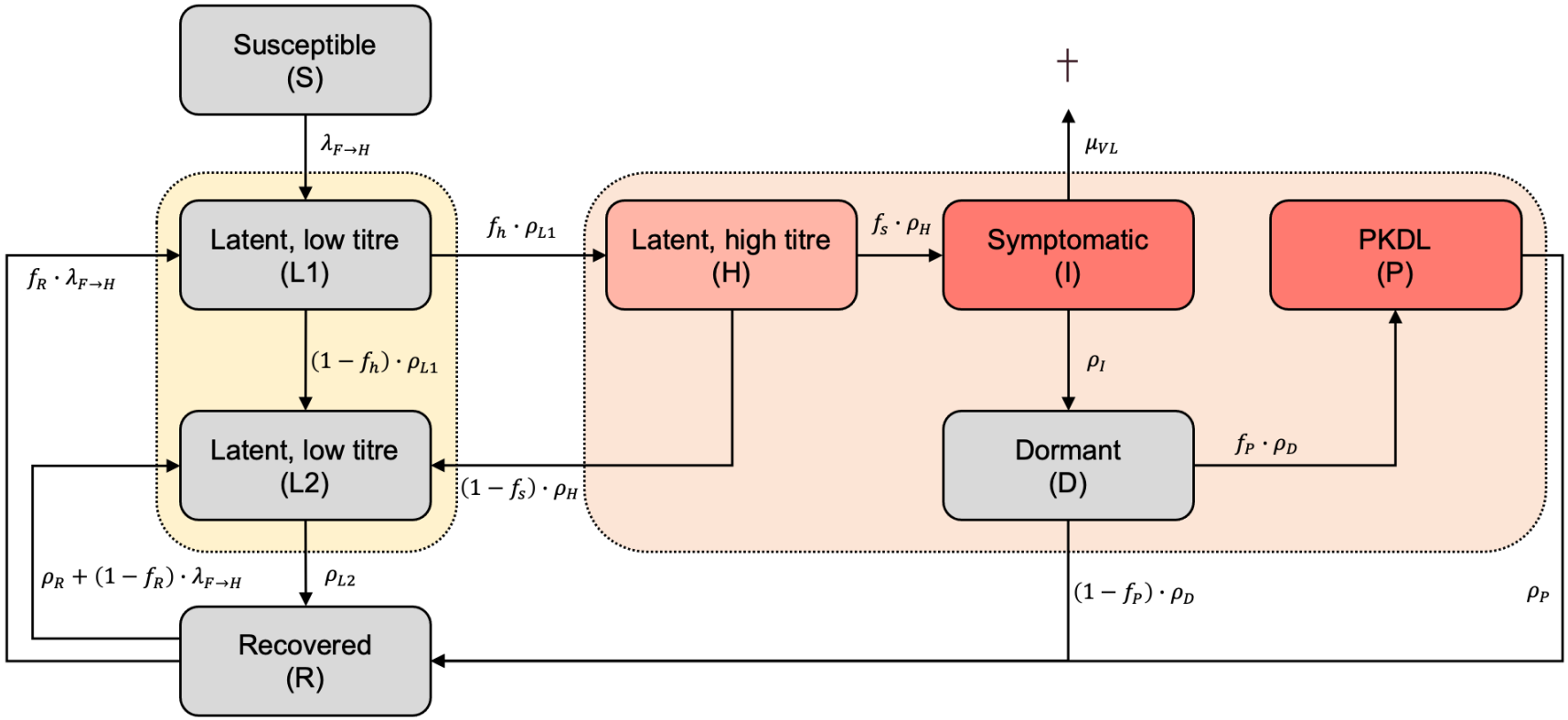
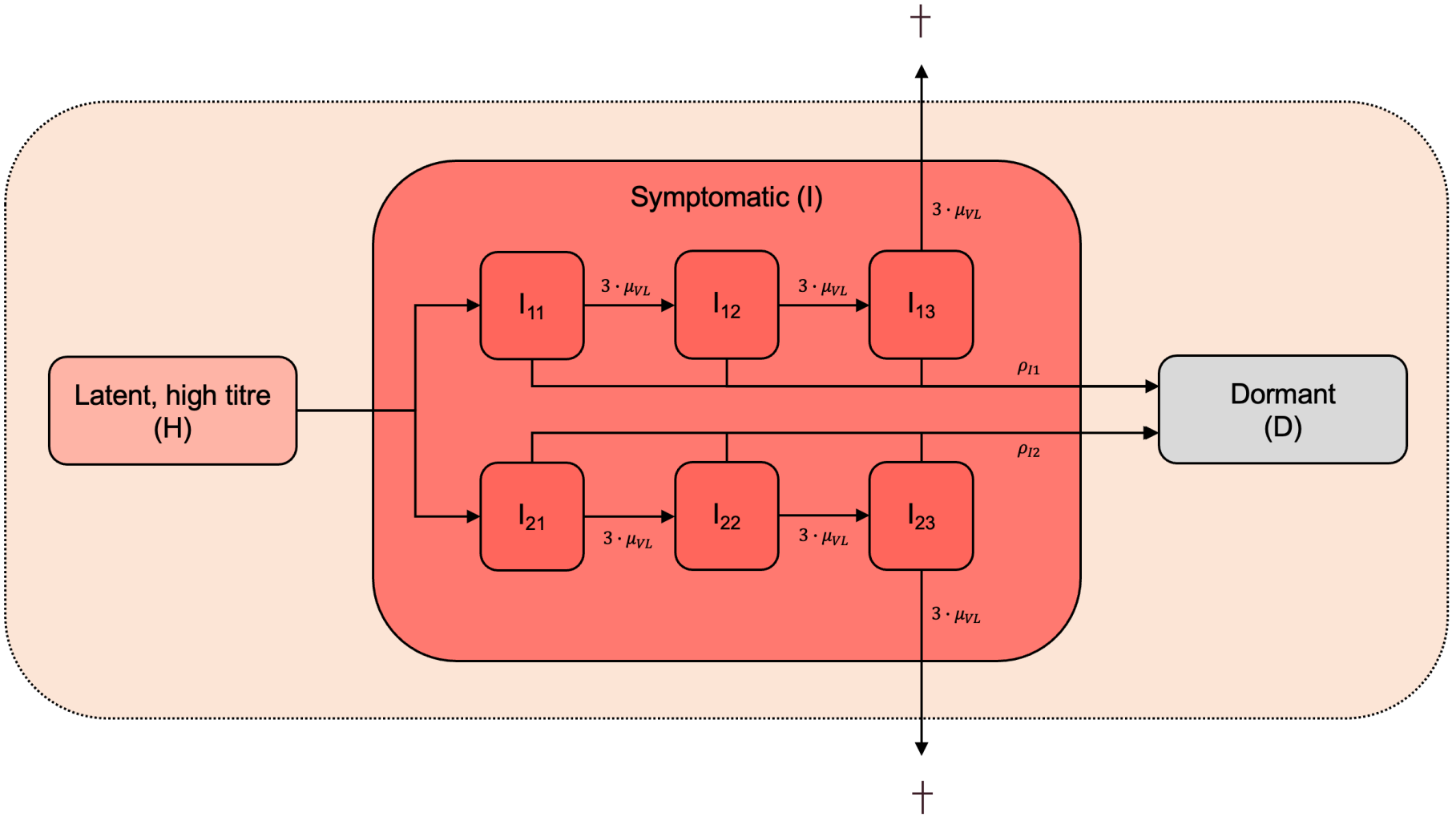
NTDmc / NDMC VL workshop hand-out – Luc E. Coffeng & Ananthu James (2023)

