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Transmission dynamics and underreporting of Kala-azar in the Indian state of Bihar

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ABSTRACT

"Kala-azar" (or *Indian Visceral Leishmaniasis*) is a vector-borne infectious disease affecting communities in tropical and subtropical areas of the world. Bihar, a state in India, has one of the highest prevalence and mortality reported levels of Kala-azar. Yet, the magnitude of the problem is difficult to assess because most cases are handled by private health providers who are not required to and do not report them to the Ministry of Health. The impact of underreporting using district-level reported incidence data from the state of Bihar is the main goal of this manuscript. We derive expressions for, and compute estimates of Kala-azar's reproduction numbers, an indirect measure of disease prevalence, and levels of underreporting for the 21 most affected districts of Bihar. The average reproduction number (number of secondary cases generated per infective) estimates for Bihar range from 1.3 (2003) to 2.1 (2005) with some districts' estimates with mean values lower than one. Model estimates (using available data and a model-derived expression) show that the proportion of underreported cases declined from an average of 88% in 2003 to 73% in 2005. However, eight districts in 2003 and five districts in 2005 had more than 90% levels of underreporting. Model estimates are used to generate underreporting adjusted incidence rates. The analysis finds that reported data misidentify four of the eight (2003) and three of the nine (2005) districts classified as high-risk. In fact, seven (2003) and five (2005) of the most affected Kala-azar districts had been classified as low-risk when only reported incidence data were used.

1. Introduction

Leishmaniasis is a family of infectious diseases caused by parasites of the Leishmania genus that spreads in mammals (human and animal hosts) through the bites of sandflies. The geographical distribution of Leishmaniasis is tied in to the abundance of sandflies, their life cycle, and the presence of the parasite reservoirs. The Leishmaniasis is classified from its clinical manifestation (*Visceral Leishmaniasis* (*VL*), *Cutaneous Leishmaniasis* (*CL*), *Muco-Cutaneous Leishmaniasis* (*MCL*) or *Diffuse-Cutaneous Leishmaniasis* (*DCL*)) and host–reservoir (*Anthroponotic* (*A*) or *Anthropo-zoonotic* (*AZ*) or *Zoonotic* (*Z*)) (Molina et al., 2003). The world's Leishmaniasis prevalence is between 10 and 12 million while the incidence of clinical cases is between 1.5 and 2.5 million (including 500,000 new cases of VL) each year (Desjeux, 1999; Herwaldt, 1999; Singh et al., 2006a, b; World Health Organization, 1998, 2004a). The World Health Organization (WHO) classifies Leishmaniasis as a *neglected* disease affecting the poorest communities around the world. It is believed that about 30% of the new clinical cases (World Health Organization, 2004a) and around 58,000 Leishmaniases-indiced deaths (mostly attributed to VL; World Health Organization, 2002, 2003, 2004b) are reported worldwide each year. Ninety per cent of worldwide VL cases, the most severe form of the disease, occur in Bangladesh, India (mainly, northeastern region), Nepal, Sudan and Brazil (northeastern region). VL *may* infect 300,000 people annually causing over 20,000 deaths, each year in India alone (Sundar et al., 2008; The Times of India, 2008).

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Locally known as "Kala-azar" (Hindi for 'black fever'), VL, in India is considered to be *anthroponotic*, and it is nearly always fatal if untreated within 2–3 years after infection. The likelihood of deaths among patients receiving treatment is between 4% and 15% (Bora, 1999) with the rest recovering with immunity to re-infection albeit, occasional relapses have been documented (Garg and Dube, 2006). Drugs used to treat Kala-azar, developed more than 60 years ago, include pentavalent antimonial compounds (Sb^v). These drugs are no longer effective in Bihar due to high levels of resistance in the population. Alternative therapeutic measures are available but with varying level of effectiveness and side effects (see Table S4) (Bhattacharya et al., 2007; Cattand et al., 2006; Guerin et al., 2002; Roberts, 2006; Sundar, 2001, 2003; Sundar et al., 2007; World Health Organization, 1996, 2004c). Bihar is believed to house more than 90% of India's Kala-azar burden (Bora, 1999; Singh et al., 2006a) (or about 270,000 new cases per year). On the other hand, the official number of *reported cases* (deaths) in Bihar was approximately 14,000 (200) in 2003 and 23,000 (125) in 2005. Reporting has been estimated (guessed) to be between 5% and 8% of the total number of estimated cases in Bihar.

A mathematical model of Anthroponotic Visceral Leishmaniasis (AVL) or Kala-azar transmission at the district-level is introduced. Estimates of the local reproduction number are generated from the model as well as an estimate $\hat{p}$ of the proportion of reported cases. Reported incidence data (2003 and 2005) are used to obtain a distribution of model-dependent underreporting levels per district. We compare reported incidence with computed model-adjusted incidence rates. Correlations between these incidence (reported and adjusted) estimates and district demographic and socioeconomic factors (Table 1) are calculated.

There are plenty of studies of the dynamics of vector-borne diseases using mathematical models (e.g., Dengue, Esteva and Vargas, 1998; Malaria, Koella and Boete, 2003; West Nile virus, Wonham et al., 2006). The only mathematical study of the dynamics of AVL (Kala-azar) appears to be that of Dye and Wolpert (1988). They used a deterministic dynamical model to explain the observed AVL inter-epidemic periods between 1875 and 1950 in Assam, India. Their study concluded that recurrent outbreaks (every 10–15 years) appear to be the result of intrinsic factors (vector and host dynamics, birth and death rates, population immunity) and not extrinsic processes (drugs, natural disasters, other infectious diseases). Qualitative studies of the dynamics of Leishmaniasis have focused on either ZCL (zoonotic CL) or ZVL (zoonotic VL) e.g. Bacaer and Guernaoui (2006), Burattini et al. (1998), Chaves and Hernandez (2004), Courtenay et al. (2002), De La Pava (2006), Dye (1992, 1996) and Palatnik-De-Sousa et al. (2004).

