB}$) of the model. Since the insecticide effect diminishes over time, our model suggests a 76% (from 0.0924 sandflies killed/day/sandfly after 30 days to 0.0334 sandflies killed/day/sandfly after 90 days, Supplemental Figure 5) higher average optimal death rate 30 days after spraying compared with 90 days after spraying.

Uncertainty analysis of the optimal insecticide-induced death rate (d_v^*) as a function of uncertainty in a_h , C_{t0} , b_1 , and b_2 for different fixed values of available budget ($\widetilde{C}_{UB}$). The uncertainty analysis showed that the expected insecticide-induced death rate increases (initially at a constant rate followed by no change after a *threshold budget value*) with an increase in the available budget for the insecticide spraying campaign (Figure 4).

The increase in insecticide-induced death rate is negligible beyond $\widetilde{C}_{UB} = \text{Rs. } 594.4$ million (Figure 4). This value is referred to as the threshold budget value. It reaches a maximum value of 0.064 sandflies dead/day/sandfly when the budget allocated is sufficient to cover 100% of both sites.

Distribution of insecticide allocation strategies (FS 1–FS 5) recommended by the model. The probability that the model recommends one of the five different insecticide allocation strategies was studied by varying $\widetilde{C}_{UB}$ from its minimum ($\widetilde{C}_{min}$) to maximum ($\widetilde{C}_{max}$) values and assigning assumed distributions to the four uncertain parameters (a_h , C_{t0} , b_1 , and b_2). When the available budget is between the following:

- Rs. 101 and 200 million: Probability (FS 1: spray in maximum possible no. of H) = 80% and Probability (FS 3: spray in maximum possible no. of Z) = 20%
- Rs. 201 and 470 million: Probability (FS 1: spray in maximum possible no. of H) = 80% and Probability (FS 4: spray in 100% of Z and then maximum possible no. of H with remaining budget) = 20%
- Rs. 471 and 590 million: Probability (FS 2: spray in 100% of H and maximum possible no. of Z) = 80% and Probability (FS 4: spray in 100% of Z and then maximum possible no. of H with remaining budget) = 20%
- Greater than Rs. 590 million: Probability (FS 5: spray in 100% of H and 100% of Z) = 100%

Where H and Z denote the number of houses and cattle sheds in Bihar state (also defined in Table 1).

When the available budget is between Rs. 101.0 million and Rs. 470 million, the most frequently (for 80% of the sampled instances) recommended optimal insecticide allocation

strategy is to spray the maximum possible number of houses (i.e., the current policy followed in Bihar). However, when the available budget is between Rs. 471 million and Rs. 590.0 million, the optimal insecticide allocation strategy is to spray 100% of the houses and then the maximum possible number of cattle sheds with the remaining budget.

Sensitivity analysis of the optimal insecticide-induced death rate value (d_v^*). The uncertainties in the parameters that can affect the model outcome are examined in this section. Changes in the value of the four uncertain parameters (a_h , C_{10} , b_1 , b_2) do not affect the pair of conditions (Supplemental Table 4). However, changes in the values of $\bar{C}_{UB}$ do affect the conditions, resulting in one of the five insecticide allocation strategies (FS1–FS5). By contrast, the value of the objective function (insecticide-induced sandfly death rate) depends on changes in the three uncertain parameters: a_h , b_1 , and b_2 . Using a Monte Carlo sample size of 10^5 , sensitivity analysis of d_v^* was performed by assigning distributions to a_h , b_1 , b_2 and $\bar{C}_{UB}$. As shown in Supplemental Figure 6 (Supplemental Appendix S5), the optimal insecticide-induced death rate value (d_v^*) is most sensitive (negatively correlated) to the insecticide's decay rate in houses (b_1), when the insecticide allocation strategies: FS1, FS2, and FS4 are recommended by the model (Table 4). However, the optimal insecticide-induced death rate value (d_v^*) is the most sensitive to the insecticide's decay rate in cattle sheds (b_2) when the model recommends insecticide allocation strategy FS3. The optimal insecticide-induced death rate value (d_v^*) is the second most sensitive to the sandfly's feeding preference for human blood (a_h), when the model recommends insecticide allocation strategy FS2.

DISCUSSION

VL is the second largest parasitic killer in the world. Almost two-fifths of the world's VL cases occur in Bihar.²⁹ Because of the serious effect of VL burden on the local economy and the severe detrimental health outcomes for the population of Bihar, the state is in urgent need of an effective and lasting vector control program. Given that insecticide-spraying programs have been a successful disease control measure in many parts of the world, we developed a novel mathematical model in the present study, to design the optimal insecticide intervention policy and compare it with similar existing control programs in Bihar. In our insecticide-spraying policy, we not only maximize the sandfly death rate and minimize the disease transmission risk, but we also optimize the state budget.