Schematic representation of the modelled natural history of VL in humans (Coffeng *et al*. Clin Infect Dis 2021; but without explicit age structure), extended with concepts for risk of VL depending on antibody titres (Hasker *et al*. PLoS Negl Trop Dis 2014). Yellow shaded area with dashed border indicates antibody (DAT) titres of 1:1600; red area with dashed border indicates high antibody (DAT) titres of ≥1:25,600. Red compartments are considered infective towards sandflies; latent (H, lighter red) can be optionally considered infective towards sandflies. See next page for a zoom-in on what happens inside compartment I.



Note: vector dynamics are an explicit component of the model, but are not shown here for simplicity. See the ordinary differential equations below.

Zoom-in on sub-model for impact of case detection effort on survival and death of infection (I) individuals (Coffeng *et al*. J Infect Dis 2020).



Symbol	Description
S	Susceptible humans
L	Latent infection with low serological titre
H	Latent infection with high serological titre
$I_{g,m}$	Symptomatic infection (visceral leishmaniasis), with group membership $g \in \{1,2\}$ indicating whether or not the individual is covered by the improved detection programme (1 = yes, 2 = no), and $m \in \{1,2,3\}$ indicating the m^{th} compartment of the Erlang distribution for progress until death due to untreated disease. Note that in the schematic representation above, all $I_{g,m}$ compartments are captured by the single compartment "Symptomatic (I)".
D	Dormant infection.
P	Post-kala-azar dermal leishmaniasis
R	Recovered
S_F	Sandflies susceptible to infection (per human)
E_F	Infected sandflies (per human)
I_F	Infectious sandflies (per human)
ρ_X	1 / Average duration of stay in compartment X. For compartment $X = I$, ρ_I represent the case detection effort in terms of the detection, but note that due to the competing (Erlang-distributed) risk of excess mortality, the average duration until detection is not $1/\rho_I$. For more details, see overview of parameter values at the end of this document.
μ	Background mortality rate among humans
μ_{VL}	Excess mortality rate due to untreated visceral leishmaniasis, assuming that time until death follows an Erlang distribution with shape 3 (i.e., the $m \in \{1,2,3\}$ compartments in $I_{g,m}$).
f_h	Proportion of infections that develop high serological titres
f_s	Proportion of latent infections with high titres that progress to visceral leishmaniasis
f_d	Proportion of cases with visceral leishmaniasis that are covered by the improved detection program
f_P	Proportion of cases with visceral leishmaniasis that develop post-kala-azar dermal leishmaniasis
f_R	Proportion of recovered individuals in whom reinfection may possibly result in clinical disease (via $L1$); in others $(1 - f_R)$, reinfection only triggers seroconversion ($L2$).
$\breve{N}_F$	Fly abundance (a constant or time-varying input parameter and not a state variable)
μ_F	Background mortality rate among sandflies
μ_{IRS}	Excess mortality rate among sandflies due to IRS
ρ_{EF}	1 / Average duration for infected sandflies to become infective towards humans
f_{IRS}	Relative reduction in sandfly abundance due to IRS
$\lambda_{F\to H}$	Force of infection from flies to humans
$\lambda_{H\to F}$	Force of infection from humans to flies
β	Sandfly biting rate
β_H	Infectiousness of humans with latent infection and high serological titres, relative to visceral leishmaniasis
β_P	Infectiousness of humans with post-kala-azar dermal leishmaniasis relative to visceral leishmaniasis

Ordinary differential equations for integrated model with diagnostic delays and detection effort

$$\frac{dS}{dt} = \mu_0 \cdot N + 3 \cdot \mu_{VL} \cdot \left(I_{1,3} + I_{2,3}\right) - (\lambda_{F\to H} + \mu_0) \cdot S$$

$$\frac{dL1}{dt} = \lambda_{F\to H} \cdot S + f_R \cdot \lambda_{F\to H} \cdot R - (\rho_{L1} + \mu_0) \cdot L1$$

$$\frac{dL2}{dt} = (1 - f_h) \cdot \rho_{L1} \cdot L1 + (\rho_R + (1 - f_R) \cdot \lambda_{F\to H}) \cdot R + (1 - f_s) \cdot \rho_H \cdot H - (\rho_{L2} + \mu_0) \cdot L2$$

$$\frac{dH}{dt} = f_h \cdot \rho_{L1} \cdot L1 - (\rho_H + \mu_0) \cdot H$$

$$\frac{dI_{1,1}}{dt} = f_d \cdot f_s \cdot \rho_H \cdot H - (\rho_{I1} + \mu_0 + 3 \cdot \mu_{VL}) \cdot I_{1,1}$$

$$\frac{dI_{1,2}}{dt} = 3 \cdot \mu_{VL} \cdot I_{1,1} - (\rho_{I1} + \mu_0 + 3 \cdot \mu_{VL}) \cdot I_{1,2}$$

$$\frac{dI_{1,3}}{dt} = 3 \cdot \mu_{VL} \cdot I_{1,2} - (\rho_{I1} + \mu_0 + 3 \cdot \mu_{VL}) \cdot I_{1,3}$$

$$\frac{dI_{2,1}}{dt} = (1 - f_d) \cdot f_s \cdot \rho_H \cdot H - (\rho_{I2} + \mu_0 + 3 \cdot \mu_{VL}) \cdot I_{2,1}$$

