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Modelling visceral leishmaniasis transmission and control

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Introduction

Visceral leishmaniasis (VL), also known als Kala Azar, is a vector-borne disease which causes about 500.000 new cases per year and more than 50.000 deaths per year worldwide. More than 90% of cases occur in the six countries of Bangladesh, India, Nepal, Sudan, Ethiopia and Brazil. In the Indian subcontinent, VL is caused by the protozoan parasite *Leishmania donovani* transmitted by sand flies of the genus *Phlebotomus*.

Main clinical symptoms of Kala Azar are an enlarged spleen and lever and irregular fever. If treated unsuccessfully VL can manifest as nodules or rash on the skin, a condition called Post-Kala-Azar dermal leishmaniasis (PKDL). VL as a co-infection of HIV has been reported in 35 countries worldwide. Immune responses to Leishmania parasites are diminished in HIV patients, who have an increased risk of developing VL infection as symptomatic disease.

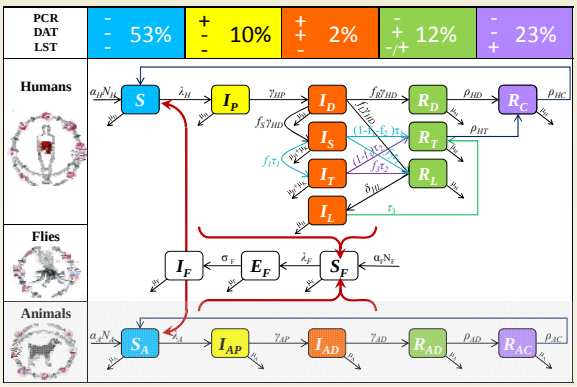
As part of the project KalaDrug-R, mathematical modeling studies shall contribute quantifications of the epidemiological parameters the transmission dynamics of VL and data-based predictions into the effects of different intervention strategies and into the risk of the emergence and spread of resistance as a possible complication of treatment.

Model

The mathematical model describes the transmission dynamics between vectors and human and animal hosts by ordinary differential equations. The natural history of infection in human and animal hosts is based on a SIR structure representing the infection states of being susceptible, becoming infected, and recover from infection.

Five combinations of diagnostic states are distinguished, originating from the different combinations of PCR-, DAT-, and LST-positivity or negativity as shown in the model diagram to the right. Immune-compromised persons and potential carriers of resistant *Leishmania* strains are considered (not shown in the diagram to avoid graphical overloading.

Parameter values in the box to the right refer to VL in India, Nepal, and/or Bangladesh. If not available from the literature, parameter values have been estimated from data of the preceding EU study KalaNet, neglecting the potential role of animal hosts as reservoir or sink of infection.



Humans

α_H	Birth rate of humans based on a life expectancy of **40 years**; for patients with symptomatic Kala Azar it is 5 months; for immune-compromised persons it is 5 years.
$1/\gamma_{HP}$	Duration early asymptomatic stage: **2 months** (WHO 1996, Hailu 2009)
$1/\gamma_{HD}$	Duration late asymptomatic stage: **12 days** (estimated)
$1/\rho_{HD}$	Duration loss of DAT positivity after asymptomatic disease: **71 days** (estimated)
$1/\rho_{HC}$	Duration loss of LST positivity: **140 days** (estimated)

Treatment

$1/\tau_{U2}$	Duration Kala Azar treatment: **1months** (with SSG Griensven 2010)
$1/\tau_3$	Duration PKDL treatment: **6months** (with SSG Rahman 2010)
$1/\delta_{HL}$	Duration of non-infectious stage before relapse to PKDL: **21 months** (Rahman 2010, Ramesh 1995)
f_1	Treatment failure rate to Kala Azar for SSG without resistance: **5%** (Griensven 2010)
$f_{2/3}$	Treatment failure rate to PKDL for SSG: **10%** (Rahman 2010, Ramesh 1995)

