

## Optimization of Insecticide Allocation for Kala-Azar Control in Bihar, India

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*Abstract.* The visceral form is the most deadly form of the leishmaniasis family, which affects poor and developing countries. The Indian state of Bihar has the highest prevalence and mortality rate due to visceral leishmaniasis in the world, where it is also referred to as Kala-Azar. Insecticide spraying is the current vector control procedure for controlling its spread in Bihar. This study proposes a novel optimization model in order to identify an optimal allocation of insecticide (DDT or Deltamethrin) based on the sizes of both human and cattle populations. As an example, DDT and Deltamethrin have been compared using the model. The model maximizes the insecticide-induced death rate caused by spraying human and cattle dwellings given the limited financial resources available to the public health department. The results suggest that until the first 90 days after spraying, DDT yields more than three times the insecticide-induced death rate achieved by Deltamethrin in the absence of any insecticide resistance. The study implies that ignoring the resistance developed by sandflies to DDT, Deltamethrin might not be a good replacement for DDT. The study also confirms that the present practice of first spraying houses to optimize sandfly mortality ahead of spraying cattle sites is appropriate.

## INTRODUCTION

Visceral leishmaniasis (VL) is a sandfly-borne infectious disease that is fatal if left untreated.<sup>1</sup> 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*. Male sandflies are also known to feed on blood,<sup>2</sup> and blood is a crucial source of protein and iron for female sandflies to develop eggs. *Phlebotomus argentipes* (a sandfly species) is the primary vector of *L. donovani* in southern Asia<sup>3</sup> including India. 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%)<sup>4</sup>, hence showing them to be 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.<sup>5</sup> Cattle sheds, where the soil might have a high content of moisture and organic matter such as cow dung, provide an ideal breeding site for *P. argentipes*.<sup>6</sup> The foregoing discussion verifies the importance of considering cattle sites in insecticide residual spraying efforts. Previous studies<sup>7</sup> showed that spraying cattle sheds in Brazil caused increased sandfly density in unprotected human dwellings. Therefore, we develop a model that focuses on insecticide spraying programs in both human and cattle sites.

The burden of VL in terms of disability-adjusted life years lost in India was estimated in 1990 to be 0.5 million and 0.68 million for women and men, respectively.<sup>8</sup> The average number of annual VL cases in India between 2004 and 2008 was reported to be 34,918, although this total

dropped to 28,382 cases in 2010.<sup>9</sup> The provisional number of Kala-Azar cases in India in 2011 was 31,000.<sup>10</sup> 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 one per 10,000 persons by 2015.<sup>11</sup> As an intervention measure, the Bihar government now carries out insecticide residual spraying every year starting in February.<sup>12</sup>

The current policy of the public health department of the Indian state of Bihar considers only the human population size<sup>13</sup> of each district for computing the amount of insecticide (presently DDT) to be allocated for spraying. The cattle population in a district is not included in these insecticide allocation calculations. Because allocating an amount of insecticide to spraying cattle sheds might control the spread of VL more effectively, a mathematical framework that identifies an optimal allocation of insecticide based on local human as well as cattle populations would therefore be valuable. For this purpose, two modeling approaches are presented herein: an optimization model and a Benefit to Materials Cost Ratio (*BMCR*) function. The present study uses these models in order to investigate an optimal allocation of insecticide based on both cattle and human population sizes.<sup>13</sup> Please note that because the *BMCR* function approach is completely independent of the optimization model, it provides us with a different perspective on choosing sites for spraying.

The model developed herein can be used for comparing insecticides considered for future use in spray campaigns in Bihar. The current insecticide (DDT) residual spray program in Bihar has been reported to have low effectiveness due to the emergence of *P. argentipes*'s resistance to DDT. Replacing DDT by an alternative insecticide has been suggested.<sup>14</sup> The model in this study can thus be used when considering this replacement. The maximum achievable insecticide-

induced death rate within the available budget constraint is used as a criterion by the presented optimization model.

Our results suggest that despite spending approximately Rs. 590 million in spray campaigns, spraying more sites does not increase the sandfly population's insecticide-induced death rate substantially. The model estimates an 18% increase in natural sandfly death rate in Bihar, 90 days after spraying, based on the present insecticide allocation policy. Hence, after covering a certain spray area, it might be better to invest funds in other sandfly control interventions such as bed-nets and ecological vector management.<sup>15</sup>

The remainder of the paper is structured as follows. The *Data Sources* section describes the data sources used to estimate the model parameters. The *Methods* section explains the equations and assumptions of the three components of the linear optimization model. The *Analysis* section presents the analytical results and recommendations for choosing a spray coverage option by using a *BMCR* function. The *Numerical Results* section presents the numerical results derived from the model. Finally, the *Discussion* section discusses the implications of the model's results and offers suggestions for future ideas to improve the model.

## DATA SOURCES

The 1982 Cattle Census<sup>16</sup> and 2010--2011 budget allocation document from the public health department of Bihar<sup>13</sup> were used to estimate the sizes of the cattle and human populations in the VL-affected districts in Bihar, respectively. 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.<sup>17</sup>

The cost of the insecticide spray campaign was also formulated using data from the 2010--2011 budget document.<sup>13</sup> The costs related to materials and implementation (including salaries, spray equipment, and miscellaneous expenses) were added in order to calculate the total cost of the insecticide spray campaign. Both the direct and the indirect costs associated with implementation were used to derive the cost equation (Appendix 3). The data include 354 public health centers (PHCs) and 10,686 villages.<sup>13</sup> Furthermore, the number of occupied residential houses was estimated for VL-affected districts (excluding data for the Arwal district) from the 1991 Census of India.<sup>18</sup>

Financial constraints preclude the spraying of all houses in a district. Because the model proposed herein aims to optimize the amount of insecticide sprayed per person and per cattle (per capita hereafter), the two decision variables 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 constraints in the model (Appendix 4).

The natural sandfly death rate was estimated using 2 years of monthly data representing the daily survival probability of *P. papatasi*<sup>19</sup>. Moreover, the appropriate literature sources were referred to in order to estimate *P. argentipes*'s mortality, 24 hours after spraying with DDT<sup>20</sup> and Deltamethrin<sup>14</sup>. An insecticide's lethal effect is assumed to decay exponentially over time.<sup>21</sup> The decay rates inside houses<sup>14</sup> and cattle sheds<sup>22</sup> were then estimated using data from the literature (Appendix 1). Previous studies (see the references in Table 1 and Table 2) were also consulted in order to estimate the epidemiological and demographical parameters for the host and vector populations.

## METHODS

The proposed optimization model comprises three components. The first component is the **objective function** (Equation 3), which captures the insecticide-induced death rate and which is maximized in the model. The insecticide-induced death rate is achieved by spraying insecticide in houses and cattle sheds (derivation in Appendix 2). The decision variables (output from the model) in the objective function are then the amount of insecticide allocated per person and per cattle. The demographic parameters used in the objective function as well as in the constraints are described in Table 1.

**Table 1. Demographic parameters for Bihar state**

Symbol	Definition	Unit	Estimates : Mean (SD)
$g$	Number of PHCs in Bihar	Number of government clinics	354 <sup>13</sup>
$N_h$	Size of the human population in the 31 VL-affected districts in Bihar	Number of humans	33,898,857 <sup>13</sup>
$N_c$	Size of the cattle population in the 31 VL-affected districts in Bihar	Number of cattle	21,571,585 <sup>16</sup>
$N_v$	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 <sup>18</sup>
$\beta$	Average herd size per cattle shed	Number of cattle equivalents	4.6 (2.6) <sup>17</sup>
$Z = \frac{N_c}{\beta}$	Number of cattle sheds	Number of cattle sheds	4,689,475 <sup>16</sup>

SD: standard deviation

The insecticide toxicity and entomological parameters used in the objective function and in the constraints are described in Table 2.

**Table 2. Insecticide toxicity and entomological parameters**

Symbol	Definition	Unit	Estimates Mean (SD) (95% CI)
$a_h$	Female sandflies' feeding preference for human blood	Dimensionless	$179.2 \times 10^{-03}$ (95% CI, 15.14--20.72) <sup>4</sup>
$a_c = 1 - a_h$	Female sandflies' feeding preference for cattle blood	Dimensionless	$820.8 \times 10^{-03}$ <sup>4</sup>
Q	Human visitation proportion of <i>P. argentipes</i> based on blood preference	A proportion between 0 and 1	0.2554 [Estimated in Appendix 1]
$\tau$	Time elapsed after the spray of insecticide	Days	User-defined value
$\mu_v$	Per capita death rate of sandflies	Sandfly deaths per day per sandfly	0.0759 (0.0162) <sup>19</sup>
$I_h$	Amount of DDT consumed per 200 m <sup>2</sup> house	kg per house	$533 \times 10^{-03}$ <sup>23</sup>
$I_h$	Amount of Deltamethrin consumed per 200 m <sup>2</sup> house	kg per house	$400 \times 10^{-03}$ <sup>23</sup>
$I_z$	Amount of DDT consumed per cattle shed	kg per cattle shed	$533 \times 10^{-03} / 2 = 266.5 \times 10^{-03}$ <sup>23</sup>
$I_z$	Amount of Deltamethrin consumed per cattle shed	kg per cattle shed	$400 \times 10^{-03} / 2 = 200 \times 10^{-03}$ <sup>23</sup>
$C_{t0}$	Initial efficacy of DDT (in houses and cattle sheds)	Dimensionless	0.54 (95% CI, 48.7--59.3) <sup>20</sup>
$C_{t0}$	Initial efficacy of Deltamethrin (in houses and cattle sheds)	Dimensionless	$9.75 \times 10^{-01}$ <sup>14</sup>
$b_l$	Decay rate of both insecticides' lethal effect inside houses	Fraction per day	0.012 (0.009) (Estimated in Appendix 1, using data from <sup>20</sup> )

$b_2$	Decay rate of both insecticides' lethal effect inside cattle sheds	Fraction per day	0.081 (0.055) (Estimated in Appendix 1, using data from <sup>22</sup> )
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CI: confidence interval, kg : kilogram

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

**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 per day per sandfly	Objective function value obtained from the model (equation derived in Appendix 2)
$\tilde{C}(x,y)$	Total cost of insecticide materials and spray campaign implementation	Rs.	Budget constraint in the model (equation derived in Appendix 3)
$\tilde{C}_{UB}$	Upper bound on the budget available for the spray campaign	Rs.	User-defined (budget) value in the model
$x$	Insecticide allocated per capita for a 60-day spray period	kg per person	Decision variable value obtained from the model
$y$	Insecticide allocated per cattle for a 60-day spray period	kg per cattle	Decision variable value obtained from the model

Rs: Rupees

A parameter termed the “*human visitation rate*” of mosquitoes<sup>24</sup> was used to analyze malaria transmission dynamics. A similar parameter (*human visitation proportion, Q*), captured in the objective function of our model, is used to quantify the proportion of sandflies visiting human and cattle sites based on the attraction rate of the vector *P. argentipes* towards the blood of each host. The feeding behavior of the vector is thus directly incorporated into the model.