$$\frac{dI_{2,2}}{dt} = 3 \cdot \mu_{VL} \cdot I_{2,1} - (\rho_{I2} + \mu_0 + 3 \cdot \mu_{VL}) \cdot I_{2,2}$$

$$\frac{dI_{2,3}}{dt} = 3 \cdot \mu_{VL} \cdot I_{2,2} - (\rho_{I2} + \mu_0 + 3 \cdot \mu_{VL}) \cdot I_{2,3}$$

$$\frac{dD}{dt} = \rho_{I1} \cdot \sum_{m=1}^{3} I_{1,m} + \rho_{I2} \cdot \sum_{m=1}^{3} I_{2,m} - (\rho_D + \mu_0) \cdot D$$

$$\frac{dP}{dt} = f_p \cdot \rho_D \cdot D - (\rho_P + \mu_0) \cdot P$$

$$\frac{dR}{dt} = \rho_{L2} \cdot L2 + \left(1 - f_p\right) \cdot \rho_D \cdot D + \rho_P \cdot P - (\rho_R + \mu_0 + \lambda_{F\to H}) \cdot R$$

$$\frac{dS_F}{dt} = (1 - f_{IRS}) \cdot (\mu_F + \mu_{IRS}) \cdot \tilde{N}_F - (\lambda_{H\to F} + \mu_F + \mu_{IRS}) \cdot S_F$$

$$\frac{dE_F}{dt} = \lambda_{H\to F} \cdot S_F - (\rho_{EF} + \mu_F + \mu_{IRS}) \cdot E_F$$

$$\frac{dI_F}{dt} = \rho_{EF} \cdot E_F - (\mu_F + \mu_{IRS}) \cdot I_F$$

$$N = S + L1 + L2 + H + \sum_{g=1}^{2} \sum_{m=1}^{3} I_{g,m} + D + P + R$$

$\tilde{N}_F =$ constant or time-varying user input

$$\lambda_{H\to F} = \beta \cdot \left(\beta_H \cdot H + \sum_{g=1}^{2} \sum_{m=1}^{3} I_{g,m} + \beta_p \cdot P \right) \Big/ N$$

$$\lambda_{F\to H} = \beta \cdot p_H \cdot I_F$$

Matrix to pre-multiply with column vector of human states to get a column vector of human state derivatives (useful to check whether every term occurs twice in each column):

	$\boldsymbol{S}$	$\boldsymbol{L1}$	$\boldsymbol{L2}$	$\boldsymbol{H}$	$\boldsymbol{I_{1,1}}$	$\boldsymbol{I_{1,2}}$	$\boldsymbol{I_{1,3}}$	$\boldsymbol{I_{2,1}}$	$\boldsymbol{I_{2,2}}$	$\boldsymbol{I_{2,3}}$	$\boldsymbol{D}$	$\boldsymbol{P}$	$\boldsymbol{R}$
$\boldsymbol{S}$	$-\lambda_{F\to H}$	0	0	0	0	0	$3\mu_{VL}$	0	0	$3\mu_{VL}$	0	0	0
$\boldsymbol{L1}$	$\lambda_{F\to H}$	$-\rho_{L1}$	0	0	0	0	0	0	0	0	0	0	$f_R\cdot\lambda_{F\to H}$
$\boldsymbol{L2}$	0	$(1-f_h)\cdot\rho_{L1}$	$-\rho_{L2}$	$(1-f_s)\cdot\rho_H$	0	0	0	0	0	0	0	0	$(1-f_R)\cdot\lambda_{F\to H}+\rho_R$
$\boldsymbol{H}$	0	$f_h\cdot\rho_{L1}$	0	$-\rho_H$	0	0	0	0	0	0	0	0	0
$\boldsymbol{I_{1,1}}$	0	0	0	$f_d\cdot f_s\cdot\rho_H$	$-(3\mu_{VL}+\rho_{I1})$	0	0	0	0	0	0	0	0
$\boldsymbol{I_{1,2}}$	0	0	0	0	$3\mu_{VL}$	$-(3\mu_{VL}+\rho_{I1})$	0	0	0	0	0	0	0
$\boldsymbol{I_{1,3}}$	0	0	0	0	0	$3\mu_{VL}$	$-(3\mu_{VL}+\rho_{I1})$	0	0	0	0	0	0
$\boldsymbol{I_{2,1}}$	0	0	0	$(1-f_d)\cdot f_s\cdot\rho_H$	0	0	0	$-(3\mu_{VL}+\rho_{I2})$	0	0	0	0	0
$\boldsymbol{I_{2,2}}$	0	0	0	0	0	0	0	$3\mu_{VL}$	$-(3\mu_{VL}+\rho_{I2})$	0	0	0	0
$\boldsymbol{I_{2,3}}$	0	0	0	0	0	0	0	0	$3\mu_{VL}$	$-(3\mu_{VL}+\rho_{I2})$	0	0	0
$\boldsymbol{D}$	0	0	0	0	ρ_{I1}	ρ_{I1}	ρ_{I1}	ρ_{I2}	ρ_{I2}	ρ_{I2}	$-\rho_D$	0	0
$\boldsymbol{P}$	0	0	0	0	0	0	0	0	0	0	$f_p\cdot\rho_D$	$-\rho_P$	0
$\boldsymbol{R}$	0	0	ρ_{L2}	0	0	0	0	0	0	0	$(1-f_p)\cdot\rho_D$	ρ_P	$-(\rho_R+\lambda_{F\to H})$