Table 1
Statistics of demographic and socio-economic variables in 2001 for the 21 districts of the state of Bihar on which our study focuses (Census of India, 2001).

Variables	Min.	Max.	Mean	Median	Std.
Population size	1.28M[a]	4.72M[a]	2.69M[a]	2.68M[a]	0.9M[a]
Rurality index[b]	58%	97%	91%	93%	8%
Population density[c]	582	1471	1033	1006	248
Literacy rate	35%	63%	44%	42%	8%
No. of medical facilities[d]	46.9	111.5	80.9	73.8	123.5
No. of PHCs[d,e]	10.9	16.1	12.9	12.7	16.5
No. of Sub-Centers[d,e]	16.4	59.1	39.6	37.3	60.8

[a] M stands for million.
[b] Percentage of rural population.
[c] Per km^2.
[d] Per one million population.
[e] The state health system is divided into District Health Societies (DHS). Each DHS is further subdivided into block-Primary Health Centers (PHCs) which consists of Sub-Centers.

1.1. Data sources

Government agencies in India collect data via *passive case detection*[1] (Desjeux, 1999) which grossly underestimates the number of cases. Most cases are diagnosed but not reported by private medical practitioners. Private doctors are not required to report cases to the state health system. The social and cultural stigma linked to VL and high prevalence among the poor results in a large percentage of individuals failing to seek treatment at public health facilities (Ranjan et al., 2005). Hence, it is not possible to obtain directly reliable estimates of VL incidence using the surveillance system in place. The focus of this paper is to quantify the reproduction numbers and the levels of under-reporting via modeling framework and, if possible, to identify improvements in the surveillance system.

The state system (State Health Society) of Bihar is divided into 38 District Health Societies (DHS). Each DHS is further subdivided into a variable number of block-Primary Health Centers (PHCs). PHC consists of Sub-Centers providing health care to a variable number of villages (e.g. the Muzaffarpur district (population 3.7 million) has 14 Block PHCs while the Kanti Block (population 337,670, Census of India, 2001) has 48 Sub-Centers, each covering a population of roughly 8000 individuals, Singh et al., 2006b). PHCs, district hospitals and government medical colleges are the sources of reported cases (National Vector Borne Disease Control Programme, 2009). The private health sector includes not-for-profit and for-profit organizations. For-profit venues include corporations (e.g., private nursing homes), trusts, stand-alone specialist services, pharmacy shops, and self-appointed practitioners. Estimates suggest that 80% of the outpatients and 57% of the inpatients are handled in the private sector (The World Bank report, 2001). NGOs usually provide awareness and education programs, carry out research, and provide access to regular health services. Ninety per cent of Bihar's population lives in rural areas where less than 1% of health services are provided by not-for-profit/Non-Government Organizations (NGOs) (The World Bank, 2001).

The monthly number of reported Kala-azar cases from Bihar's 21 most affected districts (out of 38 districts) as well as from the state during 2003 and 2005 are used in this study. Data sets belong to the State Health Society of Bihar and access was provided by the Rajendra Memorial Institute of Medical Sciences. Leishmaniasis occurs in annual epidemics because of seasonal fluctuations in sandfly populations (Bacaer and Guernaoui, 2006; Dye and Wolpert, 1988; Williams and Dye, 1997). Annual data are used to compute 2003 and 2005 epidemic estimates (data for 2004 was not available). It is worth observing that 2003 and 2005 data were collected under a different set of public health policies: 2003 under the *status quo*[2] and 2005 under *improved health policies*. This improved public health program is because of the formation of Kala-azar Task Force that was put in place by the Government of India and the WHO, in December of 2003. Under this program tools were made available for simple, and inexpensive tests for field-level diagnosis, a new oral drug (Miltefosine) that is easy to administer at community level, free diet and incentive to patient and one of his attendant, and encouragement to kala-azar activists for case detection (National Vector Borne Disease Control Programme, 2009). We use data from 2003

[1] Individuals who seek treatment from the public health system are the only cases officially reported. Active case detection policies require that new cases are recorded by public health officials. These officials frequently visit local regions and inquire about new cases.

[2] Regular control policies.

(regular public health program) and 2005 (improved public health program) to evaluate the effects of the program.

The *difference* in the district-wise monthly reported incidence rates from 2003 to 2005 are highlighted in Fig. S4. The reported incidence rates of roughly half of the 21 districts are larger than the average Bihar rates of 16.2 in 2003 and 26.0 in 2005. Monthly reported incidence rates in 2005 are higher than 2003 rates for all but five of the 21 districts (Fig. S3). The reported-incidence peak rates took place between April and September (Fig. S3), around the monsoon period, when the density of sandflies increases.

Data on population density, population size in rural and urban areas, literacy rates, and number of public health medical facilities in each of the 21 districts are generated from the 2001 census (Census of India, 2001), under the assumptions that the population of each district increases at an annual rate of 2.1% (see Census of India, 2001).