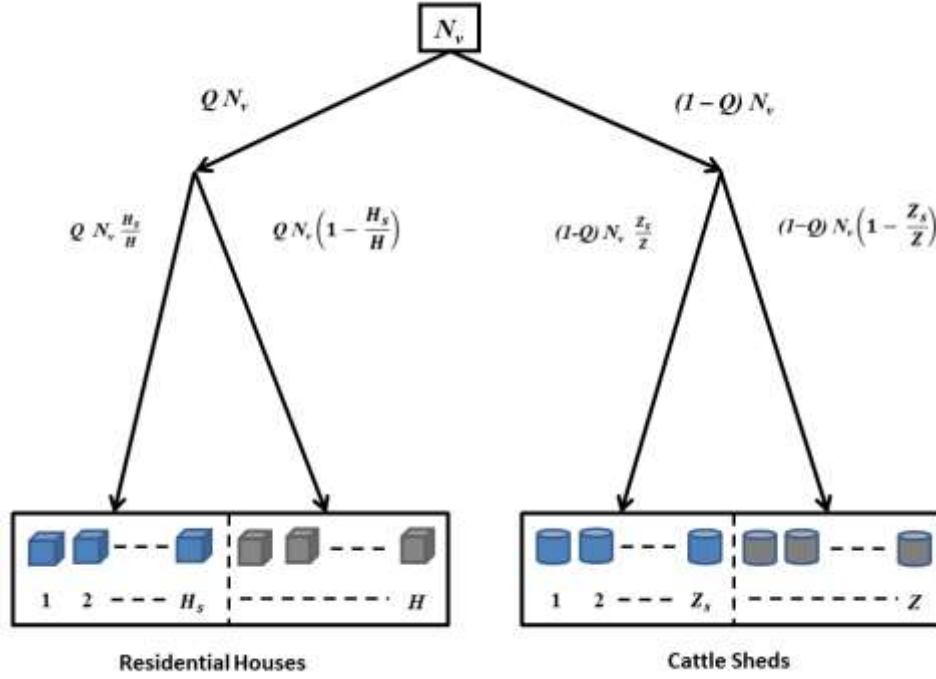
Temporal exponential functions ( $h(\tau)$ , Equation 1 and  $z(\tau)$ , Equation 2) are used to capture the deteriorating lethal effect of the insecticide on vectors, and these include parameters such as decay rate ( $b_1$  and  $b_2$ ) and initial efficacy ( $C_{t0}$ ).<sup>21</sup> The proportions of sandflies that die on the  $\tau^{\text{th}}$  day after insecticide application inside houses and cattle sheds, respectively, are thereby given by

$$h(\tau) = C_{t0}e^{-b_1\tau}, \quad \forall \tau \quad \mathbf{1}$$

and

$$z(\tau) = C_{t0}e^{-b_2\tau}, \quad \forall \tau. \quad \mathbf{2}$$

The value of initial efficacy ( $C_{t0}$ ) for both insecticides is assumed to be equal in both houses and cattle sheds. Figure 1 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 (Equation 3) uses this distribution of the sandfly population. Appendix 2 shows the derivation of the insecticide-induced death rate (objective function) at sprayed sites on the  $\tau^{\text{th}}$  day 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 thus used in this study to refer to the number of houses ( $H_s$ ) and cattle sheds ( $Z_s$ ) where insecticide is sprayed. Appendix 4 shows the model formulation in terms of  $x$  and  $y$  only.



**Figure 1. Distribution of the daily sandfly population based on their blood-feeding behavior.**

The total sandfly death rate is calculated by adding the natural death rate ( $\mu_v$ ) and the insecticide-induced death rate ( $d_v$ ) at sprayed sites. The first and second terms of the objective function (Equation 3) are therefore 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 of the model describes the **budget constraint** (Equation 4), which ensures that the total spray campaign cost (materials and implementation in Table 3) is less than or equal to the available state budget. Furthermore, insecticide applications are assumed to occur only once per year rather than the existing policy of spraying twice per year in Bihar (derivation of spray campaign cost equation in Appendix 3).

**Table 4. Materials and implementation costs related to the insecticide spray campaign**

Symbol	Materials cost	Unit	Estimate
$N_1$	Cost per kg of insecticide (DDT)	Rs./kg of DDT	90 <sup>23</sup>
$N_1$	Cost per kg of insecticide (Deltamethrin)	Rs./kg of Deltamethrin	810 <sup>23</sup>
	<b>Implementation cost: Personnel and maintenance</b>	<b>Unit</b>	<b>Estimate</b>
$N_2$	Number of spraying teams or squads allocated per 10 lakh population of a district	Squads/person	55/10 <sup>6 13</sup>
$N_3$	Number of supervisors per squad	Number of supervisors/squad	1 <sup>13</sup>
$N_4$	Number of field workers per squad	Number of workers/squad	5 <sup>13</sup>
$N_5$	Salary paid to each supervisor/day of the 60-day spray period	Rs./day/supervisor	145 <sup>13</sup>
$N_6$	Salary paid to each field worker/day of the 60-day spray period	Rs./day/worker	118 <sup>13</sup>
$N_7$	Number of days allocated for spraying activity each time spraying is carried out	Number of days	60 <sup>13</sup>
$N_8$	Funds allocated per squad for the repair and purchase of spray equipment per 60-day spray period	Rs./squad/60-day spray period	950 <sup>13</sup>
	<b>Implementation cost: Operational expenses</b>	<b>Unit</b>	<b>Estimate</b>
$N_9$	Funds allocated to the district for the transportation of DDT/PHC in the district (assumed per 60-day spray period)	Rs./ PHC	3500 <sup>13</sup>
$N_{10}$	Funds allocated to the district as office expense per squad in the district (assumed per 60-day spray period)	Rs./squad	250 <sup>12</sup>
$N_{11}$	Funds allocated as contingency/squad (assumed per 60-day spray period)	Rs./ squad	250 <sup>13</sup>
$N_{12}$	Total funds allocated per district for general vehicle mobility/month of spray period	Rs./ month	20000 <sup>13</sup>
$N_{13}$	Funds allocated per district for PHC vehicle mobility/day/PHC for the 60-day spray period	Rs./day/PHC	650 <sup>13</sup>
$N_{14}$	Funds allocated for supervision/affected PHC (assumed per 60-day spray period)	Rs./affected PHC	2000 <sup>13</sup>
$N_{15}$	Funds allocated for education and communication activities per affected	Rs./affected PHC	2000 <sup>13</sup>

	PHC (assumed per 60-day spray period)		
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Exchange rate in year 2000: 1 USD = INR 45.

The third component consists of the **remaining constraints** (inequalities 5 to 9) of the model, which are related to insecticide consumption and sites under the insecticide intervention program (Appendix 4). As before, it is assumed that the budget is not enough to spray all houses and cattle sheds during the spray campaign (resource-limited cases).

In the model, only two types of sites are sprayed: human dwellings and cattle sheds (mixed dwellings do not exist). The other assumptions are: cattle are the only non-human hosts that sandflies bite; all houses are assumed to have an average area of 200 m<sup>2</sup> based on a previous estimate;<sup>23</sup> and the insecticide necessary to spray one cattle shed is assumed to be half that required to cover one house. Using the three above-described components and their assumptions, the model can thus be described as follows:

Maximize,

$$d_v = Q[h(\tau)]\left(\frac{H_s}{H}\right) + (1 - Q)[z(\tau)]\left(\frac{Z_s}{Z}\right) \quad \mathbf{3}$$

Subject to,

$$\tilde{C}(x, y) = N_h N_1 x + N_c N_1 y + \tilde{C}_{Im} \leq \tilde{C}_{UB} \quad \mathbf{4}$$

