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# Elimination of visceral leishmaniasis in the Indian subcontinent: a comparison of predictions from three transmission models

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ABSTRACT

We present three transmission models of visceral leishmaniasis (VL) in the Indian subcontinent (ISC) with structural differences regarding the disease stage that provides the main contribution to transmission, including models with a prominent role of asymptomatic infection, and fit them to recent case data from 8 endemic districts in Bihar, India. Following a geographical cross-validation of the models, we compare their predictions for achieving the WHO VL elimination targets with ongoing treatment and vector control strategies. All the transmission models suggest that the WHO elimination target (<1 new VL case per 10,000 capita per year at sub-district level) is likely to be met in Bihar, India, before or close to 2020 in sub-districts with a pre-control incidence of 10 VL cases per 10,000 people per year or less, when current intervention levels (60% coverage of indoor residual spraying (IRS) of insecticide and a delay of 40 days from onset of symptoms to treatment (OT)) are maintained, given the accuracy and generalizability of the existing data regarding incidence and IRS coverage. In settings with a pre-control endemicity level of 5/10,000, increasing the effective IRS coverage from 60 to 80% is predicted to lead to elimination of VL 1–3 years earlier (depending on the particular model), and decreasing OT from 40 to 20 days to bring elimination forward by approximately 1 year. However, in all instances the models suggest that *L. donovani* transmission will continue after 2020 and thus that surveillance and control measures need to remain in place until the longer-term aim of breaking transmission is achieved.



## 1. Introduction

Visceral leishmaniasis (VL), also known as kala-azar, is the world's deadliest parasitic disease after malaria (Mathers et al., 2007). From 2004–2008 there were an estimated 200,000–400,000 cases and 20,000–40,000 deaths per year globally (Alvar et al., 2012). Historically, most VL cases occur in the Indian subcontinent (ISC), where the causative parasite *Leishmania donovani* is transmitted by *Phlebotomus argentipes* sandflies and the disease is considered to infect humans only (Dinesh et al., 2009; Swaminath et al., 1942). However, since 2012, there has been a significant decline in the number of VL cases identified in the ISC, attributed usually to interventions and socio-economic improvements (Chowdhury et al., 2014; Anon., 2016; WHO, 2015; Sheets et al., 2010). The World Health Organization (WHO) has targeted VL for elimination as a public health problem in the ISC by 2020 (WHO, 2015). This is defined as <1 new VL case per 10,000 capita per year at sub-district (block) level. In the rest of the world, where VL is mainly zoonotic and caused by another parasite species, the WHO has not set any elimination target but aims for 100% detection and treatment of human cases. Current interventions in the ISC focus on reducing transmission through vector control, mainly by indoor residual spraying (IRS) of insecticides, and early detection and treatment of cases (World Health Organization, 2014). In 2012, the London Declaration on Neglected Tropical Diseases endorsed

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the WHO elimination target on VL and pledged to increase research, funding, supplies and awareness to combat this disease (Uniting to Combat Neglected Tropical Diseases, 2012). It has been estimated that the health and economic gains from reaching the WHO targets for VL will be enormous (de Vlas et al., 2016). The governments of India, Bangladesh, Nepal, Bhutan and Thailand have signed a memorandum of understanding setting an ambitious goal of eliminating VL as a public health problem (at sub-district level in India and Bangladesh, and district-level in Nepal and Bhutan) by or before the end of 2017 (World Health Organization South-East Asia, 2014). Incidence of VL in Bhutan and Thailand is currently very low and limited to sporadic cases. Nepal reached the targeted low incidence level in 2014 and has sustained it for 2 years (WHO, 2015). Even in Bangladesh and India the target-level incidence was reached in nearly 90% and 70% of endemic sub-districts respectively by 2015 (WHO, 2015). Nevertheless, to achieve the target in the remaining endemic sub-districts in India, special attention must be paid to the state of Bihar, which borders Nepal and accounts for 60–90% of cases in the ISC (World Health Organization, 2011) and about 80% of cases and 90% of deaths in India (Anon., 2016). Hence, in this study we focus on the VL elimination status and control strategies in Bihar.

