THE UNIVERSITY OF
WARWICK

warwick**publications**wrap
highlight your research

http://wrap.warwick.ac.uk

Uniting mathematics and biology for control of visceral leishmaniasis

Kat S. Rock[1,2,6], Epke A. le Rutte[3], Sake J. de Vlas[3], Emily R. Adams[2,4], Graham F. Medley[5], and T. Deirdre Hollingsworth[1,2,6]

[1] Warwick Mathematics Institute, University of Warwick, Coventry CV4 7AL, UK
[2] Warwick Infectious Disease Epidemiology Research (WIDER), University of Warwick, Coventry CV4 7AL, UK
[3] Department of Public Health, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands
[4] Parasitology Department, Liverpool School of Tropical Medicine, Liverpool L3 5QA, UK
[5] Social and Mathematical Epidemiology Group, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK
[6] School of Life Sciences, University of Warwick, Coventry CV4 7AL, UK

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.

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

Table 1. Summary of VL modelling papers

	Refs																							
	Anthroponotic studies								Zoonotic studies															
	[16]	[61]	[13]	[62]	[10]a	[17]	[12]a	[11]a	[63]	[57]	[40]	[64]	[65]	[41]	[58]	[66]	[67]	[42]	[28]b	[29]b	[14]	[15]b	[68]	[59]
Model structure																								
Deterministic	✔c		✔		✔		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔
Host-only	✔	✔		✔		✔			✔			✔	✔	✔				✔						✔
Assumption																								
Asymptomatic humans					✔	✔	✔	✔																
PKDL					✔	✔	✔	✔											✔	✔			✔	
Humans	✔	✔	✔	✔	✔	✔	✔	✔				†					†	†	✔	✔			✔	✔
Asymptomatic dogs										✔					✔									✔
Spatial aspects																					✔	✔		
Seasonality										✔			✔	✔				✔						
Intervention																								
Human treatment		✔	✔	✔	✔	✔	✔	✔											✔	✔			✔	
Human vaccination						✔						✔											✔	
Vector control				✔				✔				✔									✔			✔
Dog culling																✔	✔	✔					✔	✔
Dog collar																	✔						✔	
Dog treatment												✔										*	✔	
Dog vaccination												✔											✔	
Region	India	Sudan	India	ISC	ISC	India	India	ISC	France	—	—	Brazil/Malta	-	Brazil	Brazil	Brazil	Brazil	Morocco	Sudan	—	France	—	Brazil	Brazil

aDenotes studies by Stauch *et al.* that use the same basic model.

bDenotes studies by ELmojtaba *et al.* that use the same basic model.

c✔, included in model; †, dead-end hosts; *, implicitly included in other terms; —, unclear or unknown region.

ISC [1] and in up to 60% of cases in East Africa [21]. Approximately 10% of PKDL cases occur in individuals with no history of KA, and occasionally it occurs concurrently with KA [22,23].

The gold standard diagnostic for KA is parasitological diagnosis of splenic aspirates, bone marrow, and lymph node samples, with decreasing sensitivity, respectively. Recently, rapid serological diagnostic tests [24,25] mainly based on the rK39 antigen have been developed and are implemented as primary diagnostic tools on ISC because of their high sensitivity when combined with clinical symptoms. The direct agglutination test (DAT) is an alternative serological test that has been proposed as an assay to detect asymptomatic humans. Recently, it was suggested that humans that are highly reactive to DAT have a greater propensity to progress to symptomatic KA than those with lower responses [6]. The leishmanin skin test (LST) also measures serological response to infection and is seen as a marker of exposure to infection, which is important for understanding transmission but is not used in clinical practice. Currently, it is unclear whether detection of asymptomatic patients can be performed by measuring the serological response to infection alone. Therefore, molecular tests, mainly PCR, based on the detection of parasitic DNA might be an alternative tool to detect humans who are actively infected rather than only exposed to disease [26]. It is important that the VL research community focuses on the use of diagnostic tools for the detection of asymptomatic cases such that clarity is reached on a possible algorithm to detect infectious patients who are not showing symptoms.

