Review

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Uniting mathematics and biology for control of visceral leishmaniasis

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The neglected tropical disease (NTD) visceral leishmaniasis (VL) has been targeted by the WHO for elimination as a public health problem on the Indian subcontinent by 2017 or earlier. To date there is a surprising scarcity of mathematical models capable of capturing VL disease dynamics, which are widely considered central to planning and assessing the efficacy of interventions. The few models that have been developed are examined, highlighting the necessity for better data to parameterise and fit these and future models. In particular, the characterisation and infectiousness of the different disease stages will be crucial to elimination. Modelling can then assist in establishing whether, when, and how the WHO VL elimination targets can be met.

How mathematics can aid elimination of VL

VL (see Glossary) is a potentially fatal protozoan infection transmitted by sandflies. Individuals with acute symptoms, referred to here as patients with kala-azar (KA), show signs of fever, weight loss, splenomegaly, and anaemia; it is believed that almost all patients will die if left untreated at this stage (http://www.who.int/mediacentre/factsheets/fs375/en/). Following recovery from KA via drug treatment, some patients go on to develop post-KA dermal leishmaniasis (PKDL), a nonfatal stage of infection with dermatological symptoms [1]. Worldwide, approximately 200 000–400 000 KA cases occur per year, the majority of which occur on the Indian subcontinent (ISC): in India, Bangladesh, and Nepal. VL on the ISC is anthroponotic (i.e., there are no non-human primary hosts), it is transmitted by just one vector species, *Phlebotomus argentipes*, and the burden of disease is highly localised. As a consequence, VL on the ISC is one of the NTDs that is targeted by the WHO for elimination as a public health problem (less than one new case of KA per 10 000 people per year) by or before 2017 (http://apps.who.int/iris/handle/10665/148778). In the rest of the world, VL is zoonotic (Box 1), limiting the possibility of elimination, and therefore the goal is 100% detection and treatment of all human cases by 2020 [2].

Within the ISC, the most affected area is the Bihar district in northern India, where VL disproportionately affects the poorest [3,4]. Despite falling numbers of cases overall in the region [5], there remain hotspots of infection; Bihar in particular accounts for approximately 80% of reported cases on the ISC [6]. Currently, control programmes are based upon scaling up active case-detection [7] and social mobilisation [5,8], which are both known to

Glossary

Asymptomatic: patients who have active VL infection, are assumed to be infective to sandflies (Box 3), but have no symptoms of KA.
Compartmental models: models in which the population is divided into groups of people who progress through various stages of the disease, represented as boxes or 'compartments' in the model. The classic example of this is the susceptible–infected–recovered (SIR) basic epidemiological model [53] in which everyone is considered to belong to one of those three stages.
Deterministic model: these models capture average behaviour of a population and give the same outcome for a set of parameters in every simulation performed.
Dormant: those patients in this stage are between KA and PKDL; they still harbour *Leishmania* parasites, but have no symptoms.
Exposed: patients who have acquired VL infection but are not yet infective to sandflies.
(Fully) recovered: patients who have previously had VL infection (of any kind) and are now parasite-free with acquired immunity.
Individual based model (IBM): a type of stochastic model where individual humans are modelled separately under an overarching set of rules. These allow for more complex simulations including differences between individual people, their movements, and geographic setting.
Kala-azar (KA): literately translated as 'black-fever', this is the acute form of visceral leishmaniasis. Patients display symptoms such as fever, weight loss, swelling of the spleen or liver, and anaemia.
Non-symptomatic: all patients with VL infection but no symptoms: includes exposed, asymptomatic, and dormant individuals (green boxes in Figure 1).
Post-kala-azar dermal leishmaniasis (PKDL): following KA, some individuals (5–10%) develop PKDL, which is characterised by a nodular or papular skin rash. It is non life-threatening.
Stochastic models: these allow for chance events as numbers of cases of disease become small (in contrast to deterministic models). Simulated disease dynamics vary every time; this allows the probability of events such as elimination or re-occurrence to be found.
Visceral leishmaniasis (VL): general term for the disease caused by *Leishmania donovani* (on the ISC) and *L. infantum* elsewhere. A VL patient refers to all individuals harbouring the parasite, including those with and without symptoms.

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Box 1. What can we learn from VL in other regions?

The global picture: there are two types of parasite which cause VL: *Leishmania donovani* and *L. infantum*. *L. donovani* is transmitted on the ISC and East Africa and is the focus of this review. *L. infantum* is responsible for most other VL infection, although some countries have had outbreaks of disease due to both species [54]. The ISC has the highest number of VL cases (58% of cases in 2012), followed by East Africa (29%) and Brazil (8%) (http://www.who.int/research/en/).