$$0 \leq H_s \leq H \quad \mathbf{5}$$

$$H_s = \left(\frac{N_h x}{I_h}\right) \quad \mathbf{6}$$

$$0 \leq Z_s \leq Z \quad \mathbf{7}$$

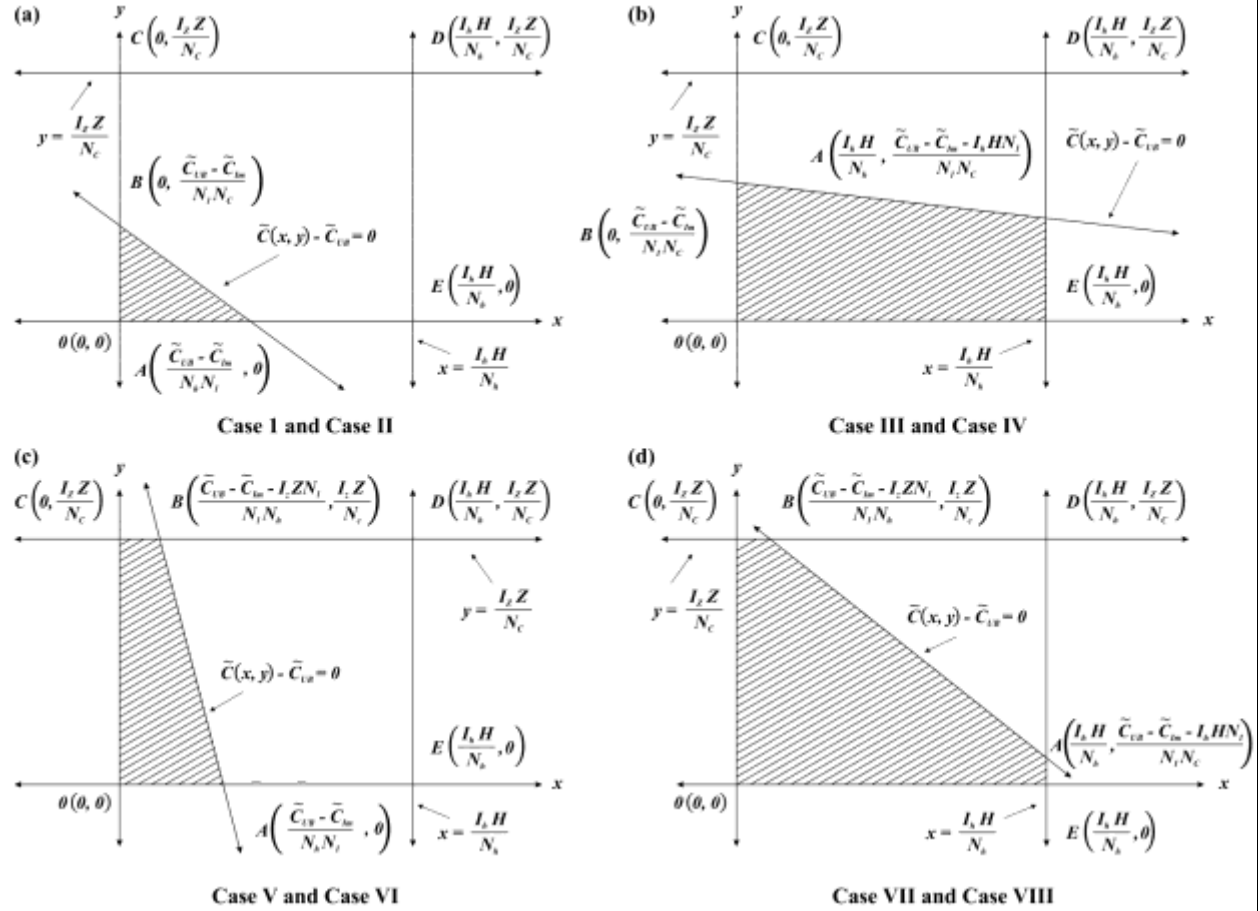
$$Z_s = \left( \frac{N_c y}{I_z} \right) \quad 8$$

$$x, y \geq 0 \quad 9$$

### ANALYSIS

**Optimal solution for the model.** This section describes the detailed steps towards finding possible solutions of the model. Clearly, an optimal solution of the model represents the allocation of per-capita insecticide at the two sites (decision variables  $x^*$  and  $y^*$ ) that maximizes the insecticide-induced death rate. An optimal solution can thus occur at one of the four distinct points in the feasible domain of the model depending on the conditions based on the model parameters (Table 5). Table S 5 in the Appendix provides the different abbreviations used in this paper.

The feasible domain of the insecticide-induced death rate (objective function)  $d_v(x,y)$ , where  $d_{vA}$  represents the value of the function at point A in the domain, is a 2D region defined by constraints 4 through 9. The horizontal axis of the feasible domain represents the per-capita amount of insecticide allocated at house sites ( $x$ ) and the vertical axis represents the per-capita amount of insecticide allocated at cattle sites ( $y$ ).



**Figure 2. The feasible domain of the optimization model. (a) Case I (Case II) arises when constraint 4 intersects with constraint 9 (between OC and OE) resulting in point A (point B) as an optimal solution. (b) Case III (Case IV) arises when constraint 4 intersects with constraint 9 and constraint 5 (between OC and DE) resulting in point A (point B) as an optimal solution. (c) Case V (Case VI) arises when constraint 4 intersects with constraint 9 and constraint 7 (between OE and CD) resulting in point A (point B) as an optimal solution. (d) Case VII (Case VIII) arises when constraint 4 intersects with constraint 5 and constraint 7 (between DE and CD) resulting in point A (point B) an optimal solution.**

Figure 2(a) illustrates Cases I and II (details in Figure 2(a) caption) within which O, A, and B are the corner points of the feasible domain. An optimal solution in these cases exists at either point

A or point B. It is simple to see that the total insecticide-induced death rate at point A is always less than or equal to the corresponding value at point E, that is,  $d_{vA} \leq d_{vE}$  (substituting the points A and E into Equation 3) or

$$\widetilde{C}_{UB} - \widetilde{C}_{Im} \leq I_h H N_1 \quad 10$$

Similarly, the total insecticide-induced death rate at point B is always less than or equal to that at point C, that is,  $d_{vB} \leq d_{vC}$ , which simplifies to

$$\widetilde{C}_{UB} - \widetilde{C}_{Im} \leq I_z Z N_1 \quad 11$$

Case I (if an optimal solution occurs at point A, Figure 2(a)): Since  $d_{vB} < d_{vA}$ ,

$$\frac{(1 - Q) z(\tau)}{I_z Z} < \frac{Q h(\tau)}{I_h H} \quad 12$$

Note that the left-hand side of inequality 12 can be interpreted as the ratio of the insecticide-induced death rate  $((1 - Q) h(\tau))$  to the insecticide consumed in cattle sheds  $(I_z Z)$ . Similarly, the right-hand side of inequality 12 can be interpreted as the same ratio for houses. Hence, inequality 12 shows that if an optimal solution occurs at point A, then the insecticide-induced death rate per kilogram of insecticide consumed for houses is greater than the corresponding ratio for cattle sheds. Inequality 12 thus simplifies to

$$(1 - Q) z(\tau) I_h H < Q h(\tau) I_z Z \quad 13$$

In this case, an optimal solution occurs at point A ( $d_{vB} < d_{vA} \leq d_{vE}$ ).

Case II (if an optimal solution occurs at point B, Figure 2(a)): Since  $d_{vA} < d_{vB}$ ,

$$Q h(\tau) I_z Z < (1 - Q) z(\tau) I_h H \quad 14$$

In this case, an optimal solution occurs at point B ( $d_{vA} < d_{vB} \leq d_{vC}$ ). Figure 2(b) illustrates Cases III and IV (details in Figure 2(b) caption). An optimal solution in these cases exists at either point A or point B, where it is simple to see  $d_{vE} < d_{vA} \leq d_{vD}$ , that is,

$$I_h H N_1 < \widetilde{C}_{UB} - \widetilde{C}_{Im} \leq I_h H N_1 + I_z Z N_1 \quad 15$$

In Cases III and IV,  $d_{vB} \leq d_{vC}$  satisfies naturally, which simplifies to inequality 11.

Case III (if an optimal solution occurs at point A, Figure 2(b)): In this case,  $d_{vB} < d_{vA}$  (inequality 13) and  $d_{vE} < d_{vA} \leq d_{vD}$  (inequality 15) are obvious to see. Hence, an optimal solution occurs at point A, as shown in Figure 2(b).

Case IV (if an optimal solution occurs at point B, Figure 2(b)): In this case,  $d_{vA} < d_{vB}$  (inequality 14) and  $d_{vB} \leq d_{vC}$  (inequality 11). Hence, an optimal solution occurs at point B, as shown in Figure 2(b). Figure 2(c) illustrates Cases V and VI (details in Figure 2(c) caption). For these cases, an optimal solution exists only at point A or at point B.  $d_{vA} \leq d_{vE}$  and  $d_{vC} < d_{vB} \leq d_{vD}$  follow naturally, which simplifies, respectively, to inequality 10 and

$$I_z Z N_1 < \widetilde{C}_{UB} - \widetilde{C}_{Im} \leq I_h H N_1 + I_z Z N_1 \quad 16$$

Case V (if an optimal solution occurs at point A, Figure 2(c)): In this case,  $d_{vB} < d_{vA}$  (inequality 13) and  $d_{vA} \leq d_{vE}$  (inequality 10). Hence, an optimal solution occurs at point A.

Case VI (if an optimal solution occurs at point B, Figure 2(c)): In this case,  $d_{vC} < d_{vB} \leq d_{vD}$  (inequality 16) and  $d_{vA} < d_{vB}$  (inequality 14). Hence, an optimal solution occurs at point B. Figure 2(d) illustrates Cases VII and VIII (details in Figure 2(d) caption). An optimal solution in these cases exists only at point A or at point B. It can be seen  $d_{vC} < d_{vB} \leq d_{vD}$  (inequality 16). The total insecticide-induced death rate ( $d_v$ ) at points A, E, and D satisfies the inequality:  $d_{vE} < d_{vA} \leq d_{vD}$  (inequality 15)

Case VII (if an optimal solution occurs at point A, Figure 2(d)): In this case,  $d_{vE} < d_{vA} \leq d_{vD}$  (inequality 15) and  $d_{vB} < d_{vA}$  (inequality 13), and hence an optimal solution occurs at A.

Case VIII (if an optimal solution occurs at point B, Figure 2(d)): In this case,  $d_{vC} < d_{vB} \leq d_{vD}$  (inequality 16) and  $d_{vA} < d_{vB}$  (inequality 14). Hence, an optimal solution occurs at point B.



Since some of these eight cases above result in the same optimal points, the results can be summarized into four distinct points (Table 5). 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  $\tau$  and  $\widetilde{C}_{UB}$  (refer to Table 2 and Table 3 for the parameter definitions).

**Table 5. Optimal solution for the model**

Existence		Solution Symbol	$(x^*(\tau, \widetilde{C}_{UB}), y^*(\tau, \widetilde{C}_{UB}))$
Condition I	Condition II		
$\widetilde{C}_{UB} - \widetilde{C}_{Im} \leq K_1 N_1$	$\frac{L_2}{K_2} < \frac{L_1}{K_1}$	FS 1	$\left( \frac{\widetilde{C}_{UB} - \widetilde{C}_{Im}}{N_1 N_h}, 0 \right)$
$K_1 N_1 < \widetilde{C}_{UB} - \widetilde{C}_{Im} \leq N_1(K_1 + K_2)$	$\frac{L_2}{K_2} < \frac{L_1}{K_1}$	FS 2	$\left( \frac{K_1}{N_h}, \frac{\widetilde{C}_{UB} - \widetilde{C}_{Im} - K_1 N_1}{N_1 N_c} \right)$
$\widetilde{C}_{UB} - \widetilde{C}_{Im} \leq K_2 N_1$	$\frac{L_1}{K_1} < \frac{L_2}{K_2}$	FS 3	$\left( 0, \frac{\widetilde{C}_{UB} - \widetilde{C}_{Im}}{N_1 N_c} \right)$
$K_2 N_1 < \widetilde{C}_{UB} - \widetilde{C}_{Im} \leq N_1(K_1 + K_2)$	$\frac{L_1}{K_1} < \frac{L_2}{K_2}$	FS 4	$\left( \frac{\widetilde{C}_{UB} - \widetilde{C}_{Im} - K_2 N_1}{N_1 N_h}, \frac{K_2}{N_c} \right)$
$\widetilde{C}_{UB} - \widetilde{C}_{Im} > N_1(K_1 + K_2)$		FS 5	$\left( \frac{K_1}{N_h}, \frac{K_2}{N_c} \right)$
$\widetilde{C}_{UB} < \widetilde{C}_{Im}$		INFS	Infeasible

$L_1 = Q h(\tau)$ ,  $L_2 = (1 - Q) z(\tau)$ ,  $K_1 = I_h H$ ,  $K_2 = I_z Z$ ; The solution is valid only when both existence conditions are satisfied. A feasible solution (FS) does not exist (INFS) if  $\widetilde{C}_{UB} < \widetilde{C}_{Im}$ .