Modelling the natural history of infection
Most VL models are 'compartmental' models, which means that hosts pass through various 'stages' of the disease at different rates. A model can be constructed in which the assumptions are closely tied to current understanding of the biology. For example, the natural history outlined above can be represented by a flow diagram (Figure 1) with the model tracking the number of individuals in each disease stage; the different rates of moving between stages, such as the average time between KA and PKDL, are defined either directly from knowledge of the disease or by fitting the model to data.

Models of VL do not include all of the known complexity of VL biology, mainly because of a lack of data to define the stages, quantify the rates of progression between stages, and chart the time-evolving distribution of the infected population between stages. Basic models including key aspects of VL transmission, guided by available data and a particular policy or research question, can yield invaluable insights.

For the ISC, the simplest model structure was the susceptible–infected–recovered (SIR) progression assumed by Dye and Wolpert [16] (Figure S1 in the supplementary material online). This model was used to explain the historical disease dynamics of VL in India between 1875 and 1950. Although the model is unsophisticated and omits much of the currently known biological process of VL infection, it was effectively fitted to longitudinal incidence data, and the intrinsic processes were able to account for the timings of the long interepidemic periods that are characteristic of VL. A slightly more complex model was that of Mubayi *et al.* which included a more realistic latency period distribution, but did not include PKDL [13].

The probability and timing of PKDL following KA are key assumptions for interpreting surveillance data and in using models to make projections. The occurrence of PKDL is thought to be governed by several factors, including the choice of drugs and adherence to treatment [27]. Some modellers (ELmojtaba *et al.* [15,28,29], Stauch *et al.* [10–12], and Lee *et al.* [17]) incorporated the potential progression to PKDL infection following KA in humans via the addition of another infective stage (Figure S2). This enables one not only to observe the effect of different treatment rates upon the two different types of disease
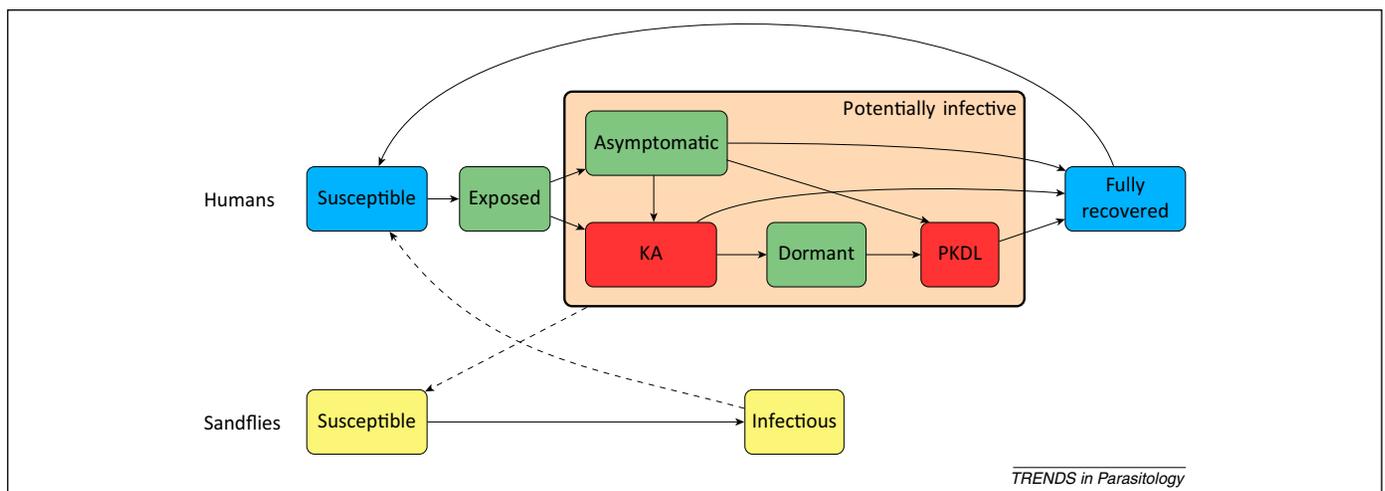