Section 2 describes the model, model assumptions, and the parameter estimation techniques used. Section 3 includes the basic mathematical analysis of the model and a method for quantifying underreporting. Estimates of the reproduction numbers and underreporting levels are found in Section 4. Section 5 includes a discussion of the results and some of their implications.

2. Model description

A system of nonlinear coupled differential equations is used to model the transmission dynamics of Kala-azar that incorporates the appropriate epidemiological states, and transmission mechanisms. The model framework allows for the incorporation of long latent and infectious periods, and two modes of transmissions. Furthermore, the model incorporates the possibility that individuals seek treatment at private or public health facilities. The infectious period is variable (20 days to 1 year, Marwaha et al., 1991); the incubation period is between 2 and 6 months (World Health Organization, 1996); and the average treatment periods is also variable in Bihar (Table S4). These variations in epidemiological factors are easily captured via a "staged-progression models" (SPM) (Chowell et al., 2007; Feng et al., 2007).

2.1. Model structure

The model (Fig. 1) assumes that individuals are born susceptible (S) at the rate μN_h, where N_h is the size of the human population. Individuals' lifespan is assumed to be exponentially distributed with an average (life expectancy) of $1/\mu$ years. Once a susceptible individual gets infected through the bite of an infected sandfly, he/she becomes latent and progresses through n_1 latent stages (E_i, $i=1,\ldots,n_1$) before becoming infectious. Latent individuals (by assumption) spend exponentially distributed times in each latent stage, that is, the latent period (assumed same as the incubation period in the model) distribution is given by the $\Gamma(n_1,\ n_1\gamma_h)$ distribution with mean $1/\gamma_h$ and standard deviation of $1/(\gamma_h\sqrt{n_1})$ (Supplementary Document). Progression to full-blown Kala-azar leads to an infectious state (I_i). The infectious period distribution is modeled by the $\Gamma(m_1,\ m_1\eta_h)$ distribution with mean $1/\eta_h$ and standard deviation $1/(\eta_h\sqrt{m_1})$. Infectious individuals are assumed to be equally infectious through all m_1 stages (I_i, $i=1,\ldots,m_1$).

Infectious individuals, if untreated, within 2–3 years following infection are unlikely to survive (Bora, 1999) while death rates among patients receiving complete treatment are extremely low. Individuals undergoing treatment in government or private health facilities are grouped into the classes G_i, $i=1,\ldots,k_1$ and T_j, $j=1,\ldots,k_2$, respectively. It is assumed that all individuals undergo treatment. Hence, the parameter "p" denotes the fraction of patients undergoing treatment in *public* health facilities and $(1-p)$ the treated fraction at *private* health venues. Individuals treated at public or private health facilities recover at the per-capita rates α_h and $\tilde{\alpha}_h$, respectively, moving to the recovered class R, where they acquire "life-long" immunity. We model $\tilde{\alpha}_h$ via $\tilde{\alpha}_h \equiv q\times\alpha_h$ where $q\in[0,1]$; $q=1$ means that the length of treatment period in public and private treatment facilities are the same but $q=0.75$ means that the average treatment length in private facilities is 4/3 (i.e., $1/q$) times longer.

During the infectious period an individual may be bitten by susceptible female sandflies (class X). Infected vectors move through n_2 latent stages (Y_i, $i=1,\ldots,n_2$) before becoming infectious (class Z). The extrinsic latent period is $1/\gamma_v$. Total birth and death rates of the vector population are assumed to be equal, that is, the size of the vector population, N_v, is constant. The average life-span of a vector is $1/\mu_v$ units of time. $E(t)=\sum_{i_1=1}^{n_1}E_{i_1}(t)$, $I(t)=\sum_{j_1=1}^{m_1}I_{j_1}(t)$, $G(t)=\sum_{l_1=1}^{k_1}G_{l_1}(t)$, $T(t)=\sum_{l_2=1}^{k_2}T_{l_2}(t)$ and $Y(t)=\sum_{i_2=1}^{n_2}Y_{i_2}(t)$ denote the total numbers of latent individuals, infectious individuals, Kala-azar patients being treated at government health clinics, Kala-azar cases getting treatment at private facilities, and infected vectors in the latent stage, respectively.

The rate of infection for susceptible hosts is modeled by $F_h(t)=\lambda_h(Z(t)/N_v(t))$ with $\lambda_h\equiv mC\beta_{hv}$. Here, m is the per-capita average number of sandflies (assumed constant), C is the mean rate of bites per sandfly, β_{hv} is the transmission "probability" per bite from an infectious sandfly, and Z/N_v is the proportion of infectious sandflies in the vector population. AVL is a deadly disease among the untreated and the population of Bihar is large and changing (because of migration, Deshingkar et al., 2006). However, the data cover only two years, for 2003 and 2005. Hence, taking N_h to be constant is roughly acceptable. Furthermore, typically, adult vector populations

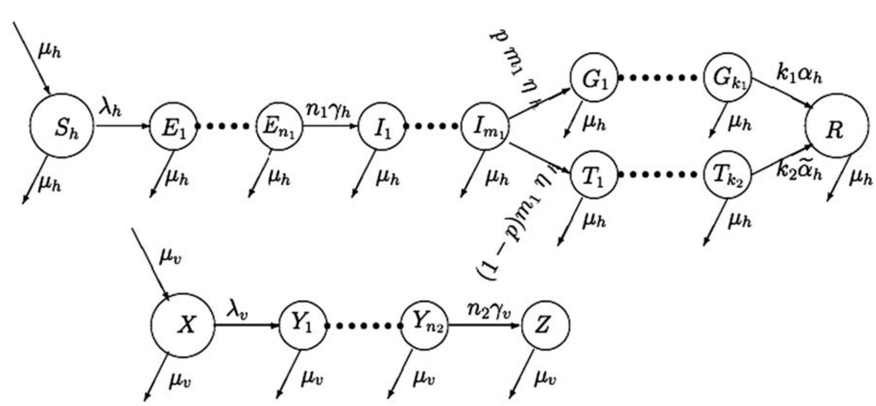

Fig. 1. A flow chart of the state progression between epidemiological classes that includes interacting human and vector populations.