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	$\boldsymbol{S}$	$\boldsymbol{L1}$	$\boldsymbol{L2}$	$\boldsymbol{H}$	$\boldsymbol{I_{1,1}}$	$\boldsymbol{I_{1,2}}$	$\boldsymbol{I_{1,3}}$	$\boldsymbol{I_{2,1}}$	$\boldsymbol{I_{2,2}}$	$\boldsymbol{I_{2,3}}$	$\boldsymbol{D}$	$\boldsymbol{P}$	$\boldsymbol{R}$
$\boldsymbol{S}$	0	μ_0	μ_0	μ_0	μ_0	μ_0	μ_0	μ_0	μ_0	μ_0	μ_0	μ_0	μ_0
$\boldsymbol{L1}$	0	$-\mu_0$	0	0	0	0	0	0	0	0	0	0	0
$\boldsymbol{L2}$	0	0	$-\mu_0$	0	0	0	0	0	0	0	0	0	0
$\boldsymbol{H}$	0	0	0	$-\mu_0$	0	0	0	0	0	0	0	0	0
$\boldsymbol{I_{1,1}}$	0	0	0	0	$-\mu_0$	0	0	0	0	0	0	0	0
$\boldsymbol{I_{1,2}}$	0	0	0	0	0	$-\mu_0$	0	0	0	0	0	0	0
$\boldsymbol{I_{1,3}}$	0	0	0	0	0	0	$-\mu_0$	0	0	0	0	0	0
$\boldsymbol{I_{2,1}}$	0	0	0	0	0	0	0	$-\mu_0$	0	0	0	0	0
$\boldsymbol{I_{2,2}}$	0	0	0	0	0	0	0	0	$-\mu_0$	0	0	0	0
$\boldsymbol{I_{2,3}}$	0	0	0	0	0	0	0	0	0	$-\mu_0$	0	0	0
$\boldsymbol{D}$	0	0	0	0	0	0	0	0	0	0	$-\mu_0$	0	0
$\boldsymbol{P}$	0	0	0	0	0	0	0	0	0	0	0	$-\mu_0$	0
$\boldsymbol{R}$	0	0	0	0	0	0	0	0	0	0	0	0	$-\mu_0$