Figure 1. Compartmental diagram showing possible visceral leishmaniasis (VL) progression paths. Differently coloured boxes denote humans at various stages of VL infection: blue for no current infection, green for non-symptomatic but infected humans, and red for symptomatic individuals. Yellow boxes represent sandflies with and without infection. The orange box indicates all human stages that are infected and that might be infective to sandflies (with likely varying intensities). Broken lines indicate the direction of transmission between humans and sandflies, whereas unbroken lines show possible progression paths through different disease stages. Abbreviations: KA, kala-azar; PKDL, post-KA dermal leishmaniasis.

but also to examine how treatments that reduce the probability of developing PKDL might affect infection dynamics and prevalence.

Inclusion of a dormancy period between KA and the onset of possible PKDL (Figure 1) was used by two groups (Stauch *et al.* [10–12] and Lee *et al.* [17]) to reflect the longer duration of this period on the ISC [27].

Although the different stages of infection are loosely based on current understanding of the clinical stages, the precise definition of each stage in the model depends upon the data used. For example, a KA case might be any KA case, or it might be a diagnosed KA case in a particular healthcare setting. Stauch *et al.* [10–12] particularly modelled the KALANET trial [30]; this trial evaluated the efficacy, acceptability, and cost-effectiveness of long-lasting insecticidal bed nets for the prevention of visceral leishmaniasis through a community intervention trial in the endemic Bihar focus (http://www.kalanet.info). Diagnosis of VL infection was made by three tests (PCR/DAT/LST described in Table S1). The study revealed no significant impact of bed nets [72], but it suggested that incidence of asymptomatic *Leishmania donovani* infection in VL high-endemic foci is ninefold more frequent than incident VL disease [31].

Stauch *et al.*, therefore, were able to partition the different stages of infection by their diagnostic status under the three tests, in addition to symptoms, and treatment. Although this method of compartmentalisation is only subtly different from that general framework described above, the stratification by different diagnostic tests structures the model slightly differently, with, for example, four different 'recovered' stages by diagnostic status [10–12].

Given the availability of detailed data on diagnostic outcomes, the Stauch *et al.* model included asymptomatic individuals who tested positive with any of the three tests but were unaware of their infection status in the absence of diagnostic tests (Figure S3). The fact that asymptomatic individuals can test positive leads to the question of their

infectivity to sandflies and of their role in the transmission cycle (see below) and the specificity of the tests used.

An area of much debate in the VL research community is the existence and action of immunity, which is currently considered as a gap in our knowledge of VL [32,33]. The models of Stauch *et al.* are the only ones to feature a return to susceptibility after recovery from either KA or PKDL. Under this model, immunity from reinfection lasts approximately 307 days, which is short in comparison to the life-long immunity assumed by other authors [10–12].

Different modellers have not only made different assumptions about the natural history of VL but, importantly, also used different parameter ranges. The huge variability in parameters and their values (Table S2) is attributable not only to the underlying model structures but also to the uncertainty in many factors in transmission and progression, such as rates or probabilities, which are either hard to measure or vary by region. Access to more detailed datasets using modern diagnostics is essential to revolutionise the study of VL transmission dynamics and the utility of models to inform policy.

Transmission of VL

During the different stages of VL infection, individuals harbour different levels of the parasite in their peripheral blood and lymphatic systems [26]. Given that there is apparently no sterile cure, once someone is infected they can be infectious to sandflies throughout their lifetime, including during the dormancy period before PKDL and once PKDL develops (orange box in Figure 2). In particular, PKDL nodules are known to contain a detectable parasitic load, implying potential significant infectivity [34].