Therefore, FS 5 (Table 5) implies that surplus money will be left over (Rs.  $(\widetilde{C}_{UB} - \widetilde{C}_{Im} - N_1(K_1 + K_2))$ ) after spraying 100% of both sites (point D in Figure 2). The notations used for the optimal solution are presented in Table 6.

**Table 6. Notations used for the optimal solution**

Notation	Explanation
FS 1	Spray the maximum possible number of houses with the given budget
FS 2	Spray 100% of houses and then the maximum possible number of cattle sheds with the remaining budget

FS 3	Spray the maximum possible number of cattle sheds with the given budget
FS 4	Spray 100% of cattle sheds and then the maximum possible number of houses with the remaining budget
FS 5	Spray 100% of houses and cattle sheds

**Benefit to Material Cost Ratio.** The analysis in this subsection, by using a simple *BMCR* function, is developed independent of the optimization model and is used to analyze spray coverage. The optimization model discussed in the above subsection maximizes the instantaneous (on the  $\tau^{th}$  day after spraying) insecticide-induced sandfly death rate within the available budget. By contrast, the *BMCR* approach identifies the cumulative number of sandflies killed (“benefit”) per unit of materials cost until the  $\tau^{th}$  day after spraying. However, while the optimization model assumes a constant  $N_v$  (Table S 3. in Appendix 2), the *BMCR* assumes an exponentially decaying sandfly population.

Using the notation presented in Table 2, the benefit in houses and cattle sheds  $\tau$  days after spraying depends on  $Q, H_s, Z_s, h(\tau)$ , and  $z(\tau)$ . The amount of insecticide consumed for spraying  $H_s$  houses and  $Z_s$  cattle sheds is  $I_h H_s$  and  $I_z Z_s$ , respectively. The materials cost of spraying houses and cattle sheds can be expressed as (Rs.)  $N_1 I_h H_s$  and (Rs.)  $N_1 I_z Z_s$ , respectively.

In the next step, the two contrasting extreme spray coverage options ( $O_h$  and  $O_z$ ) are compared using the *BMCR* function.  $O_h$  and  $O_z$  are the options of spraying insecticide only in 100% houses ( $O_h: H_{s1} = H, Z_{s1} = 0$ ) and only in 100% cattle sheds ( $O_z: H_{s2} = 0, Z_{s2} = Z$ ), respectively. When  $H_{s1}$  houses are sprayed (Equation 3), the insecticide-induced death rate per sandfly on the  $\tau^{th}$  day is given by

$$Q C_{t0} e^{-b_1 \tau} \frac{H_{s1}}{H} \quad 17$$

For  $O_h$ , by substituting  $\frac{H_{s1}}{H} = 1$  in Equation 17, the solution representing the number of sandflies alive on the  $\tau^{th}$  day can be expressed as

$$N(\tau) = \frac{N_0}{e^{\frac{Q C_{t0}}{b_1}}} e^{Q C_{t0} \frac{e^{-b_1 \tau}}{b_1}}$$

where  $\tau = 0, N(0) = N_0$ .

Hence,  $BMCR$  for option  $O_h$  is given by

$$BMCR_h(\tau) = \frac{N_0 \left( 1 - \frac{e^{Q C_{t0} \frac{e^{-b_1 \tau}}{b_1}}}{e^{\frac{Q C_{t0}}{b_1}}} \right) \text{ sandflies killed}}{N_1 I_h H \text{ Rupees spent}} \quad 18$$

Similarly,  $BMCR$  for  $O_z$  is

$$BMCR_z(\tau) = \frac{N_0 \left( 1 - \frac{e^{(1-Q) C_{t0} \frac{e^{-b_2 \tau}}{b_2}}}{e^{\frac{(1-Q) C_{t0}}{b_2}}} \right) \text{ sandflies killed}}{N_1 I_z Z \text{ Rupees spent}} \quad 19$$

By using the two  $BMCR$ s (Equations 18 and 19) corresponding to the two extreme options  $O_h$  and  $O_z$ , four scenarios can be derived (Table 7). Only one of these four scenarios occurs for a given parameter set. For scenarios III and IV only, the  $BMCR$ s for these two options become equal at a particular  $\tau$  ( $= \tau^*$ ) value. The last two columns of Table 7 recommend the values of time after spraying ( $\tau$ ) until which the  $BMCR$  is higher for a particular option. When the  $BMCR$  is equal for both options, the default policy of spraying houses for all values of  $\tau$  is recommended.

**Table 7. A particular scenario exists if its corresponding pair of parameter conditions is satisfied. For an existing scenario, one of the two spray options can be selected (knowing that a high *BMCR* is desirable  $\tau$  days after spraying).**

Scenario	Pair of conditions satisfied	Existence of $\tau^*$ (when $BMCR_h(\tau) = BMCR_z(\tau)$ )	The <i>BMCR</i> is higher in	
			houses for	cattle sheds for
I	$\Theta_1 K_2 \leq K_1$ , $\Theta_2 e^{(b_2-b_1)\tau+Ve^{-b_1\tau}-We^{-b_2\tau}} K_2 < K_1$	No	$\forall \tau$	
II	$K_1 \leq \Theta_1 K_2$ , $K_1 \leq \Theta_2 e^{(b_2-b_1)\tau+Ve^{-b_1\tau}-We^{-b_2\tau}} K_2$	No		$\forall \tau$
III	$\Theta_1 K_2 < K_1$ , $K_1 < \Theta_2 e^{(b_2-b_1)\tau+Ve^{-b_1\tau}-We^{-b_2\tau}} K_2$	Yes	$0 \leq \tau \leq \tau^*$	$\tau^* < \tau$
IV	$K_1 < \Theta_1 K_2$ , $\Theta_2 e^{(b_2-b_1)\tau+Ve^{-b_1\tau}-We^{-b_2\tau}} K_2 < K_1$	Yes	$\tau^* \leq \tau$	$0 \leq \tau < \tau^*$

Here,  $V = \frac{Q C_{t0}}{b_1}$  and  $W = \frac{(1-Q) C_{t0}}{b_2}$ ;  $\Theta_1 = \frac{e^W (e^V - 1)}{e^V}$  and  $\Theta_2 = \frac{V b_1 e^W}{W b_2 e^V}$ ;  $O_h$ -spray coverage of 100% houses;  $O_z$ -spray coverage of 100% cattle sheds

Although the discussion below is based on the assumed spray coverage options  $O_h$  and  $O_z$ , it can be applied for any values of spray coverage. The foregoing allows us to conclude the following:

**Remark 1.** In summary, after the first round of spraying ( $\tau = 0$ ), if the aim is to always maintain a higher *BMCR* in houses, then scenarios I and II might be helpful. If scenario I exists, implementing  $O_h$  is recommended. If scenario II exists, then implementing  $O_z$  is recommended.

**Remark 2.** If sandfly density peaks  $\tau_1$  days after the first round of spraying (e.g., due to the start of the rainy season) and a second round of spraying is not possible at time  $\tau_1$  within the available budget, then it is advisable to implement the spray option that maintains a higher *BMCR* at time  $\tau_1$ .

Scenario III (IV) suggests that, for  $\tau < \tau^*$ , the *BMCR* will be higher for  $O_h(O_z)$  and that, for  $\tau^* < \tau$ , the *BMCR* will be higher for  $O_z(O_h)$ . Thus:

- i) If scenario III occurs and  $\tau_1 < \tau^*$  days, implementing  $O_h$  is recommended, because after  $\tau_1$  days, the *BMCR* is higher for  $O_h$  ( $BMCR_z(\tau_1) < BMCR_h(\tau_1)$ ), (implying that by implementing  $O_h$ , a higher reduction in sandfly density per rupee invested will have been

achieved in  $\tau_1$  days). However, if  $\tau_1 > \tau^*$  days, then implementing  $O_z$  is recommended, because  $BMCR_h(\tau_1) < BMCR_z(\tau_1)$ .

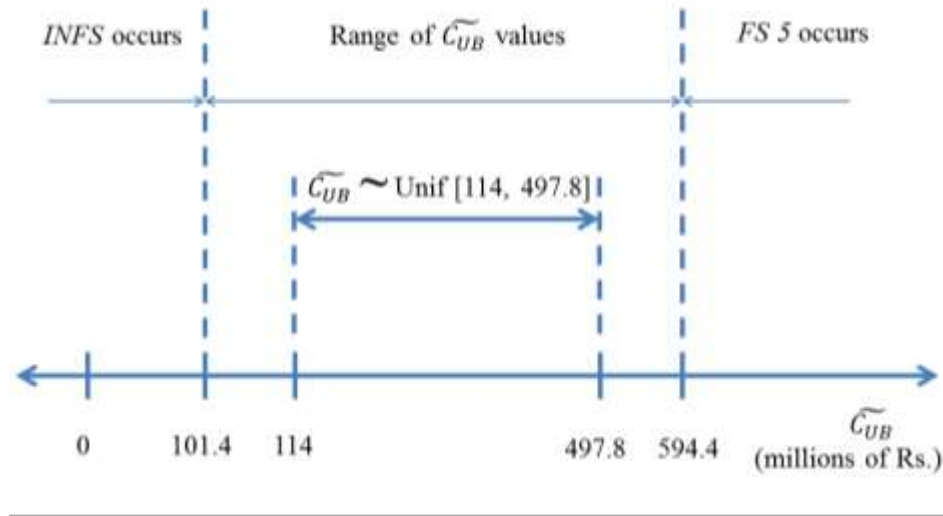
- ii) If scenario IV occurs and  $\tau_1 < \tau^*$  days, implementing  $O_z$  is recommended, because  $BMCR_h(\tau_1) < BMCR_z(\tau_1)$ . However, if  $\tau_1 > \tau^*$  days, then implementing  $O_h$  is recommended, because  $BMCR_z(\tau_1) < BMCR_h(\tau_1)$ .