Table 2
Model parameter notation, definition, estimates and their corresponding sources.

Definition	Parameters	Mean (months)	Std. (months)	No. of stages	Ref.
Life span of humans	$1/\mu_h$	722.4	–	–	Census of India (2001)
Treatment period in government health facilities	$1/\alpha_h$	0.76	0.21	$k_1 \approx 13$	Estm. from Table S4
Treatment period in private health facilities	$1/\tilde{\alpha}_h$	1.02	0.28	$k_2 \approx 13$	Estm.
Latent period	$1/\gamma_h$	4.00	1.01	$n_1 \approx 16$	World Health Organization (1996)
Infectious period	$1/\eta_h$	3.80	3.55	$m_1 \approx 2$	Sud et al. (2004)
Proportion of patients choosing private clinics	1-p	0.88	–	–	Singh et al. (2006b)
Life span of adult sandfly	$1/\mu_v$	0.47	0.42	–	Srinivasan and Panicker (1993)
Latent period in Sandfly	$1/\gamma_v$	0.17	0.03	$n_2 \approx 25$	Sacks and Perkins (1985)

sizes or densities are limited by the mortality rates experienced in the early stages of the life history of the sandfly. Hence, in areas where there are no drastic changes in adult sandfly population sizes or densities, the assumption of constant N_v is probably acceptable.

The proportion of bites of susceptible sandflies on infectious humans is modeled by $\sum_{j_1=1}^{m_1} I_{j_1}/N_h$, that is, sandflies bite the host population at random. The infection rate of susceptible sandflies is $F_v(t) = \lambda_v(\sum_{j_1=1}^{m_1} I_{j_1}(t)/N_h(t))$ with $\lambda_v = C\beta_{vh}$ where β_{vh} is the transmission "probability" per infectious human bite by a susceptible sandfly. $\sum_{j_1=1}^{m_1} I_{j_1}(t)/N_h(t)$ is the "probability" that a sandfly bites a randomly selected infectious human (Chowell et al., 2007).

2.2. Model parameters

The period of parasite sequential development in a sandfly lasts from 3 to 7 days (Sacks and Perkins, 1984, 1985) and so, it is assumed that vector latent period is roughly between 3 and 7 days. The average life of an adult sandfly in Bihar is 14 days (95% CI: (1.5, 26.5)) (Srinivasan and Panicker, 1993). The average treatment period in public health facilities, $1/\alpha_h$, is calculated using a weighted average with weights tied in to efficacy estimates (given in Table S4) of available therapeutic measures. There is a large proportion of unqualified medical practitioners working in non-governmental health facilities who may over or under prescribe (usually over prescribe) drugs. It is assumed that the average treatment length in private health facilities is $\frac{4}{3}$ times the one in public facilities ($q = 0.75$) but this parameter seems not important as the model results are not sensitive to variations in q in the "expected range".

Estimates and ranges of some model epidemiological parameters are taken from the literature (Table 2). The latent period range for humans is between 2 and 6 months (additional estimates, all in same range, are found in Badaro et al., 1986a; Bora, 1999; World Health Organization, 1996). An average infectious period of 3.80 months (standard deviation of 3.55 months) are taken from Sud et al. (2004); its 95% confidence intervals (assuming normally distributed infectious period) includes other estimates of infectious period (4.47 months, Ethopia, Alvar et al., 2007; 4.88 months, India, Chakraborty et al., 1982; 3.18 months, Bihar, Singh et al., 2006b and the range 5.3–6.7 months, Chandigarh, Marwaha et al., 1991). The average life span of the adult sandfly is about 14 days (standard deviation 12.5 days) (Srinivasan and Panicker, 1993). These estimates are comparable to others in the literature (8.6 days with 95% CI (4, 15) days) in Ferro et al., 1998).

The average number of class-stages (i.e., n_1, m_1, n_2, k_1 and k_2) is estimated from the standard deviation and the average estimate of the corresponding epidemiological parameters (Table 2). For example, the number of infectious stages, m_1, is computed from the statistics of the infectious period as follows. Since the infectious period follows the gamma distribution, $\Gamma(m_1,\ m_1\eta_h)$, with mean $(1/\eta_h)$ of 3.80 months and the standard deviation (std) of 3.55 months therefore

$$std(\text{Infectious period}) = \frac{1}{\eta_h\sqrt{m_1}} = 3.55 \Longrightarrow m_1 = \left(\frac{3.80}{3.55}\right)^2 \approx 2.$$

The values of k_1, k_2, n_1 and n_2 are estimated in the same way.

Monthly reported case data from 2003 and 2005 are used to generate initial estimates of λ_h, λ_v, $E_1(0)$, and $I_1(0)$, for each district, and each year (2003 and 2005). The "best" fit of the model (with p at 0.12 Singh et al., 2006b) to the cumulative number of reported Kala-azar cases per district (official data) using a least-square fitting procedure in MATLAB (built-in routine *lsqcurvefit* found in the optimization toolbox) is used to generate these four estimates. Not only p but also other model parameters (given in Table 2) are kept fixed (mean values) during the estimation procedure.