Parameter values

Parameter	Symbol	Value	Source
Average duration of latent infection stages (days)			
Low serological titre $L1$	$1/\rho_{L1}$	140	Set such that the timing of annual peak in VL incidence (detected or undetected) matches the seasonal peak in onset of VL symptoms (January-March) in data from Bihar (January 2012-June 2013) [1]. Given that sandfly abundance peaks in the middle of the year (June-August), the peak in VL incidence occurs about seven months later on average, and therefore $1/\rho_{L1} = 210 - 1/\rho_H$.
Low serological titre $L2$	$1/\rho_{L2}$	21	Set such that the average duration of asymptomatic infection $\frac{1}{\rho_{L1}} + \frac{1}{\rho_{L2}} + \frac{f_h \cdot (1-f_s)}{(1-f_h f_s) \cdot \rho_H}$ is ~200 days. This is based on the estimate of 150 days by Chapman et al [2], but which is an underestimation because their definition of asymptomatic infection included seropositive individuals who previously recovered from an infection (i.e., individuals who entered compartment $L2$ from R after re-exposure to infection).
High serological titre H	$1/\rho_H$	70	Set such that ~95% leaves this compartment within 7 months, to either progress to VL or return to low serological titre $L2$ [3].
Improved detection rate for VL in presence of active case detection (per day)	ρ_{I1}	1 / 32	Calibrated such that the average diagnostic delay among detected symptomatic cases is 30 days, conditional on the distribution of time until death due to untreated VL, which follows an Erlang distribution ($k = 3$) with a mean μ_{VL} that was jointly calibrated with ρ_{I2} (details below). The associated proportion of VL cases that die undetected is 7.7%.
Baseline detection rate for VL in absence of active case detection (per day)	ρ_{I2}	1 / 243	Jointly calibrated with the excess mortality rate μ_{VL} such that the average time until death is 150 days and 50% of VL cases die undetected, conditional on the assumption that time until death due to untreated VL follows an Erlang distribution with shape $k = 3$. This detection rate corresponds to an average diagnostic delay among detected symptomatic cases of 92 days, which is in close agreement with historical data from Bihar (average delay of 98 days between onset of symptoms and diagnosis, of which 90 days due to diagnostic delay) [4].
Fraction of the population that is covered by improved case detection	f_d	0-100%	Assumption: between 2010 and 2012, population coverage of active case detection is assumed to scale up linearly from 0% to 100%.
Average duration dormant stage (months)	$1/\rho_D$	21	[5–7]
Average duration PKDL (years)	$1/\rho_P$	5	[5]

Parameter	Symbol	Value	Source
Average duration recovered stage (years)	$1/\rho_R$	5	Set such that the prevalence of seropositivity ($L1 + L2 + H$) increases monotonically with age due to regular "spontaneous" seroconversion (i.e., transition from R to $L2$).
Relative sandfly abundance (sandfly per human)	$\breve{N}_F$	-	Calibrated to reproduce VL incidence.
Mortality rate of sandflies (per day)	μ_F	1/14	[8]
Sandfly biting rate (per day)	β	1/4	[9]
Relative infectivity of latent infection with high serological titre, relative to VL	β_H	0	Based on xenodiagnostic experiments in which none of 78 VL-naive individuals with a DAT titre of ≥1:25,600 were able to infect sandflies [10].
Relative infectivity of PKDL, relative to VL	β_P	1.0	In xenodiagnostic experiments, compared to VL cases, PKDL cases were half as likely (Bangladesh) [11] or just as likely (India) [10] to infect at least one sandfly. Here, we adopt the estimate for the Indian context, which was based on the same sandfly colony used to assess the infectiousness of asymptomatically infected individuals (above).
Average duration until infected sandflies become infectious towards humans (days)	$1/\rho_{EF}$	5	[12]
Probability that an infectious sandfly successfully infects a human upon biting (%)	p_H	1	Assumption which scales inversely with sandfly abundance $\breve{N}_F$.
Percentage of latent infections that develop high serological titers (%)	f_h	60	Assumption such that 7.5% of newly infected cases become symptomatic ($f_h \cdot f_s$), This 7.5% was based on the proportion of young (age < 20) seroconverters (i.e., individuals who turned positive on DAT or rK39 ELISA) who develop VL in the TMRC and KALANET study areas [3].
Percentage of latent infections with high serological titers that progress to VL (%)	f_s	12.5	[3]
Percentage of dormant infections that progress to PKDL (%)	f_P	5	[13]
Percentage of reinfected recovered individuals that go to compartment $L1$ (%), which may lead to clinical symptoms (compartment I)	f_R	50	Based on the relative difference in cumulative incidence of VL in young (age < 20) and old (age > 50) seroconverters (i.e., individuals who turned positive on DAT or rK39 ELISA) in the TMRC and KALANET study areas [3], and such that the incidence of VL is highest in individuals of age <20 [14].

Parameter	Symbol	Value	Source
Background mortality rate (1/year)	μ	1/68	Based on average lifespan at birth in rural Bihar, 2010–2014 [15].
Excess mortality rate in untreated VL cases (per day)	μ_{VL}	1/189	Jointly calibrated with the baseline detection rate ρ_{I2} such that the average time until death is 150 days and 50% of VL cases die undetected, conditional on the assumption that time until death due to untreated VL follows an Erlang distribution with shape $k = 3$.

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