The model provides a framework within which temporal efficacies of various insecticides can be tested. As an example, we compared the efficacy of two insecticides, DDT and deltamethrin. Our framework is designed based on the recent findings¹⁶ that there is a critical need for identifying and evaluating alternative insecticides as sandflies have developed resistance to DDT, which is currently being used in Bihar. Our model results suggest that DDT yields more than three times the insecticide-induced death rate achieved by deltamethrin up to 90 days after spraying. Hence, deltamethrin might not be a cost-effective substitute for DDT.

Using data from Bihar, our model results validate the greater increase in sandfly death rate achieved by first spraying at a specific number of houses, ahead of cattle sheds. In particular, only 30% of the total number of houses in Bihar can be

sprayed, annually, under the present DDT allocation policy (0.037 kg/person). However, studies¹² have shown that when only houses are sprayed, there is no change in the density of the sandflies found in the non-sprayed region, suggesting that other regions should be considered. Hence, incorporating cattle sheds in the insecticide-spraying program (in addition to houses) may be a more effective strategy in interrupting VL transmission. Moreover, the impact of an insecticide spraying program can be optimized by spraying at (or above) the critical number of houses and cattle sheds for a given budget. The model results suggest that spraying at cattle sheds could be more effective under certain conditions, validating the fact that approximately three-quarters of sandflies are found in and around cattle sheds, where they primarily breed. Our model estimates an 18% increase in natural sandfly death rate in Bihar, 90 days after spraying, based on the present insecticide allocation policy. The model's uncertainty analysis results suggest that after spending a certain amount of money (*threshold budget value*) spraying at more sites does not significantly increase the sandfly death rate. Hence, after covering an optimal spray area, it might be better to invest funds in other sandfly control interventions such as bed nets and ecological vector management.³⁰

Owing to the diminishing effect of the insecticide over time, the estimated average insecticide-induced death rate was 0.09 and 0.03 sandflies killed/day/sandfly after 30 days and 90 days, respectively, post spraying; in other words, the insecticide-induced death rate is three times lower 60 days later. The model sensitivity results suggest that the insecticide's decay rates in houses and cattle sheds are the most important parameters in determining an optimal allocation of insecticide.

The focus of the study was to understand qualitative features of the system, and the results may not be affected by the use of data from different time points. In future research, we would like to use this model for prediction and hence, will be carrying out sampling studies to estimate cattle census with our collaborators in India. This is the first model of its kind that focuses on understanding the temporal impact of effective insecticide spraying campaign for VL control in a developing country. The literature on the modeling for VL control in India is extremely limited. However, in our present framework, we were successfully able to incorporate some relevant factors including insecticide spraying costs, epidemiological features, demographical drivers, and insecticide toxicity parameters. We plan to include additional features in our future work as well as collect additional data including distribution of cattle population.

As with many mathematical models, our model also has some limitations. For example, the model is capable of suggesting spraying intervention at only one of the two site types (either at houses or at cattle sheds). Even though insecticides have the dual effect of anti-feeding and of mortality,^{21,31} this model only considers the mortality effect. In our future research, we plan to extend the framework by incorporating the above features as well as influences of an anti-feeding effect on the sprayed sites and dynamic variation in sandfly population as it changes due to seasonal conditions and reduces over time after insecticide intervention.