The above estimation procedure is repeated 8 times (using 5, 6, 7, 8, 9, 10, 11 or 12 data points, the year starts in January) for each district in 2003 and 2005. We use the Chi-square goodness-of-fit statistical test to select the best fitting parameters. The parameter-set (among the eight sets of parameter estimates) that gives a minimal χ^2- density is selected for each district (see details in Chowell et al., 2007). The χ^2- statistic was calculated from the formula

$$\chi^2 = \sum_{i=1}^{n} \left\{ \frac{(x_i - g_i)^2}{g_i} \right\},$$

where $i = 1$ is the month of January, 'n' is the number of data points (each corresponding to 12 months) used in the estimation, x_i' s are data points (cumulative), and g_i' s are points on the solution curve (cumulative case treated at government health facilities) of the model fitted to the cumulative data. The test statistic follows, approximately, a chi-square distribution with $(n-4)$ degrees of freedom because in each case we estimated four parameters.

3. Key quantities derived from the model

We re-scale the system by setting $s \equiv S_h/N_h$, $x \equiv X/N_v$, etc. The re-scaled system supports two steady states: the disease-free state (DFS) and the endemic state (ES) (Supplementary Document).

3.1. Reproduction number and model analysis

Zoonotic Leishmaniasis mathematical studies have computed the "basic"—(R_0), "control"—(R_*), and "effective"—(R_e) reproduction numbers (Bacaer and Guernaoui, 2006; Burattini et al., 1998; Chaves and Hernandez, 2004; De La Pava, 2006). The reproduction number quantifies whether a disease will persist in the population or not and typically if its value is less than one, the disease dies out but if it is greater than one the disease becomes endemic. R_0 is computed in the absence of control measures when no one in the population is immune to the disease. The effective reproduction number (R_e) gives the average number of secondary cases generated by a disease in a population, at a particular time t. Roughly, $R_e(t) \cong R_0 \times S(t)/N_h$. The control reproduction number (R_*), the average number of secondary cases generated by primary cases under specified controls, roughly estimated by $R_* \cong R_0(1-h)$, where h captures the reduction in R_0 from the interventions measures. AVL is endemic in the regions of interest, hence, we define R_c, *the reproduction number*, by $R_c \cong (1-v)R_*$ where v is the proportion of the population effectively protected (herd immunity) at the start of the outbreak. R_c computed (van den Driessche and Watmough, 2002) from the model as

$$R_c \equiv \sqrt{\left(\frac{n_1\gamma_h}{n_1\gamma_h+\mu_h}\right)^{n_1}\left[\sum_{i=1}^{m_1}\frac{\lambda_v}{(m_1\eta_h+\mu_h)}\left(\frac{m_1\eta_h}{m_1\eta_h+\mu_h}\right)^{i-1}\right]\left(\frac{n_2\gamma_v}{n_2\gamma_v+\mu_v}\right)^{n_2}\left(\frac{\lambda_h}{\mu_v}\right)} \tag{1}$$

$$= \sqrt{\left(\frac{B_1}{1-A_1}\right)\left(\frac{A_1}{1-B_1}\right)}, \tag{2}$$

where

$$A_1 = \frac{\lambda_v AB}{\lambda_v AB+\mu_v}, \quad B_1 = \frac{\lambda_h P_3^{n_2}}{\lambda_h P_3^{n_2}+\mu_h}, \quad A = (P_2)^{n_1}\times(1-P_1),$$

$$B = \sum_{i=0}^{m_1-1}(P_1)^i, \quad P_1 = \left(\frac{m_1\eta_h}{m_1\eta_h+\mu_h}\right), \quad P_2 = \left(\frac{n_1\gamma_h}{n_1\gamma_h+\mu_h}\right) \quad \text{and}$$

$$P_3 = \left(\frac{n_2\gamma_v}{n_2\gamma_v+\mu_v}\right).$$

The components of R_c are:

- $(n_1\gamma_h/(n_1\gamma_h+\mu_h))^{n_1}$ is the proportion of infected humans that survive the latent period.
- $\sum_{i=1}^{m_1}(\lambda_v/(m_1\eta_h+\mu_h))(m_1\eta_h/(m_1\eta_h+\mu_h))^{i-1}$ represents the average number of infected vectors generated by infectious humans over their entire infectious period.
- $(n_2\gamma_v/(n_2\gamma_v+\mu_v))^{n_2}$ is the proportion of infected vectors surviving their latent period.
- (λ_h/μ_v) represents the number of newly infected humans generated per infectious vector.

The DFS is always a viable steady state, and it is locally asymptotically stable if $R_c<1$. When $R_c>1$ two states (DFS and ES) coexist, DFS unstable. Numerical simulations suggest that ES is not only locally asymptotically stable but that the disease becomes endemic whenever $R_c>1$.

R_c, given by Eq. (1), does not depend on the reporting proportion (p) or on the treatment rates (α_h and $\tilde{\alpha}_h$). R_c depends on the average length of the effective infectious period (modified by treatments), the contact rate, the intrinsic and extrinsic average latent periods and the susceptible proportion. Increases in the per-capita treatment rates reduce the average length of the effective infectiousness decreasing the value of the effective reproduction number. The impact of vector control measures (e.g., spraying of insecticides) are typically evaluated from their impact on R_c (relative to R_0).