Flies

$1/\mu_F$	Life expectancy flies: **14 days** (Srinivasan & Panicker 1993)
$1/\sigma_F$	Duration Latency: **5 days** (Sacks 1985, Smyth 1994)
$1/\beta$	Feeding cycle duration: **6 - 7 days** (estimated)
N_F	Vector population size: **~4 x N_H** (estimated)

Parameter estimates are based on an equilibrium prevalence of:

S	Prevalence of susceptibles: **53%** (KalaNet data)
I_P	Prevalence of PCR-pos & DAT-neg humans: **10%** (KalaNet data)
I_D	Prevalence of PCR-pos & DAT-pos: **2%** (KalaNet data)
R_D	Prevalence of PCR-neg & DAT-pos humans: **12%** (KalaNet data)
R_C	Prevalence of DAT-neg & LST-pos humans: **23%** (Hailu 2009, Bern 2006)
I_S+I_T	Prevalence of Kala Azar: **0,015%** (KalaNet data)
I_L	Prevalence of PKDL: **0,005 – 0,01%** (Rahman 2010)
HIV	Prevalence of humans with HIV: **0,3% (**National AIDS Control Organization NACO)
I_F	Prevalence of infectious sand flies: **0,5%** (Bhattarai 2009, Sharma 2008)

Results

General modeling results:

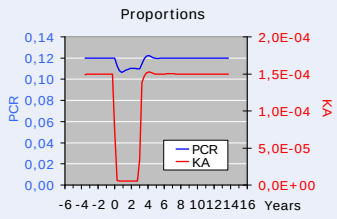
Initial results originate from fitting the model to KalaNet data, yielding parameter estimates as listed in the Box above, for instance:

An equilibrium prevalence of about 50% susceptibles (humans who are negative for all diagnostic markers) cannot be explained without the assumption of loss of immunity.

Dynamics of VL transmission is determined by the (slow) rates of infection and the losses of humoral and cellular immunity. This means that a human host will be infected on average every one or two years (see parameters above).

Until now the contribution of animals to the transmission of VL is not considered in parameter estimates albeit they may have an important impact depending on whether they act as a reservoir or as a sink of infection

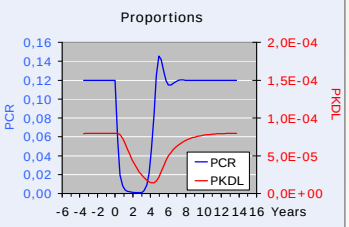
Effects of treatment



This simulation assumes optimal treatment (e.g. Ambisome) for all patients over 3 years. Although the prevalence of disease is effectively reduced (red curve representing prevalence of Kala Azar), the impact on transmission is marginal (blue curve, representing the proportion of PCR-positive humans in the population).

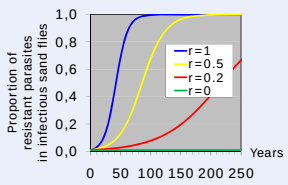
Reason: Infection dynamics is predominantly driven by asymptomatically infected hosts.

Effects of vector control



This simulation assumes that breeding site control reduces the sand fly population by 80% over 3 years. The intervention can efficiently reduce the prevalence of infection (blue curve: proportion of PCR-positive humans). The effect on the prevalence of PKDL cases is delayed because their final recovery may take months or years. The effect of breeding site control on the prevalence of PKDL will become apparent only after years.

Effects of resistance



A resistant parasite strain will always replace the sensitive strain under continuous treatment of cases, when both strains have the same fitness. Based on current assumptions on the dynamics of developing resistance, the process of strain replacement may, however, require decades. The 4 curves assume treatment failure rates of resistant parasite strains: for resistant infections, treatment success is prevented in r=0%, 20%, 50% or 100%, respectively, of cases who would otherwise have been cured.

contact: **www.uni-tuebingen.de/modeling** website: **www.leishrisk.net/kaladrug** funding: EC-FP7-222895