Both asymptomatic humans (Box 2) and those with PKDL are unlikely to seek medical advice or treatment [35] owing to the costs of treatment and the fact that neither condition causes any physical limitation [36]; these individuals are therefore behaviourally distinct from those
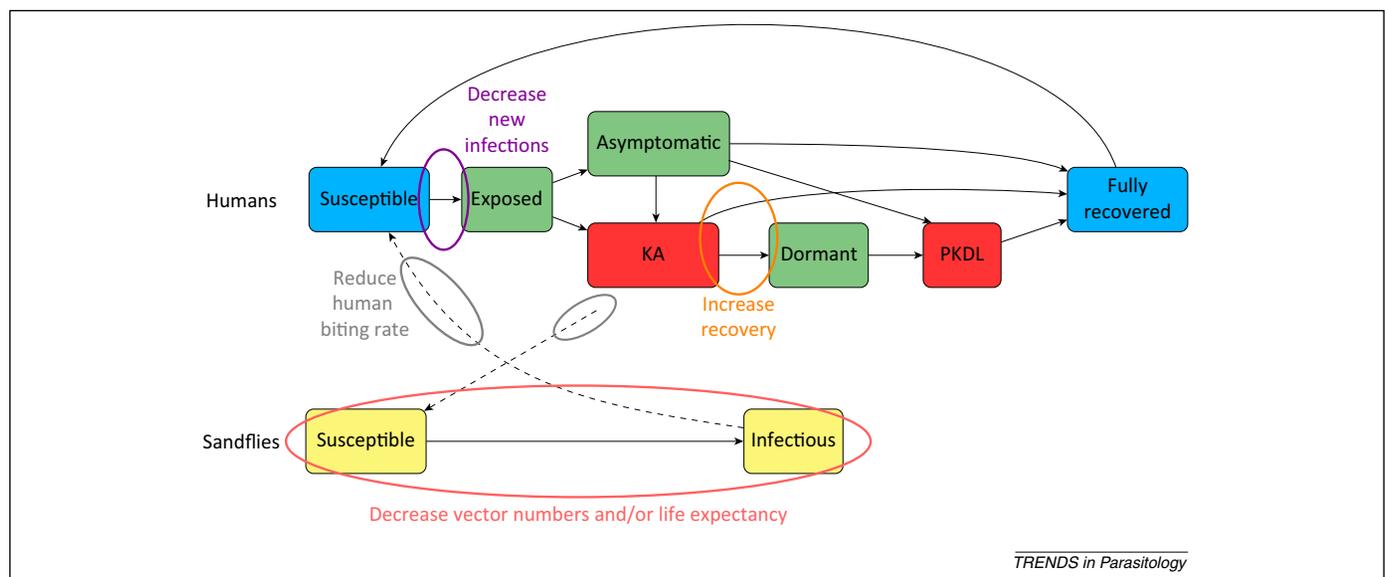

Figure 2. Main ways to interrupt the transmission cycle of visceral leishmaniasis (VL) through interventions. Orange shows the effect of standard (first- or second-line) treatment of symptomatic individuals. Pink shows the effect of vector controls. Grey shows the potential effect of bed nets. Purple shows the effect of a (potential) human vaccine or other prophylactic intervention.

Box 2. What is an asymptomatic VL case?

The green boxes in Figure 1 in main text identify infected individuals without symptoms. Identifying this group of non-symptomatic humans in cross-sectional or longitudinal studies is difficult because of contradictory diagnostic results [6]. For the purposes of transmission modelling, the subsets of these (termed here as exposed, asymptomatic, and dormant) are different because only those within the orange box can contribute to onwards infection.

There is ambiguity in the term 'asymptomatic' as it is used in the context of VL. It can include or exclude those humans with subsymptomatic early infection, non-symptomatic early infection, as well as post-treatment or recovery dormancy. From an epidemiological perspective, the term is used for individuals who display no outward symptoms of VL infection but do harbour parasites. For the purposes of this review and to assist in future modelling studies, the term 'asymptomatic' is used here to describe the subset of these humans capable of contributing towards transmission. Non-symptomatics are identified together with asymptomatics in some types of data collection, but in terms of transmission models they are entirely distinct or absent, with no role in transmission. This distinction is made because of the difficulty in separating exposed, uninfected, possibly seropositive, individuals from subpatent infections in cross-sectional studies because of conflicting diagnostic results (see main text). The definition of these groups by particular diagnostics is an area of ongoing research and debate, which future xenodiagnostic studies will clarify; these studies involve exposing vectors to blood containing various levels of parasites and then establishing infection probabilities.