3.2. Computation of underreporting percentage

Kala-azar is endemic in Bihar and therefore, the rate at which new cases seek treatment at public health facilities (i.e., rate of reporting of cases) is $p\ m_1\eta_h I^*_{m_1}$ ($I^*_{m_1}$ the endemic state value of the last infectious class). *If the units of this rate are individuals per month then it must be equal to the average number of reported cases per month*. Equating this rate with the actual rate of reported cases per month leads to an expression for p in terms of m_1, η_h, $I^*_{m_1}$, and the monthly reported cases. We find that

$$p = \frac{(\text{Reported Cases per Month})}{\left(\frac{m_1\eta_h}{k_1\alpha_h+\mu_h}\right)(P_1)^{m_1-1}(P_2)^{n_1}(1-P_1)\left(1-\frac{1-B_1}{A_1}\right)} \tag{3}$$

where

$$A_1 = \frac{\lambda_v A\ B}{\lambda_v A\ B+\mu_v}, \quad B_1 = \frac{\lambda_h P_3^{n_2}}{\lambda_h P_3^{n_2}+\mu_h}, \quad A = (P_2)^{n_1}\times(1-P_1),$$

$$B = \sum_{i=0}^{m_1-1}(P_1)^i, \quad P_1 = \left(\frac{m_1\eta_h}{m_1\eta_h+\mu_h}\right), \quad P_2 = \left(\frac{n_1\gamma_h}{n_1\gamma_h+\mu_h}\right)$$

and $P_3 = \left(\frac{n_2\gamma_v}{n_2\gamma_v+\mu_v}\right)$.

p depends on λ_h (in B_1) and λ_v (in A_1), which have been estimated for the 21 districts of interest. Using model estimates and data we compute an "empirical" *distribution* for p for each district as follows:

The parameters η_h, μ_h, γ_h, γ_v and N_h are fixed (Table 2). Distributions are assigned to the parameters μ_v, λ_v, λ_h, m_1, n_1 and n_2 based on "experience." The parameter $1/\mu_v$ (average life span of the vector) follows an inverse gamma distribution with the mean and standard deviation in Table 2; and, the parameters λ_h and λ_v are assigned exponential distributions with means as earlier estimates. The variability in the infectious period, intrinsic and extrinsic incubation/latent periods, is in the distributions for m_1, n_1 and n_2, respectively. Discrete (integer value) uniform distributions are chosen for m_1, n_1 and n_2 with estimated ranges in the intervals $[1,3]$, $[4,28]$ and $[11,39]$, respectively (see references in Table 2 and references Alvar et al., 2007; Badaro et al., 1986a, b; Bora, 1999; Marwaha et al., 1991; Sacks and Perkins, 1985).

For each district, the variable *Reported Cases* is assumed to be uniformly distributed. The lower and upper limits of this uniform distribution are computed from reported incidence in such a way as to make the interval both symmetric about the mean, and a subset of the interval into which the real data fall. The variation from the mean to the upper and lower limits of the distribution is taken to be the smaller of the distances from the mean to the minimum and maximum values assumed by the reported case data for that district. A conditional sample (conditioned on $R_c>1$) is chosen from these distributions using Monte-Carlo sampling (Blower and Dowlatabadi, 1994; Chowell et al., 2004). The sample set is plugged in Eq. (3) to generate a single estimate of p. This process is repeated 10^4 times choosing independently a sample of parameters (paired at random) each time. The average estimate of p (i.e., $Mean(p)=\hat{p}$) is computed from these 10^4 samples but more generally, we generate an empirical (model-dependent) distribution for p.

4. Results

4.1. Estimates of the control reproduction number

Each of the 21 districts and Bihar's best parameter estimates for λ_h, λ_v, $E_1(0)$ and $I_1(0)$ are obtained for 2003 and 2005 (Table S6). These estimates (using reported incidence data) are used to compute estimates of the reproduction number (R_c) for all 21 districts (Table S8). R_c- estimates for Bihar are obtained in two ways: averaging district-estimates over all 21 districts (R_c^*) or from aggregated reported state data (R_c). These estimates are in Table S6. We observed R_c- estimates less than 1 in 2003 for some districts where the infection was found to be endemic in 2005.

Table 3
District-wise mean underreporting percentages ($(\widehat{1-p}) \times 100$) and their respective ranks for 2003 and 2005.

Estm./Districts	Araria	Begusarai	Darbhanga	Jahanabad	Katihar	Khagaria	Madhepura	Madhubani	Muzaffarpur	Nalanda	W. Champaran
2003											
$(\widehat{1-p}) \times 100$	50.8%	93.1%	90.9%	96.1%	65.1%	62.9%	44.0%	89.1%	65.9%	95.1%	93.7%
Rank[a]	2	15	14	21	5	4	1	13	6	19	17
2005											
$(\widehat{1-p}) \times 100$	48.3%	83.7%	87.5%	96.7%	78.4%	62.5%	32.6%	91.7%	38.2%	94.1%	87.2%
Rank[a]	6	12	16	21	11	7	1	19	3	20	14
Estm./Districts	Patna	E. Champaran	Purneas	Saharsa	Samastipur	Saran	Sitamarhi	Siwan	Supaul	Vaishali	Bihar
2003											
$(\widehat{1-p}) \times 100$	95.7%	74.6%	67.6%	54.8%	79.4%	93.2%	88.1%	94.1%	77.1%	74.9%	88.7%
Rank[a]	20	8	7	3	11	16	12	18	10	9	–
2005											
$(\widehat{1-p}) \times 100$	90.6%	63.2%	47.7%	33.1%	90.9%	71.3%	86.0%	87.4%	71.9%	44.7%	73.7%
Rank[a]	17	8	5	2	18	9	13	15	10	4	–

[a] Based on amount of underreporting among 21 districts.