## NUMERICAL RESULTS

This section compares the impact on the sandfly death rate of the two studied insecticides (DDT and Deltamethrin) by developing and analyzing a deterministic optimization model. The estimates of certain model parameters for Bihar are not available in the literature. This study thus estimates and provides a procedure to extract information on these parameters indirectly by using the available data. The estimates of all these parameters are shown in Table 2. The *human visitation proportion* ( $Q$ ) and the decay rates in houses<sup>14</sup> ( $b_1$ ) and cattle sheds<sup>22</sup> ( $b_2$ ) are estimated by using multiple existing datasets as described in Appendix 1. By using estimated values of  $Q$ ,  $b_1$ , and  $b_2$ ,  $h(\tau)$  and  $z(\tau)$  are then estimated (Figure 9 in Appendix 1). Moreover, by using assumed probability distributions for the input parameters, the test instance (sample) of input parameters are generated in order to examine the distribution of the model outputs. Since the parameter estimates are obtained from various datasets, the uncertainty and sensitivity analyses of the model output are performed using the assumed distributions of the estimated parameters.

**Uncertain parameter estimates.** The parameters  $a_h$ ,  $C_{t0}$ ,  $b_1$ ,  $b_2$ , and  $\widetilde{C}_{UB}$  are primarily uncertain and the source of uncertainty in the model output. The female sandfly's feeding preference for human hosts ( $a_h$ ) in North Bihar,<sup>4</sup> sandfly lifespan ( $\mu_v$ ) in Pondicherry,<sup>25</sup> and insecticide's initial efficacy ( $C_{t0}$ ) are assumed to follow a truncated (at zero) normal distribution.

A discrete uniform distribution is estimated<sup>26</sup> for  $b_1$  and  $b_2$  by using various data sources (Appendix 1). In order to capture the different possibilities of the future state budgets for the spray campaign, we assume a uniform distribution for  $\widetilde{C}_{UB}$ , with the minimum and maximum values estimated based on the budget estimates of 2010--2011<sup>13</sup> (Rs. 114 million) and 2012--2013<sup>27</sup> (Rs. 497.8 million), respectively (Figure 3). The minimum ( $\widetilde{C}_{min} = \text{Rs. } 101.4 \text{ million}$ ) and maximum ( $\widetilde{C}_{max} = \text{Rs. } 594.4 \text{ million}$ ) money amounts (unlimited financial resources) required to conduct the spray campaign are estimated in Appendix 3.  $\widetilde{C}_{min}$  and  $\widetilde{C}_{max}$  represent the worst and best case scenarios, respectively.



**Figure 3. Total range and distribution assumed for  $\widetilde{C}_{UB}$ . FS: Feasible solution; INFS: Infeasibility. Figure not to scale. The estimate of  $\widetilde{C}_{Im}$  (= Rs. 101.4 million) is the addition of all non-materials costs in the 2010 budget and  $\widetilde{C}_{max} = \text{Rs. } 594.4 \text{ million}$  is the amount of money required to spray 100% of sites in Bihar.**

**Comparison of insecticides.** The results from the optimization model provide an optimal insecticide allocation (kg per capita) (decision variables:  $(x^*, y^*)$ ) over the maximum insecticide-induced death rate (objective function) for the available state budget. This model requires two

inputs, namely decay time ( $\tau$ ) and available budget ( $\widetilde{C_{UB}}$ ), in order to yield these results and provides an optimal solution by finding the pair of conditions satisfied in Table 5 as well as using the corresponding feasible solution.

Table 8 compares the optimal insecticide-induced death rate for different scenarios  $\tau$  days after spraying (e.g.,  $\tau = 30$  and 90 days) by using the estimated model parameters (Table 2 and Table 4). If the aim is to achieve the highest possible sandfly mortality 30 days after spraying, then the model results suggest implementing the campaign in cattle sheds. However, if the aim is to achieve the highest possible sandfly mortality 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 would be a better option.

**Table 8. Optimal insecticide allocation ( $x^*$ ,  $y^*$ ) ( $\widetilde{C_{UB}} = Rs. 114 \text{ million}$ ,  $\tau$  varied). Unit:  $x^*$  is kg/person,  $y^*$  is kg/cattle; the results show  $d_v^*$ ,  $x^*$ , and  $y^*$  in brackets  $\tau$  days after spraying. The numerical results that compare the insecticides are shaded.**

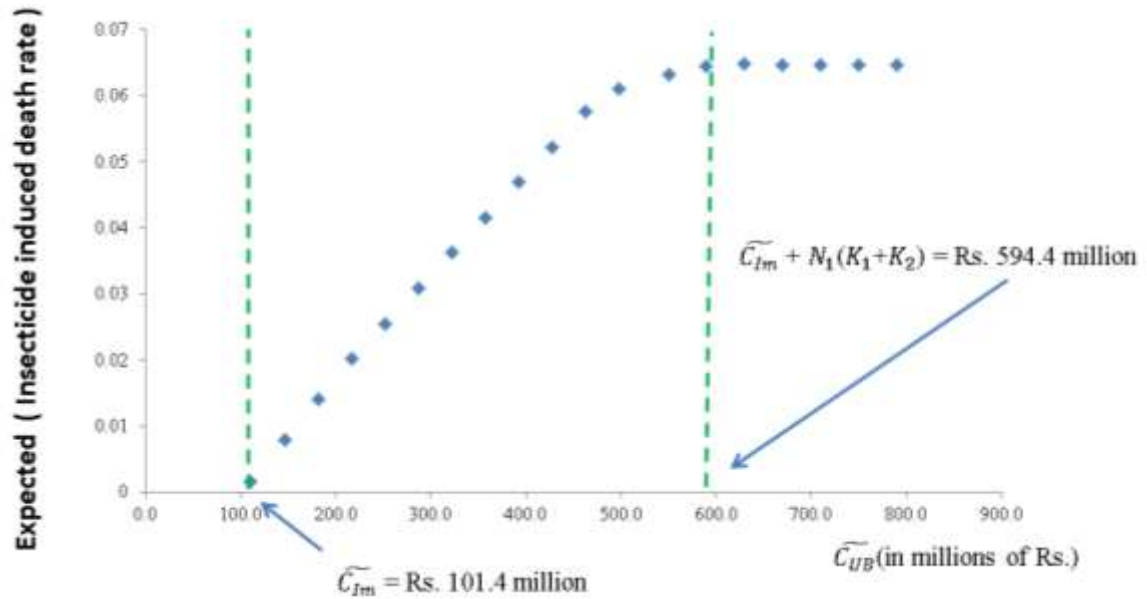
$\tau$	$d_v^*$ ; ( $x^*$ , $y^*$ )	
	DDT	Deltamethrin
30	0.39 E-02; (0, 0.64 E-02)	0.10 E-02; (0, 0.71 E-03)
90	<b>0.15 E-02; (0.41 E-02, 0)</b>	<b>0.41 E-03; (0.45 E-03, 0)</b>

The model results using the estimated parameters (Table 8) 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) (last row and last two columns in Table 8). The model thus suggests that Deltamethrin might not be a good replacement for DDT.

Moreover, Bihar presently allocates 0.375 E-01 kilograms of DDT per person and 0 kilograms of DDT per cattle.<sup>12</sup> 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 2 in Appendix 2, 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  $(x,y) = (0.0375,0)$  into constraint 6, 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 2 in Appendix 2, the percentage increase in the death rate that can be achieved a certain number of days after spraying insecticide can be estimated.

**Uncertainty analyses of the optimal insecticide-induced death rate under different budgets.** The uncertainty analysis showed that the expected insecticide-induced death rate increases (initially at a constant rate followed by no change after a critical budget value) with an increase in the available budget for the insecticide spraying campaign (Figure 5).





**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.  $\widetilde{C}_{Im}$  is implementation cost.

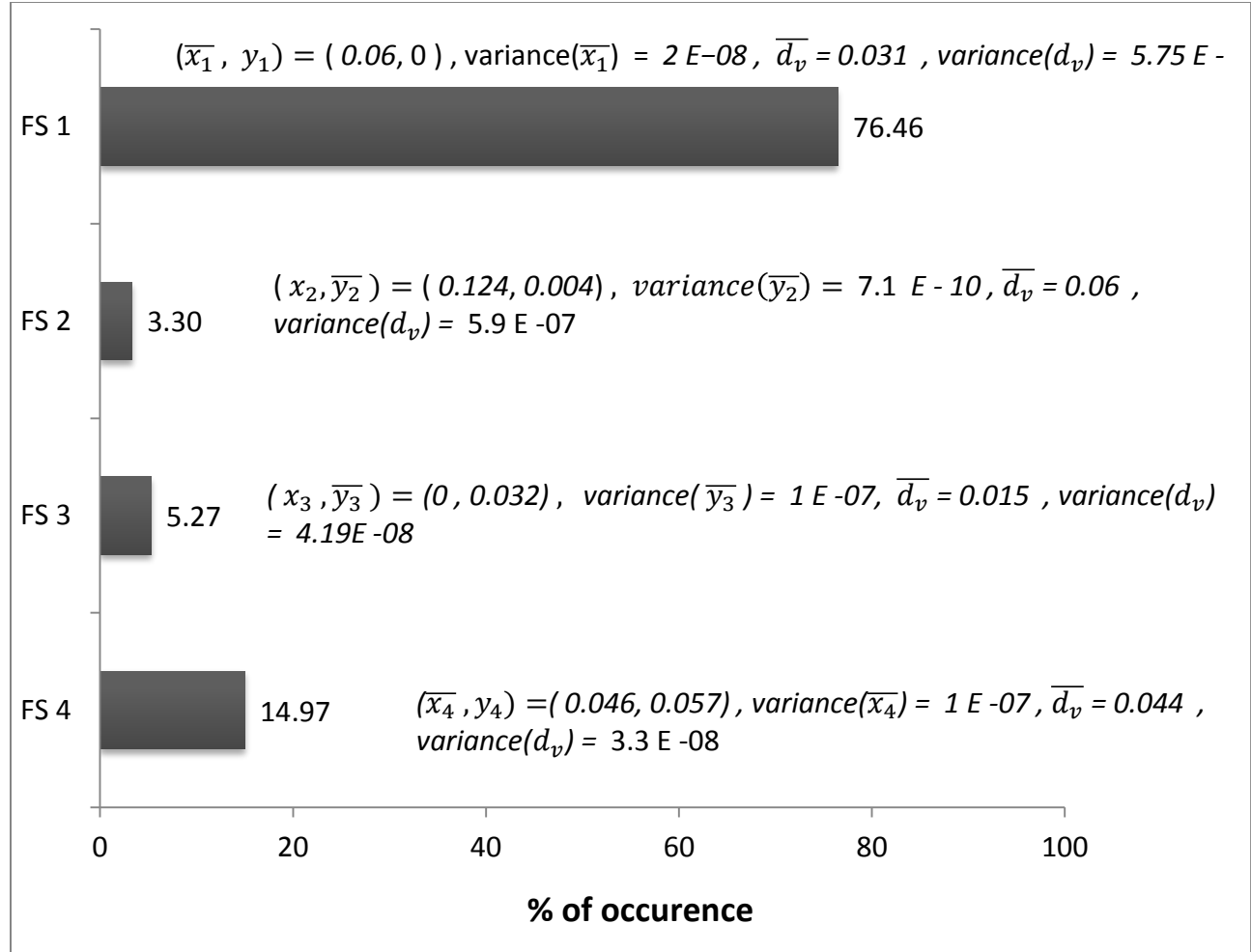
The rate of increase in the insecticide-induced death rate is relatively less beyond  $\widetilde{C}_{UB} = \text{Rs. } 594.4$  million. This value is referred to as the critical budget value. It reaches a maximum value of 0.064 sandflies dead/day/sandfly when the budget allocated is sufficient to cover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