Box 3. Relative infectivity of asymptomatic humans

In the model by Stauch et al. [10–12], PCR- and/or DAT-seropositive individuals, who are not symptomatic (termed 'asymptomatics' in the papers), included both pre-KA patients and non-KA individuals. These persons were estimated to be 40–80-fold less infective to sandflies than their KA and PKDL counterparts, depending upon their PCR/DAT status. This estimation is a result of model-fitting to data from one study (KALANET) rather than direct biological measurement.

Empirical evidence for relative infectivity of asymptomatics is sparse [69,70], although one xenodiagnostic study [71] has enabled the assessment of the relative infectivity of humans with different parasitaemias (parasite burden) in Ethiopia. The data show similar trends to those seen in Brazilian dogs (Box 1), and the corresponding model analysis attributed between 53% and 79% of all sandfly infections to the top 3.5% most-infected people, suggesting that intervention strategies should focus on individuals with high parasitaemia. Xenodiagnostics to determine relative infectivity on the ISC have not yet been undertaken; however, the models of Miller et al. and Courtney et al. [58,60,71] can be used as a basis for incorporating relative infectiousness of different human disease states into models before the outcomes of future human/sandfly xenodiagnostic studies are known.

with KA. Current active case detection relies on finding KA symptoms before testing and, therefore, humans who are asymptomatic are missed. The WHO has recommended various regimens for PKDL based on geographical location, but each has a long course and is associated with toxicities [37]. In resource-poor settings, where VL is most prevalent, these long parenteral regimens invariably lead to either non-acceptance or poor compliance [38].

Infectivity to vectors
The infectivity of humans in different disease stages was only identified in one model in which the authors explicitly modelled asymptomatic humans with a decreased infectivity within the transmission cycle [10–12] (Box 3). Currently, only two groups ([10–12] and [15,28,29]) have incorporated PKDL into transmission models by assuming comparable infectivity of KA- and PKDL-infected humans because of lack of evidence to the contrary. The models with an interim dormancy period before the onset of PKDL [10–12] assumed that, during this time, the human host is not infective to sandflies, whereas the other models [15,28,29] assumed that individuals progress straight from KA to PKDL, and are infective to sandflies throughout.

The cost–benefit analysis model [17] included both asymptomatic humans and those with PKDL but, because a constant force of infection was used, the role of these patients towards onwards infection cannot be discerned.

These assumptions on the infectivity of asymptomatic humans and patients with PKDL are crucial in determining the estimated efficacy of increased detection and treatment of patients with KA. If there is a large asymptomatic population, as indicated in the literature [31], then they will probably lead to most of the onwards infection, even with low infectivity, as might be the case with malaria [39]. It could be argued that the decline in cases in Nepal

and Bangladesh under increased active case detection suggests that the contribution from asymptomatics is small, but this depends on the timescale and acquisition of immunity as well as on the number of asymptomatic humans and the impact of IRS in interrupting transmission. Although it is unlikely that direct estimates of asymptomatic infectivity will be available soon, models could be fitted to high-quality surveillance data, giving some bounds to the contribution of different stages to transmission.

Vector biology
Sandflies are key in VL transmission, but little is known about their life cycle, biting rates, and transmission probabilities, all of which are crucial to increase understanding of transmission dynamics. Even estimates of a parameter as fundamental as sandfly life-expectancy have large confidence intervals. Whereas models typically use an estimate of 2 weeks, such estimates range from 2.4 to 16.7 days (Table S3). Likewise, the seasonal fluctuations of sandfly populations are only featured in some transmission models of zoonotic VL [40–43], despite these fluctuations being one of the easier parameters to measure. In future models consideration should be made to the impact of sandfly seasonality on the ISC and how this might affect vector controls and their timing; this can be achieved by utilising frameworks from zoonotic VL models as well as other vector-borne disease models.