The use of local R_c values implicitly assumes that the districts are "disconnected" but in fact, there is high movement of workers between neighboring districts (De La Pava, 2006; Deshingkar et al., 2006; Stoddard et al., 2009), so local values less than one are not unusual. R_c- estimates greater than one are found for 11 districts (2003) and four districts (2005) where Kala-azar is endemic (Patna and Saharsa are in both lists). R_c- estimates are highest in Samastipur (2003) and Saharsa (2005), districts of Bihar. The R_c- estimates for Bihar are 1.3 (2003) and 2.1 (2005).

4.2. Underreporting in districts

Districts are ranked according to their estimated average levels of underreporting in 2003 and 2005 (Table 3). Most of these averages decreased except for the districts of Jahanabad, Madhubani, Samastipur, and Katihar. The biggest decrease took place in Vaishali (74.9% in 2003 and 44.7% in 2005) and the largest increase in Katihar (65.1% in 2003 and 78.4% in 2005). The lowest number of reported cases took place in Jahanabad (4% in both 2003 and 2005) and the highest in Madhepura (56% in 2003 and 32% in 2005). High underreporting ($>90\%$) was found in eight districts in 2003 and five in 2005. Patna, Nalanda, and Jahanabad belonged to the class of high underreporting in both years (Table 3). Bihar's overall underreporting declined by about 17% from 88% in 2003 to 73% in 2005.

Model results and model-generated estimates are used to explore potential correlations between underreporting and demographic and socioeconomic variables such as population size, population density, urbanization levels (fraction of the district population living in rural areas), literacy rates, and number of public health facilities per million residents. No significant correlation was found between the model-generated underreporting estimates and population size-dependent measures (rural community size, number of PHC, Sub-Centers, or Medical Facilities per million residents) at the district level ($n=21$) in 2003 and 2005. However, population density (i.e., population per square km) is positively correlated with model-generated underreporting estimates (see Table S9) in 2003: "People are more likely to use private health care facilities in districts with higher population density," not surprising since there are more private than public health facilities per surface area. Further the number of private clinics grows faster than the number of public clinics with increases in population density. Literacy rates and underreporting percentage per district are statistically correlated: $\rho=0.76$, $P=0.0001$ in 2003 and $\rho=0.51$, $P=0.0191$ in 2005 (Table S9). Hence, it can be said that "literate individuals seem to prefer private health services over public clinics."

4.3. Spatial pattern of high-risk districts

The total number of reported cases in Bihar is 1.5 times higher in 2005 than in 2003. However, the computed adjusted (for underreporting) incidence rate (Table S7) in Bihar suggest decreases in the total number of adjusted cases by 28% from 2003 to 2005.

Adjusted incidence rates changes the ranking of districts (Table S7). Jahanabad experienced the largest decrease while Samastipur the largest increase in adjusted incidence rates from 2003 to 2005. Nine districts and Bihar experienced decreases in adjusted incidences rates from 2003 to 2005. On the other hand, adjusted incidence rates are the highest in Araria (164.4) in 2003 and Madhepura (212.3) in 2005. Bihar's adjusted incidence is 142.9 in 2003 and 98.7 in 2005.

For each district, the case-fraction is computed by dividing the number of cases by total cases (21 districts) per year using *both* reported and adjusted number of cases. The case-fraction for each district is compared with its population-fraction (population of district divided by populations of 21 districts). We call a district "high-risk" *if the case-fraction of the district is greater than its population-fraction*. Bihar's high-risk districts are shown separately for 2003 (Fig. 2(a)) and 2005 (Fig. 2(b)). We marked high-risk districts in the map with *stripes* if reported data are used (Fig. 2). High-risk districts are *shaded* when adjusted cases data are used (Fig. 2). The fractions are reported in percentages in Table S7. Adjusted incidence data suggest Araria, Begusarai, Madhepura, Madhubani, Saran, and Siwan are high-risk districts common in both years (Fig. 2).

Eight high-risk districts are identified with reported case data and seven (Begusarai, Darbhanga, Madhabani, W. Champaran, Patna, Saran, and Siwan) with adjusted case data in 2003. Reported cases data (2003) classified four districts as high-risk districts that adjusted (for underreporting) case data classified as low-risk (Fig. 2(a)). Reported incidence data "misidentified" four high-risk and seven low-risk districts in 2003.

Eleven districts are classified as high-risk using adjusted data but only nine using reported cases data in 2005. Begusarai, Katihar, Madhubani, Samastipur, and Siwan are high-risk districts under adjusted data but not if reported data are used. Khagaria, E. Champaran, and Vaishali are high-risk districts based on reported data but are removed from this group under adjusted

Fig. 2. Spatial pattern of Kala-azar: drawn using the proportion of population and the proportion of cases (reported and underreporting-adjusted) in the districts. (a) Shaded or stripes districts are Kala-azar *high-risk* districts in 2003. (b) Shaded or stripes districts are Kala-azar *high-risk* districts in 2005.

data (Fig. 2(b)). The use of reported data "mis-classified" three as high-risk and five as low-risk districts in 2005.

There are no significant correlations between population size and incidence rates at the district level. The highest correlation is found between adjusted incidence rate and rurality in 2003 (and literacy rate in 2005). In fact, adjusted incidence rates are positively correlated with rurality index ($\rho = 0.45$, $P = 0.04$) and negatively correlated with literacy rate ($\rho = -0.48$, $P = 0.01$).