**Uncertainty and sensitivity analyses of the model solutions.** 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.<sup>28</sup> Mathematical models used for recommending optimal intervention strategies must account for such parameter uncertainty.<sup>29</sup> Uncertainty analyses were performed in this study to investigate the uncertainty in the model outputs caused by the assumed distributions in the input parameters. The model outputs studied

were the occurrences of the feasible solutions (*FS 1*, *FS 2*, *FS 3*, and *FS 4*) and the distribution of the objective function value (insecticide-induced death rate).

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 are most statistically influential in determining the magnitude of the output parameters. Partial rank correlation coefficients were used in this study as a sensitivity index to estimate the strength of the linear association between the input parameters ( $a_h$ ,  $\mu_v$ ,  $C_{i0}$ ,  $b_1$ , and  $b_2$ ) and output parameter ( $d_v$ ).<sup>26</sup>

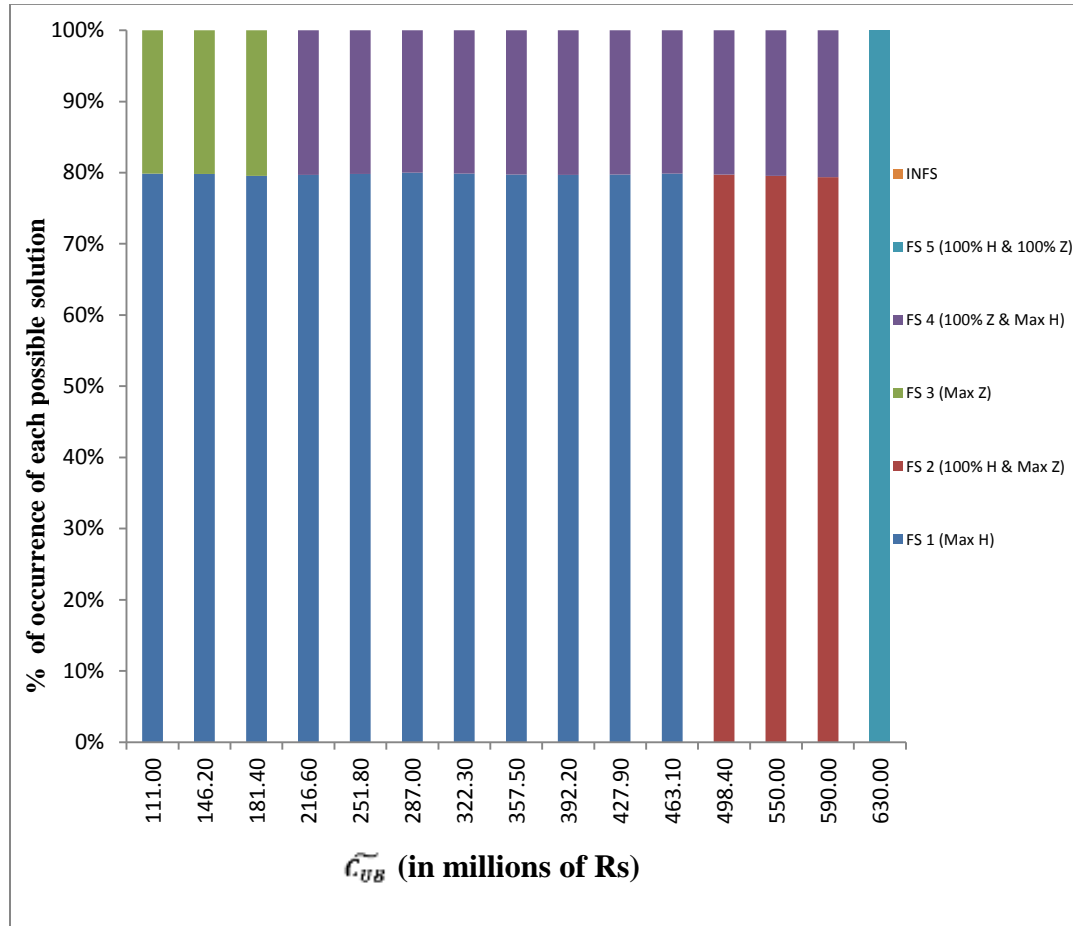
**Parameter distributions.** Independent samples were drawn  $10^5$  times from the probability distributions assigned to the five uncertain parameters ( $a_h$ ,  $\mu_v$ ,  $C_{i0}$ ,  $b_1$ ,  $b_2$ , and  $\widetilde{C}_{UB}$ ) using a Monte-Carlo simulation. The percentage occurrences of each of the five possible solutions and the decision variable statistics are plotted in Figure 5. The percentage distributions of these feasible solutions were calculated by averaging 10 Monte-Carlo samples each with a size of  $10^5$  sampled parameter values. Figure 5, Figure 6, and Figure 8 are generated by assuming  $\tau = 90$  days and DDT as the insecticide.



**Figure 5. Percentage occurrences of the four feasible solutions of the model.  $d_v$ : the insecticide-induced death rate. Variance is calculated only when the decision variable or insecticide-induced death rate varies with the uncertain parameters. Note: For the distribution assigned to  $\widetilde{C_{UB}}$ , *INFS* and *FS 5* cannot occur.**

Based on the test instance values of the input parameters, *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 model solutions expressed in words in Table 6, spraying the required percentage of houses only (*FS 1*) is recommended the most number of times.

**Distribution of model outputs.** The occurrences of the six possible model solutions were plotted (Figure 6) by varying  $\tilde{C}_{UB}$  from its minimum ( $\tilde{C}_{min}$ ) to maximum ( $\tilde{C}_{max}$ ) values.

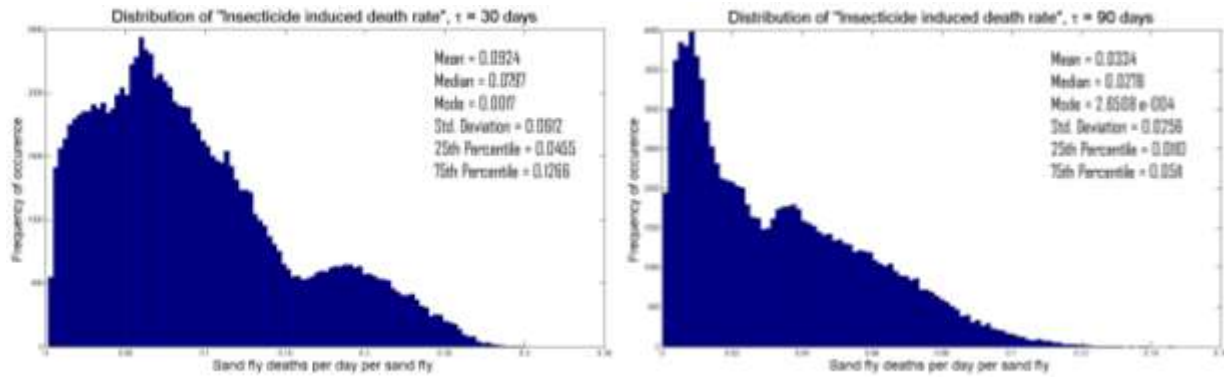


**Figure 6. Occurrences of the six possible solutions versus  $\tilde{C}_{UB}$  (in millions of Rs). FS 1 (Max H), FS 2 (100% H and Max Z), FS 3 (Max Z), FS 4 (100% Z and Max H), and FS 5 (100% H and 100% Z); H and Z denote the number of houses and cattle sheds in Bihar state (also defined in Table 1).**

The most frequently (for 80% of the sampled instances) recommended optimal solution, when the available budget is between Rs. 111.0 million and Rs. 463.1 million is spraying the maximum possible number of houses (i.e., the current policy). However, when the budget rises

to between Rs. 463.1 million and Rs. 590.0 million, the optimal solution is spraying 100% of the houses and then the maximum possible number of cattle sheds. Further, when the available budget is between Rs. 594.4 million and Rs. 630.0 million, the optimal solution is spraying 100% of the houses and 100% of the cattle sheds.

**Sensitivity analyses of the value of the objective function.** The distributions of the optimal insecticide-induced death rate for  $\tau = 30$  days and  $\tau = 90$  days are shown in Figure 7. This distribution is obtained by varying the input parameters of the model.