Mathematical models capturing disease transmission dynamics and control measures have proven to be useful tools in predicting the feasibility of achieving elimination targets with existing strategies (Hollingsworth et al., 2015; Rock et al., 2015; Hirve et al., 2016; Rock et al., 2016). Deterministic VL transmission models have been developed previously based on the KalaNet dataset from Bihar (India) and Nepal (Stauch et al., 2011; Stauch et al., 2014). More recently, Le Rutte et al. (Le Rutte et al., 2016) published a set of 3 age-structured model variants, each with individuals from a different disease stage being the main contributors to transmission: asymptomatic individuals, previously immune individuals in whom infection has reactivated, and individuals with post-kala-azar dermal leishmaniasis (PKDL). A sensitivity analysis for the duration of immunity was included, as both the disease stage which contains the main contributors to transmission and the duration of immunity remain unknown factors in the transmission dynamics of VL (Hirve et al., 2016). Available data on the impact of IRS on VL incidence suggested that the most accurate predictions are given by the model variant in which asymptomatic individuals are the main contributors to transmission, with which elimination of VL (annual incidence rate of <1 per 10,000 per year) by 2017 was predicted to be feasible only in settings that experience optimal IRS (continuously implemented from 2012 onwards) and have a maximum baseline endemicity of 5–10 VL cases per 10,000 capita per year. In highly endemic settings (<20 VL cases per 10,000) and in settings with sub-optimal IRS that are facing challenges with IRS implementation, coverage and insecticide resistance, additional interventions will be required (Le Rutte et al., 2016). Chapman et al. (2015) have recently estimated key epidemiological parameters for VL, including the duration of asymptomatic infection and the proportion of asymptomatic individuals who develop clinical symptoms, by fitting a multi-state Markov model for the natural history of VL to serological and case data from a highly endemic region of Bangladesh (Bern et al., 2007). It was estimated that asymptomatic infection lasts 5 months on average and approximately 1 in 7 asymptomatic individuals progress to VL. However, the extent to which these parameters depend on geographical location, endemicity, and other risk factors remains unclear.

To improve the robustness of predictions of the impact of intervention strategies against VL it is vital to compare and combine the outcomes of different mathematical modelling approaches, as has been done previously for HIV (Hontelez et al., 2013; Eaton et al., 2012; Brisson et al., 2003). Here we present the first VL modelling comparison study in which we compare the predictions from (1) the VL transmission model variant of those developed by Le Rutte et al. (2016) that provides the most accurate predictions, (2) a similar model in which symptomatic individuals are the sole contributors to transmission, and (3) a newly developed transmission model based on the simplified model of the natural history of VL presented by Chapman et al. (2015). The three models were fitted to VL case data collected by CARE India in 2012 and 2013 from 8 endemic districts in Bihar, India (Das et al., 2016; Jervis et al., 2017), that are currently under intensive vector control with IRS. The models were compared via their predictive ability in a geographical cross-validation. The models were then used to predict whether the elimination target could be achieved in each district. We further predicted whether the elimination target could be achieved in settings with different pre-control endemicity levels, using current and improved interventions.

## 2. Methods

### 2.1. Mathematical models

The modelling study described in this paper was performed by two research groups: Erasmus MC, Department of Public Health in Rotterdam, The Netherlands and the Warwick Infectious Disease Epidemiology Research (WIDER) group, University of Warwick, United Kingdom.

Erasmus MC developed two VL models: model E0, in which symptomatic individuals are the sole contributors to transmission, and model E1 (the best-performing model from their recent study (Le Rutte et al., 2016)) in which the main contributors to transmission are asymptomatic individuals. Supplementary File 4 contains guidelines to run the R-package 'VLode' of their age-structured system of ordinary differential equations for visceral leishmaniasis transmission, which is provided in Supplementary File 5. Warwick developed model W, which converts their recent Markov model of the natural history of VL (Chapman et al., 2015) into a transmission model with vector population dynamics, in which asymptomatic individuals are the main contributors to transmission. The MATLAB code for Warwick model fitting and predictions is provided in Supplementary File 6. A schematic presentation of the three models (E0, E1 and W) is given in Fig. 1 and the main model characteristics are listed in Table 1. The models are all deterministic compartmental transmission models inspired by an earlier VL transmission model developed by Stauch et al. (Stauch et al., 2011; Stauch et al., 2014). In the models, susceptible humans can become asymptomatically infected when bitten by an infectious sandfly. The majority of infected humans recover without developing clinical symptoms and only a small proportion develop clinical VL. Symptomatic cases can receive one or two VL treatments, and in models E0 and E1 treated individuals can develop PKDL after some period of apparent, but not absolute recovery (this putatively recovered stage is included because some VL cases seem to harbor dormant infection after treatment which leads to this late post-treatment dermatological complication of VL (Ramesh et al., 2015)). Susceptible sandflies become infected when they bite infectious humans (who may include asymptomatically infected individuals, symptomatic cases, treated individuals and PKDL cases), and remain latently infected for some period before they become infectious to humans. As an important new aspect, relative to previous VL transmission models, all models presented here include seasonality in the sandfly density, an important feature in VL transmission dynamics on the ISC (Singh and Singh, 2009). The differences between the models are described in detail below.

#### 2.1.1. Erasmus MC models (E0 and E1)

The set of Erasmus MC VL transmission models is defined in terms of a system of ordinary differential equations (ODE) and