(i) Zoonotic transmission

Transmission of VL that affects animals is largely associated with *L. infantum* and is called zoonotic (ZVL). *L donovani* has been found in animals in East Africa; however, it is considered to have no animal reservoir on the ISC [55,56]. In Brazil, high levels of infection occur in dog populations (canine or CVL), and transmission between these populations and sandflies is thought to drive VL transmission to humans.

(ii) Targeting the animal reservoir

Where there is ZVL, the animal reservoir provides important opportunities for intervention, many of which have been modelled (see Table 1 in main text). The control measures used are largely inappropriate for consideration in the human population and include strategies such as insecticidal dog collars and culling, which reduce the force of infection towards humans. Despite the crucial differences between these two types of disease, lessons can be learnt (below), which can help in the future modelling of VL on the ISC.

(iii) Parasite burden and transmission

Interestingly, as in humans, many PCR-positive dogs are also asymptomatic, and this has been reflected in models of CVL [57–59]. Different methods were used to compartmentalise the dog population; either from clinical signs (i.e., symptomatic/asymptomatic) or by infectivity of dogs to sandflies (i.e., ever-infectious/never-infectious). Clinical status has been suggested as a proxy for infectivity, as it has in humans, with one study indicating that non-symptomatic infected dogs were around threefold less infectious to sandflies than infected dogs with multiple clinical signs of VL infection [58]. However, an individual dog's parasite burden also appears to be highly correlated with relative infectivity, even if asymptomatic [58,60], and this may be a better quantitative marker for infectiousness in future models.

(iv) Diagnostics

Modelling of CVL in Brazil [59] indicates that high-specificity diagnostics are crucial to correctly identify infectious individuals and intervene to reduce transmission. This provides a modelling framework which could be adapted to explore the issues of sensitivity/specificity of human diagnostics on the ISC.

be beneficial in reducing VL. Another essential part of intervention programmes is vector control, usually through indoor residual spraying (IRS) [9]; however, it is not clear whether additional control measures are necessary.

To ensure the success of the interventions in reaching the WHO goals, it is vital to be able to examine critically and quantitatively the outcome of different interventions and to make quantitative assessments which will help in the fight against this disease, particularly in the context of limited resources and over a relatively short timescale. Mathematical modelling provides tools to help evaluate interventions to indicate both the intensity and timescale over which an intervention might have to be carried out. Modelling can also inform how long surveillance should be in operation before elimination can be confirmed and how elimination might be sustained. Therefore, it is important to understand the limitations of existing models of VL on the ISC, and how better data can improve the models and generate results that are more directly useful for policy. Insights from mathematical modelling studies are summarised here through a literature review, and the differences in results or limitations are explained such that lessons can be learnt for future models and current knowledge gaps are identified.

Current state of mathematical modelling of VL

A thorough literature review was conducted to find all mathematical transmission models of VL (further details are given in the supplementary material online). Twenty-four papers addressing relevant modelling of VL are summarised in Table 1. Of these, only seven focused on the ISC; the remainder mostly addressed transmission between dogs in Brazil or France. These zoonotic papers were included because of the cross-applicable insights that they give (Box 1). Many of the articles were by the same authors and thus there is a distinct overlap between many models. For example, three of the most recent VL modelling papers on the ISC were based on the same model [10–12]. The models were rarely validated against recent data, with the exception on the ISC being the papers by Stauch *et al.* [10–12] and, to some extent, Mubayi *et al.* [13].

The models used a range of different assumptions regarding disease progression in humans, the intensity of transmission, and the role of sandflies (discussed below). Only two studies explicitly considered spatial aspects of transmission [14,15].

The authors modelled a range of potential control strategies to simulate the possible effects of intervention strategies. On the ISC, treatment was modelled explicitly in all but one paper (which is based on historical trends [16]) because this is the current course of action upon a diagnosis of VL. Two papers (by the same group [10,11]) explored the impact of vector control on disease prevalence, and one article computed the cost-effectiveness of a vaccine, should one be developed [17].

Natural history of infection

An important difference between the models is the varying assumptions about how the disease progresses, including the probability of symptoms, the time between infection and symptoms, and the dynamics post-treatment. The limited knowledge about this process, also known as the natural history of the infection, will affect the interpretation of model results and, therefore, they are discussed in some detail here. There exists a general understanding of the clinical progression of VL, but few datasets can assist in quantifying the rates of progression or the probability of different events. In general, following infection, most individuals remain non-symptomatic [18] whereas a few develop KA. Those with KA have a high mortality rate in the absence of treatment, often quoted in the literature to be up to 100% within 2 years [2]. Relapses of KA sometimes occur following treatment and this can be triggered by HIV coinfection [19,20]. After successful treatment, patients with KA recover, but this can be followed by the onset of PKDL, possibly preceded by a period of dormancy of the intracellular parasite. Unlike KA, PKDL is characterised by a nodular or papular skin rash, has no associated mortality and symptoms are dermatological. The occurrence of PKDL varies geographically: 5–10% of cases on