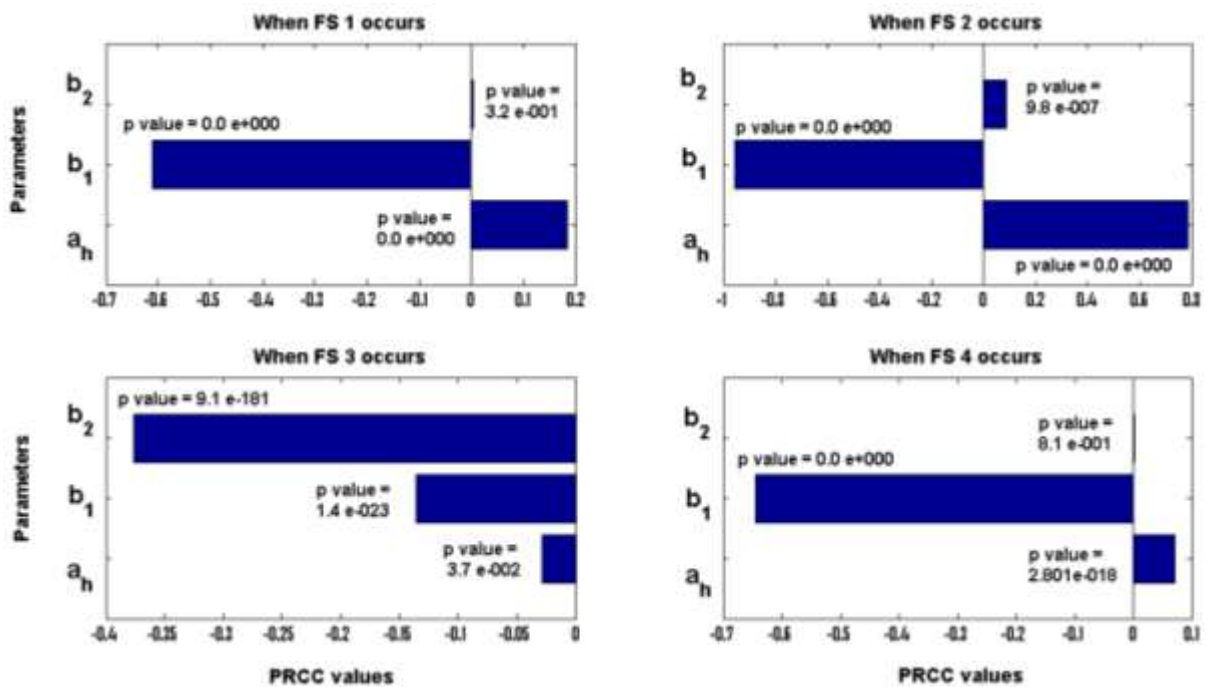


**Figure 7. Distributions of optimal insecticide-induced death rate values for  $\tau = 30$  days and  $\tau = 90$  days. Both distributions are generated by using a Monte-Carlo sample size of  $10^5$  from the input parameter distributions and DDT as the insecticide.**

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, Figure 7) higher average optimal death rate 30 days after spraying compared with 90 days after spraying. The distribution of the available budget was assumed to be the same in this simulation.

**Sensitivity analysis.** 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 ( $a_h$ ,  $C_{t0}$ ,  $b_1$ ,  $b_2$ ) do not affect the pair of conditions (Table 5). However, changes in the values of  $\widetilde{C}_{UB}$  do affect the conditions, resulting in one of the five solutions ( $x^*$  and  $y^*$ ). By contrast, the value

of the objective function (insecticide-induced death rate) depends on changes in the four uncertain parameters. As shown in Figure 8, the optimal solution ( $d_v^*$ ) is most sensitive (negatively correlated) to the insecticide's decay rate in houses ( $b_1$ ), for FS 1, FS 2, and FS 4 (Table 6). However, in the case of FS 3, the optimal solution is most sensitive to the insecticide's decay rate in cattle sheds ( $b_2$ ). For FS 2, the optimal solution is the second most sensitive to the sandfly's feeding preference for human blood ( $a_h$ ).



**Figure 8.** Partial rank correlation coefficients of the insecticide-induced death rate when a particular feasible solution from Table 5 occurs. This figure uses a Monte-Carlo sample size of  $10^5$ .

## DISCUSSION

Almost half the cases of VL, a neglected vector-borne disease, in the Indian subcontinent affect Bihar state.<sup>30</sup> Because of the effect of VL 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 control policy. Given that insecticide spraying has been a successful control measure in many parts of the world, we developed a novel mathematical model in the present study in order to design the optimal insecticide intervention policy, namely the one that would maximize the death rate of the sandfly population and minimize the risk of disease transmission to humans in the most cost-effective manner.

The presented model also provided a framework within which to test the efficacies of various insecticides. As an example, we compared the efficacy of two insecticides (i.e., DDT and Deltamethrin) herein. This approach builds on the findings<sup>14</sup> that suggest considering alternative insecticides because of the resistance developed by sandflies to DDT in Bihar. In this regard, our model results suggested 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.

By using data from Bihar and the proposed model framework, our results verify the present practice of spraying a specific number of houses. Nevertheless, the model also suggests that spraying cattle sheds could be more effective under certain conditions, validating the fact that approximately three-quarters of sandflies are found in and around cattle. Owing to the diminishing effect of the insecticide over time, the estimated average insecticide-induced death rate is 0.09 and 0.03 sandflies killed/day/sandfly after 30 days and 90 days, respectively; in other words, the 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 the optimal allocation of insecticide. Additionally, a *BMCR* function was generated

to provide the criteria for deciding on the spray coverage for houses and cattle sheds, depending on the cumulative number of sandflies killed.

As with other mathematical models, our optimization model has limitations. For example, it suggests spraying only one of the two site types (houses or cattle sheds). Furthermore, although it is well established in the field that insecticides have the dual effect of anti-feeding and mortality,<sup>21,31</sup> the present model only considers the mortality effect. Future research should aim to extend this work by additionally incorporating how the anti-feeding effect influences both sites and account for the varying sandfly population as it reduces over time after insecticide intervention. Our hope is that the future model would predict simultaneous spray in both types of sites.

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## Supporting Information

In Appendix 1, the estimation process for parameters  $Q$ ,  $b_1$ , and  $b_2$  is described. In Appendix 2, the equation for the objective function of the model is derived. In Appendix 3, the spray campaign cost and estimates for  $\widetilde{C_{UB}}$  (available budget) are derived. In Appendix 4, the analytical expressions for constraints 4 through 9 of the model are derived, and the model is presented in terms of the decision variables ( $x$  and  $y$ ) only. The procedure for obtaining the coordinates of points in the feasible domain (Figure 2) is presented in Appendix 5. Abbreviations of different symbols are listed in Appendix 6 for a quick reference.

### APPENDIX 1

#### PARAMETER ESTIMATES

The *human visitation proportion* is the proportion of sandflies that visit human dwellings based on their feeding preference ( $a_h$ ) towards human blood:

$$Q = \frac{a_h N_h}{(a_h N_h + a_c N_c)} = 255.4 \times 10^{-3} \quad 1$$

Only 25.5% of total sandflies ( $N_v$ ) visit houses each day. Table S 1 presents the percentage mortality in sprayed houses<sup>20</sup> ( $b_1$ ) and cattle sheds<sup>22</sup> ( $b_2$ ), for different days after DDT was sprayed.  $b_1$  and  $b_2$  are assumed to be equal for DDT and Deltamethrin and have the same value for each day after the insecticide application. The numerical results from control group  $C^{22}$  are used to estimate  $b_2$ . The average number of live sandflies counted on six consecutive days prior to the DDT application was assumed to be the average number of sandflies that visited the control group houses on each day even after DDT was sprayed. The proportion of sandflies

killed each day is calculated by subtracting the sandfly count on that day from the average number of sandflies present prior to spraying.

**Table S 1. Percentage mortality values for estimating  $b_1$  and  $b_2$**

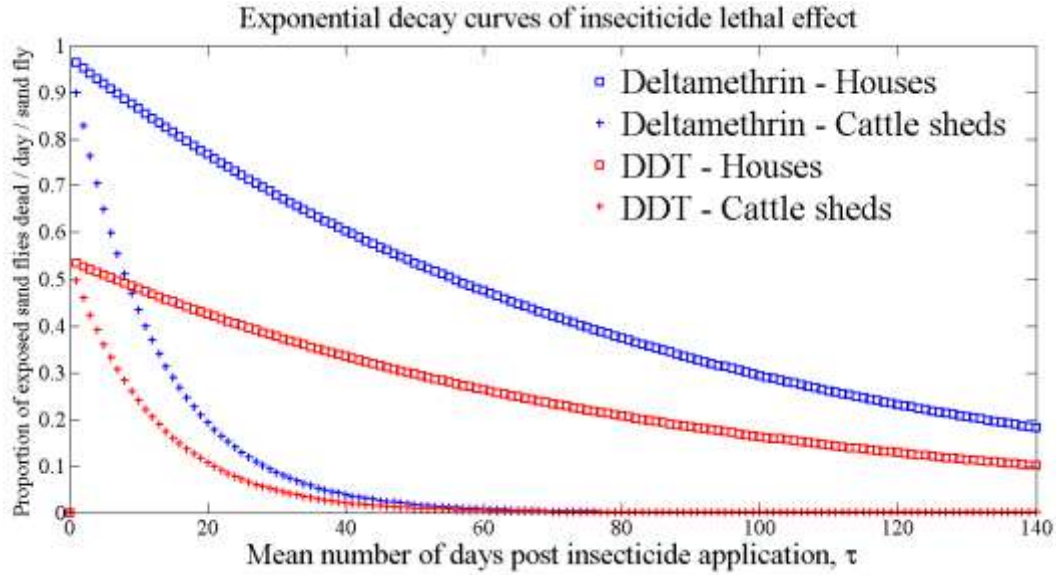
$b_1$ estimates for districts: Muzafferpur, Vaishali, Samastipur, in Bihar state, India		$b_2$ estimates from group C: two-storied house, having a cattle shed on the ground floor and living quarters on the first floor	
$\tau$	Percentage mortality	$\tau$	Percentage mortality
1	0.54	2	0.855
14	0.4796	3	0.711
28	0.3228	6	0.653
140	0.2156	7	0.596

Six estimates of  $b_1$  and  $b_2$  were obtained by fitting a function (by using Excel 2010) to all possible pairs of values in Table S 1. The final statistics of  $b_1$  and  $b_2$  were obtained by averaging their respective values in Table S 2.