4.4. Parameters uncertainty

The uncertainty in the parameters is modeled through assigned distributions (Figs. S5 and S6). The distributions of the reproduction numbers are collected in Fig. S5. We observe, for example, that the standard deviation of Bihar's R_c values decreased from 4.6 (2003) to 2.0 (2005) but the standard deviation of Bihar's underreporting (percentages) increased from 11.8 in 2003 to 20.3 in 2005 (Fig. S6). The reproductive number values have little effect on underreporting levels if they are significantly larger than one. Underreporting is the most sensitive parameter to changes in incidence rates followed by the variations in life span of the adult sandfly as well as in parameters linked to the transmission of the parasites through sandflies' bites (see Table S5).

5. Discussion

High rates of frequent inter- and intra- (rural-to-urban) district migration (mostly work-related), lack of access to adequate and accessible public health care facilities, and extreme poverty are some of the factors that facilitate the prevalence of Kala-azar in Bihar (Singh et al., 2006b). Large scale underreporting of Kala-azar cases in the state is tied in to the lack of reporting requirements for private health facilities. Approximately 73% of the patients first consult poorly qualified practitioners, most commonly in private practice (Sundar et al., 1994). A sampling study from a district by Singh et al. (2006b) reports that only 12% of the Kala-azar cases in

Muzaffarpur, Bihar were reported (and treated) in the public health facilities in 2003. There have been no studies that systematically quantify Kala-azar underreporting at the district and state level in India. Empirical studies on Kala-azar in Bihar have been carried out with only samples of selected villages in certain districts (Bora, 1999; Singh et al., 2006b). Such statistics, while useful, are unlikely to be representative.

We have quantified Kala-azar underreporting in Bihar and its 21 most affected districts using a mathematical model and reported monthly incidence data from 2003 and 2005. Our model takes into account the variability in infectivity, latent period, and treatment duration that occur with regard to Kala-azar in Bihar. This modeling framework, which uses existing reported data to generate adjusted disease trends, provides the first quantitative measure, as rough as it may be, of the magnitude of the Kala-azar problem in Bihar and its 21 districts.

Model analysis centers around the reproduction number (R_c), defined as the mean number of secondary cases (either human or vector) a typical Kala-azar infected case (either human or vector) generates in a susceptible population during the period of infectiousness when Kala-azar treatment is available. Analysis shows that the Kala-azar exhibits classic threshold behavior, with the infection persisting precisely when $R_c>1$. Our estimate of R_c for Kala-azar in Bihar using reported data is indeed greater than one (1.3 in 2003 and 2.1 in 2005). These estimates are comparable with the reproduction number estimate (mean of 1.9 for 2000–2004 epidemic of Anthroponotic Cutaneous Leishmaniasis) from Chichaoua province of Morocco (Bacaer and Guernaoui, 2006). In spite of our R_c- estimates of some districts being less than one, the disease remains endemic in Bihar state because of the larger values (>1) of R_c- estimates of most districts. The movement or migration of individuals from endemic districts must have played a role in maintaining disease prevalence in areas where local estimates of R_c are less than one (De La Pava, 2006).

Model-dependent estimates suggest that the mean case-underreporting for Bihar declined by one sixth from 88% in 2003 to 73% in 2005. Our average estimate of underreporting for the entire state in 2003 is in agreement with that reported by Singh et al. (2006b). Although our mean underreporting seems to be decreasing at the state level, the trend within the state is heterogenous. In some districts the average underreporting is as high as 90% whereas in some others it is as low as 30%. We found that underreporting increased from 2003 to 2005 in only 4 of the 21 districts (Jahanabad, Madhubani, Samastipur, and Katihar).

The model-adjusted (for underreporting) incidence rates are found to be declining in Bihar from 2003 to 2005, even though the reported cases data suggest increases in incidence rates. We found our adjusted incidence rates classify seven districts as *high-risk* (Araria, Begusarai, Madhepura, Madhubani, Purnia, Saran, and Siwan) in both years 2003 and 2005.

Reduction in both underreporting and adjusted incidence rates from 2003 to 2005 suggest improvement in Bihar's public health measures. The efforts of the Kala-azar Task Force (formed at the end of 2003) might be behind this decrease. The task force implemented programs under which cost-effective case management tools were made available, referral services were strengthened, monetary relief was provided to patients, and reporting was encouraged (National Vector Borne Disease Control Programme, 2009).

While Kala-azar incidence and case underreporting rates in Bihar can clearly be reduced by improving infrastructure in rural areas, providing education for both health care providers and those at risk, reducing population densities and other control policies that reduce parasite transmission, these measures all require financial resources. Developing an *active* case detection surveillance system, which would reduce spread of the infection, would also require resources. The problem of underreporting can also be addressed by making private medical practitioners accountable to the state public health system for proper administration of treatment and reporting; however, while this measure would be considerably less expensive than the others mentioned above, it may be difficult to enforce without community-level support.

More generally, the results of this research highlight the role of mathematical models of vector-borne disease dynamics in quantifying the magnitude of underreporting. The uncertainty in our estimates is high and strongly dependent on the model and naturally on modeling assumptions, but the trends are clear. Underreporting prevents the development and implementation of targeted policies that may be effective in reducing the burden of Kala-azar in Bihar. Furthermore, the framework identifies areas that would improve if some data were collected and provides a methodology that would allow public health officials to carry out similar studies in India and elsewhere underreporting is an issue.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jtbi.2009.09.012.

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