Effectiveness of interventions
There are several public health control measures that aim to reduce the transmission of VL [44]. Some controls, such as treatment of patients with KA, effectively speed up the progression of patients through disease stages and minimise the time that these individuals spend in the symptomatic period, potentially reducing onwards infection to sandflies. Other controls, such as insecticide spraying, aim to reduce the vector population and its effectiveness in transmitting infection. The four main parts of the

transmission cycle that are affected by interventions (both current and hypothetical) are highlighted in Figure 2. Each of these interventions has been discussed within one or more of the articles found by this review, and their modelling methods and results are discussed below.

Treatment of KA

Given the high mortality rate for untreated KA, most patients are believed to seek care eventually, although the time-delay before treatment can be long [8]. There are a variety of treatments available for KA, but some studies suggest that adherence, rather than treatment type, is the key factor that might result in differing probabilities of progression to PKDL or relapse to KA [45].

In the model analysis by ELmojtaba *et al.* [28], both first-line treatment rate and effectiveness of preventing PKDL are varied. The authors found that, with high treatment rates alone, there was a reduction in KA cases, but, because a proportion of these treatments produced a PKDL case, infection rates were still high. Unsurprisingly, increasing both treatment and effectiveness was more efficacious at reducing transmission.

Stauch *et al.* [10–12] included three treatment types: first-line treatment of KA, second-line treatment following first-line treatment failure, and PKDL treatment. The authors showed that high treatment rates reduced the number of KA and PKDL cases. However, the intervention had almost no impact upon the large asymptomatic population and, consequently, transmission intensity was little affected [10].

These two groups of papers suggest that treatment alone will not be enough to truly halt the transmission of VL, and that other interventions are needed when aiming for elimination, echoing the opinion of others [5,46].

Vaccine

There is currently no human vaccine for VL; however, advances are being made and models have been used to study the benefits of potential candidates [32,47]. Lee *et al.* [17] described the possible advantages of a VL vaccine through a cost–benefit analysis. They found that even a poorly effective vaccine (25% effective – a vaccine that fully protects 25% of those immunised against infection, but makes no difference to the remaining 75%) might be cost-effective (for US$ 100 or less), whereas vaccines with higher effectiveness might even be cost-saving. For Bihar, India, in particular, this work indicated that a vaccine would be beneficial because of the high prevalence of genetic resistance to first-line treatments that has developed in this region. This model [17] used a constant (age-dependent) force of infection that did not change in response to vaccine use. Consequently, it is hard to determine what indirect effects the vaccine might have on reducing disease prevalence.

ELmojtaba *et al.* [15] showed that vaccination rates affected the transient dynamics through the rate of reduction of cases (in Sudan) but ultimately had little role in long-term prevalences where new cases are continuously imported. In particular, the authors noted that high levels of vaccine efficacy would be needed to reduce the equilibrium prevalence of VL significantly.

These contrasting results highlight the importance of understanding the underlying assumptions of the models when interpreting their results, and that the potential impact of a future vaccine is still uncertain.

Vector control

The main intervention for vector control is IRS, which is linked to a reduction in sandfly life expectancy and to a consequent reduction in sandfly populations [9]. Lowering the total vector population size reduces the biting pressure on each human by decreasing the ratio of vectors to hosts (Figure 2). By reducing the sandfly life-expectancy, the vector is less likely to survive long enough to bite twice – once to acquire infection and again to infect a host. As the vector death rate increases, vectors spend less time infected.

Other interventions include reductions in sandfly breeding sites, which also limits population sizes, and insecticide-treated bed nets [44]. The use of bed nets decreases the contact rate between vectors and humans and, consequently, should lower transmission, not only to susceptible individuals, but also from infected ones, including asymptomatic humans and those with PKDL. Unfortunately, the KALANET programme indicated that, despite a reduction in sandfly density, bed nets were not effective at reducing incidence in this setting and, thus, IRS remains the main control strategy [48,49].