**Table S 2. Six estimates of  $b_1$  and  $b_2$  using the data presented in Table S 1**

$b_1$		$b_2$	
Combination of days post-treatment	Fitted $b_1$ value	Combination of days post-treatment	Fitted $b_2$ value
1 and 14	0.009	2 and 3	0.184
1 and 28	0.019	2 and 6	0.067
1 and 140	0.007	2 and 7	0.072
14 and 28	0.028	3 and 6	0.028
14 and 140	0.006	3 and 7	0.044
28 and 140	0.004	6 and 7	0.091
Average = 0.012 per day, SD = 0.009 per day		Average = 0.081 per day, SD = 0.055 per day	

The estimated values of  $Q$ ,  $b_1$ , and  $b_2$  are used to plot  $h(\tau)$  (Equation 1) and  $z(\tau)$  (Equation 2) in Figure 9.



**Figure 9. Decay of the insecticide's lethal effect over time.**

## APPENDIX 2

### EQUATION FOR THE INSECTICIDE-INDUCED DEATH RATE

Total sandfly deaths per day comprise the six components shown in Table S 3.

**Table S 3. Sandfly deaths at different sites**

Serial no.	Number of sandfly deaths on any day after spraying	Formula
1	Natural deaths in sprayed houses	$N_v Q \left( \frac{H_s}{H} \right) \mu_v$
2	Insecticide-induced deaths in sprayed houses	$N_v Q \left( \frac{H_s}{H} \right) h(\tau)$
3	Natural deaths in unsprayed houses	$N_v Q \left( 1 - \frac{H_s}{H} \right) \mu_v$
4	Natural deaths in sprayed cattle sheds	$N_v (1 - Q) \left( \frac{Z_s}{Z} \right) \mu_v$
5	Insecticide-induced deaths in sprayed cattle sheds	$N_v (1 - Q) \left( \frac{Z_s}{Z} \right) z(\tau)$
6	Natural deaths in unsprayed cattle sheds	$N_v (1 - Q) \left( 1 - \frac{Z_s}{Z} \right) \mu_v$

By adding all six components (Table S 3.), the total death rate can be written as

$$Q \left( \frac{H_s}{H} \right) h(\tau) + (1 - Q) \left( \frac{Z_s}{Z} \right) z(\tau) + \mu_v = (1 + p)\mu_v \quad 2$$

where  $p$  is the percentage increase in the natural sandfly death rate. The third term in Equation 2 (natural death rate) is not multiplied by a weight, as sandfly natural deaths occur equally at every site (sprayed and unsprayed). The objective function of the optimization model (insecticide-induced death rate) is expressed as

$$d_v = Q [h(\tau)] \left( \frac{H_s}{H} \right) + (1 - Q)[z(\tau)] \left( \frac{Z_s}{Z} \right) \quad 3$$

### APPENDIX 3

#### EQUATION FOR INSECTICIDE SPRAY CAMPAIGN COSTS

The first constraint is the total cost of the insecticide intervention program carried out by the public health department. By adding the materials and implementation costs from Table 4, the total cost (for a one-time spraying operation using a particular insecticide) can be expressed as

$$\tilde{C}(x, y) = N_h[N_1x + N_2N_3N_5N_7 + N_2N_4N_6N_7 + N_8N_2 + N_{10}N_2 + N_{11}N_2] + N_1N_cy + g[N_9 + 60N_{13} + N_{14} + N_{15}] + [2N_{12}] \quad 4$$

The decision variable  $y$  is introduced to determine the amount of insecticide allocated to cattle sheds based on the total cattle population. Total cost can be simplified as

$$\tilde{C}(x, y) = N_hN_1x + N_cN_1y + \widetilde{C}_{Im} \quad 5$$

Equation 5 is calculated by adding three components, namely the materials cost of the insecticide allocated to houses ( $N_hN_1x$ ) and to cattle sheds ( $N_1N_cy$ ) and the spray campaign's implementation cost ( $\widetilde{C}_{Im}$ ). The latter comprises the field supervisors and spray worker's wages,

the repair and purchase of spray equipment, office expenses, a contingency, insecticide transportation and storage, supervisors' travel allowances, and public awareness activities (Table 4).

Estimation of the minimum and maximum spray campaign costs: By using the estimates from Table 2 and Table 4, the maximum cost of the insecticide spray campaign (incurred when 100% of both sites are sprayed) is derived thus:  
 $\tilde{C}_{max}(x, y) = N_1K_1 + N_1K_2 + \tilde{C}_{Im} = Rs. 594.4 \text{ million}$ . If  $\tilde{C}_{max}(x, y) \geq \tilde{C}_{UB}$ , surplus money is left after the spray campaign (*FS 5* occurs). If an infinitesimally small amount of money is allocated to the purchase of insecticide, the minimum cost of the insecticide spray campaign is  $\tilde{C}_{min}(x, y) \approx \tilde{C}_{Im} = Rs. 101.4 \text{ million}$  (budget 2010-2011<sup>13</sup>). If  $\tilde{C}_{UB} \leq \tilde{C}_{min}(x, y)$ , the model cannot find a feasible solution (*INFS* occurs). Figure 3 shows the possible range of  $\tilde{C}_{UB}$  values. A uniform probability distribution is assigned to  $\tilde{C}_{UB}$ ; the minimum value is estimated using the materials cost from the budget of 2010--2011<sup>13</sup> (Rs. 114 million) and the maximum value is assumed to be 10% more than the cost of spraying biannually (Rs. 452.56 million) from the fund allocation of the budget of 2012--2013<sup>27</sup> (Rs. 497.8 million).

#### APPENDIX 4

##### CONSTRAINTS FOR $x$ , $y$ , $H_s$ , AND $Z_s$

Since the number of houses (cattle sheds) sprayed can vary between 0 and  $H$  ( $Z$ ), the constraints for  $H_s$  and  $Z_s$  can be written as

$$0 \leq H_s \leq H \quad 6$$

and

$$0 \leq Z_s \leq Z \quad 7$$



respectively.

The number of houses and cattle sheds that can be covered by spraying insecticide can be expressed as

$$H_s = \left( \frac{N_h x}{I_h} \right) \quad 8$$

and

$$Z_s = \left( \frac{N_c y}{I_z} \right) \quad 9$$

respectively.

When all sites have been sprayed at, Equations 8 and 9 provide the maximum values for the decision variables  $x$  and  $y$  in terms of demographic parameters (Point D in Figure 2):

$$x_{max} = \frac{I_h H}{N_h} \quad 10$$

and

$$y_{max} = \frac{I_z Z}{N_c} \quad 11$$

As the two decision variables cannot have negative values,

$$x, y \geq 0 \quad 12$$

Next, the optimization model formulation is presented in terms of  $x$  and  $y$  only.

Maximize,

$$d_v(x, y) = \frac{Q h(\tau) N_h}{H I_h} x + \frac{(1 - Q)[z(\tau)] N_c}{Z I_z} y \quad 13$$

Subject to,

$$\widetilde{C}(x, y) = N_h N_1 x + N_1 N_c y + \widetilde{C}_{lm} \leq \widetilde{C}_{UB} \quad 14$$

$$0 \leq x \leq \frac{I_h H}{N_h} \quad 15$$

$$0 \leq y \leq \frac{I_z Z}{N_c} \quad 16$$

## APPENDIX 5

## COORDINATES OF INTERCEPTS IN THE FEASIBLE DOMAIN

The coordinates of the points in the feasible domain of the model (Figure 2) are obtained by solving the equation of different lines presented in Table S 4.

**Table S 4. Intercepts of constraint 4 for the subplots in Figure 2**

Figure subplot	Solving equation of	With equation of	Coordinates obtained
Figure 2 (a)	x-axis (y=0) (constraint 9)	constraint 4	$A \left( \frac{(\widetilde{C_{UB}} - \widetilde{C_{Im}})}{N_h N_1}, 0 \right)$
Figure 2 (a)	y-axis (x=0) (constraint 9)	constraint 4	$B \left( 0, \frac{(\widetilde{C_{UB}} - \widetilde{C_{Im}})}{N_1 N_c} \right)$
Figure 2 (b)	line ED $\left( x = \frac{I_h H}{N_h} \right)$ (constraint 5)	constraint 4	$A \left( \frac{I_h H}{N_h}, \frac{\widetilde{C_{UB}} - \widetilde{C_{Im}} - I_h H N_1}{N_1 N_c} \right)$
Figure 2 (b)	y-axis (x=0) (constraint 9)	constraint 4	$B \left( 0, \frac{(\widetilde{C_{UB}} - \widetilde{C_{Im}})}{N_1 N_c} \right)$
Figure 2 (c)	x-axis (y=0) (constraint 9)	constraint 4	$A \left( \frac{(\widetilde{C_{UB}} - \widetilde{C_{Im}})}{N_h N_1}, 0 \right)$
Figure 2 (c)	line CD $\left( y = \frac{I_z Z}{N_c} \right)$ (constraint 7)	constraint 4	$B \left( \frac{\widetilde{C_{UB}} - \widetilde{C_{Im}} - I_z Z N_1}{N_1 N_h}, \frac{I_z Z}{N_c} \right)$
Figure 2 (d)	line ED $\left( x = \frac{I_h H}{N_h} \right)$ (constraint 5)	constraint 4	$A \left( \frac{I_h H}{N_h}, \frac{\widetilde{C_{UB}} - \widetilde{C_{Im}} - I_h H N_1}{N_1 N_c} \right)$
Figure 2 (d)	line CD $\left( y = \frac{I_z Z}{N_c} \right)$ (constraint 7)	constraint 4	$B \left( \frac{\widetilde{C_{UB}} - \widetilde{C_{Im}} - I_z Z N_1}{N_1 N_h}, \frac{I_z Z}{N_c} \right)$

## APPENDIX 6

## ABBREVIATIONS OF SYMBOLS

The abbreviations of all symbols used in this paper are summarized in Table S 5 for a quick reference.

**Table S 5. Abbreviation of symbols used**

Symbol	Definition
FS	Feasible solution
INFS	Infeasibility
$\widetilde{C}_{im}$	Spray campaign implementation cost
$\widetilde{C}_{UB}$	Upper bound of the available money to conduct the spray campaign
$\widetilde{C}_{min}$	Minimum money available to conduct the spray campaign (worst case scenario)
$\widetilde{C}_{max}$	Unlimited financial resources (best case scenario)
Scenarios I, II, III, and IV	Scenarios are based on the BMCR function described in the <i>Analysis</i> section and their definitions are presented in Table 7
Cases I, II, III, IV, V, VI, VII, and VIII	Help in deriving the closed form solution of the model. These cases are described in the <i>Analysis</i> section