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REFERENCES

- Bora D, 1999. Epidemiology of visceral leishmaniasis in India. *Natl Med J India* 12: 62–68.
- Ilango K, 2010. A taxonomic reassessment of the *Phlebotomus argentipes* species complex (Diptera: Psychodidae: Phlebotominae). *J Med Entomol* 47: 1–15.
- Mukhopadhyay AK, Chakravarty AK, 1987. Bloodmeal preference of *Phlebotomus argentipes* and *Ph. papatasi* of north Bihar, India. *Indian J Med Res* 86: 475–480.
- Sharma U, Singh S, 2008. Insect vectors of *Leishmania*: distribution, physiology and their control. *J Vector Borne Dis* 45: 255–272.
- Sharma VP, 1996. Ecological changes and vector-borne diseases. *Trop Ecol* 37: 57–65.
- Bern C, Courtenay O, Alvar J, 2010. Of cattle, sand flies and men: a systematic review of risk factor analyses for south Asian visceral leishmaniasis and implications for elimination. *PLoS Negl Trop Dis* 4: 1–9.
- Alvar J, Vélez ID, Bern C, Herrero M, Desjeux P, Cano J, Jannin J, Margriet DB, 2012. Leishmaniasis worldwide and global estimates of its incidence. *PLoS One* 7: 1–12.
- Bhunia GS, Kesari S, Chatterjee N, Kumar V, Das P, 2012. The burden of visceral leishmaniasis in India: challenges in using remote sensing and GIS to understand and control. *ISRN Infect Dis* 2013: 1–14.
- Mubayi A, Castillo-Chavez C, Chowell G, Kribs-Zaleta C, Ali Siddiqui N, Kumar N, Das P, 2010. Transmission dynamics and underreporting of kala-azar in the Indian state of Bihar. *J Theor Biol* 262: 177–185.
- WHO, 2008. *Kala-Azar Elimination in the South-East Asia Region: Training Module*. New Delhi, India: World Health Organization, Regional Office for South-East Asia.
- WHO, 2010. *Monitoring and Evaluation Tool Kit for Indoor Residual Spraying*. Geneva, Switzerland: World Health Organization.
- Huda MM, Mondal D, Kumar V, Das P, Sharma SN, Das ML, Roy L, Gurung CK, Banjara MR, Akhter S, Maheswary NP, Kroeger A, Chowdhury R, 2011. Toolkit for monitoring and evaluation of indoor residual spraying for visceral leishmaniasis control in the Indian subcontinent: application and results. *J Trop Med* 2011: 1–11.
- Curtis CF, Mnzava AEP, 2000. Comparison of house spraying and insecticide-treated nets for malaria control. *Bull World Health Organ* 78: 1389–1400.
- Das ML, Roy L, Rijal S, Paudel IS, Picado A, Kroeger A, Petzold M, Davies C, Boelaert M, 2010. Comparative study of kala-azar vector control measures in eastern Nepal. *Acta Trop* 113: 162–166.
- State Health Society Bihar, 2010. *K.A./Budget 2010–11*. Available at: http://statehealthsocietybihar.org/pip2010-11/Fund_Guidelines/Part-D/Kala_Azar.pdf. Accessed March 7, 2010.
- Dinesh DS, Das ML, Picado A, Roy L, Rijal S, Singh SP, Das P, Boelaert M, Coosemans M, 2010. Insecticide susceptibility of *Phlebotomus argentipes* in visceral leishmaniasis endemic districts in India and Nepal. *PLoS Negl Trop Dis* 4: 1–5.
- Cattle Census, 1982. *Districtwise Number of Live-Stock and Poultry in Bihar*. Patna, India: National Informatics Centre (NIC) Bihar State Center. Available at: <http://planning.bih.nic.in/BiharStats/reptab54.pdf>. Accessed September 3, 2010.
- International Livestock Research Institute, 2007. Crop-livestock interactions and livelihoods in the Trans-Gangetic Plains, India. Addis Ababa, Ethiopia: International Livestock Research Institute.
- Census of India, 1991. *Districtwise Number of Occupied Residential Houses and Households in Reorganised Bihar*. Available at: <http://gov.bih.nic.in/Depts/PlanningDevelopment/Statistics/reptab21.pdf>. Accessed December 14, 2009.
- Srinivasan R, Panicker KN, 1992. Seasonal abundance, natural survival and resting behaviour of *Phlebotomus papatasi* (Diptera: Phlebotomidae) in Pondicherry. *Indian J Med Res* 95: 207–211.
- Courtenay O, Kovacic V, Gomes PAF, Garcez LM, Quinnell RJ, 2009. A long-lasting topical deltamethrin treatment to protect dogs against visceral leishmaniasis. *Med Vet Entomol* 23: 245–256.
- Jacusié F, 1947. Sandfly control with DDT residual spray: field experiments in Palestine. *Bull Entomol Res* 38: 479–488.
- Kawaguchi I, Sasaki A, Mogi M, 2004. Combining zooprophylaxis and insecticide spraying: a malaria-control strategy limiting the development of insecticide resistance in vector mosquitoes. *P Roy Soc B-Biol Sci* 271: 301–309.
- Walker K, 2000. Cost-comparison of DDT and alternative insecticides for malaria control. *Med Vet Entomol* 14: 345–354.
- Marino S, Hogue IB, Ray CJ, Kirschner DE, 2008. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *J Theor Biol* 254: 178–196.
- State Health Society Bihar, 2012. *Kala-Azar Budget 2012*. Available at: <http://www.statehealthsocietybihar.org/pip2012-13/fundallocation/partf/kalazar.zip>. Accessed January 10, 2013.
- Sanchez MA, Blower SM, 1997. Uncertainty and sensitivity analysis of the basic reproductive rate. *Am J Epidemiol* 145: 1127–1137.
- Luz PM, Struchiner CJ, Galvani AP, 2010. Modeling transmission dynamics and control of vector-borne neglected tropical diseases. *PLoS Negl Trop Dis* 4: 1–6.
- Joshi A, Narain JP, Prasittisuk C, Bhatia R, Hashim G, Alvar J, Banjara M, Kroeger A, 2008. Can visceral leishmaniasis be eliminated from Asia? *J Vector Borne Dis* 45: 105–111.
- Das M, Banjara M, Chowdhury R, Kumar V, Rijal S, Joshi A, Akhter S, Das P, Kroeger A, 2008. Visceral leishmaniasis on the Indian sub-continent: a multi-centre study of the costs of three interventions for the control of the sandfly vector, *Phlebotomus argentipes*. *Ann Trop Med Parasitol* 102: 729–741.
- Kendrick RK, Kendrick MK, Focheux C, Dereure J, Puech MP, Cadiergues MC, 1997. Protection of dogs from bites of phlebotomine sandflies by deltamethrin collars for control of canine leishmaniasis. *Med Vet Entomol* 11: 105–111.