Given the limited data on sandfly behaviour (as mentioned above), model assumptions and outputs are variable. Stauch *et al.* [10] examined the effect of changing the three parameters corresponding to vector life-expectancy, vector population size, and bite rate. Each of the parameters appeared to result in a quasi-linear change in prevalence and incidence of infection. Further work by Stauch *et al.* [11] examined control of vector breeding sites and killing vectors directly. These authors suggested that, to break transmission, either the vector population must be reduced by 79% through the destruction of breeding sites or it must be reduced by 67% by killing adult flies, the latter effectively decreasing the life-expectancy of the sandflies in addition to suppressing their population size.

Concluding remarks

Modelling is a useful tool in informing public health control programmes, but to date there have been relatively few VL models developed. This is partly because of the status of VL as an NTD with limited data availability. Modelling results point towards IRS in particular as a highly promising strategy to control transmission of VL. However, it is difficult to determine the best way forward to achieve the goals of the WHO given the current state of knowledge. The main weakness of the current modelling literature is the lack of fitting or validation against multiple timepoint data. The one model parameterised by a modern dataset is only fitted to the cross-sectional, rather than the dynamic data [10–12]. There is an urgent need for more models of VL to be developed which can aid public health policy by analysing surveillance data and guide policy on areas where current strategies need to be improved. PKDL cases continue to occur from historic VL cases, cost-effective strategies to monitor these cases and limit onward transmission are required.

Box 4. Outstanding questions

- How infective are individuals with asymptomatic or PKDL infection?
- How large is this potential infectious reservoir? How do we detect and/or diagnose them?
- What is the best intervention or combination of interventions when targeting sustainable elimination?
- How can we establish elimination, given the potentially huge asymptomatic population?

The current suite of models are also limited in terms of the technical complexity and analyses which have been performed, such as exploring asymptotic/PKDL infectivity, sandfly seasonality, age-dependent exposure, and differences (both age and gender related) in treatment-seeking behaviour. Currently no stochastic individual-based models (IBM) exist that capture the transmission dynamics of VL. Stochastic models can simulate the probability of elimination as well as the probability of (re)-occurrence of outbreaks, both identified as crucial questions for VL on the ISC. Another technical need is for IBMs that can include more complexity including seasonality, migration and location. IBMs for other NTDs have shown to be of great value in aiding healthcare policy, such as estimating the impact of doubling the frequency of mass drug administration to accelerate elimination of onchocerciasis [50] and lymphatic filariasis [51], as well as combining various preventive and therapeutic interventions to interrupt leprosy transmission [52].

Surveillance data, together with prior experience of the epidemiology of elimination, suggest that, although there are geographical areas where the current programmes will be successful, there will be those where additional interventions are required. If goals for the ISC, as well as long-term suppression of transmission, are to be achieved, it is essential that the transmission dynamics are understood and that intervention programmes are designed to maximise the reduction in transmission and the long-term sustainability of these goals. Availability of surveillance and research data is necessary to inform future models for them to be an effective tool to support the hugely impressive efforts to control VL on the ISC. As new datasets become available through the labours of experimental and field researchers, there are now opportunities for existing model refinement and novel model exploration to address outstanding questions (Box 4). To meet the ambitious targets of the WHO, it will be essential to maintain dialogue between modellers and programme managers, policy makers, and other researchers working to combat this disease.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pt.2015.03.007.

References

1 Zijlstra, E.E. *et al.* (2003) Post-kala-azar dermal leishmaniasis. *Lancet Infect. Dis.* 3, 87–98
2 Crompton, D.W.T. (ed.) (2013) *Sustaining the Drive to Overcome the Global Impact of Neglected Tropical Diseases*, WHO
3 Picado, A. *et al.* (2014) Risk factors for visceral leishmaniasis and asymptomatic *Leishmania donovani* infection in India and Nepal. *PLoS ONE* 9, e87641
4 Pascual Martínez, F. *et al.* (2012) Low castes have poor access to visceral leishmaniasis treatment in Bihar. *India. Trop. Med. Int. Health* 17, 666–673
5 Ahmed, B-N. *et al.* (2014) Kala-azar (visceral leishmaniasis) elimination in Bangladesh: successes and challenges. *Curr. Trop. Med. Rep.* 1, 163–169
6 Hasker, E. *et al.* (2014) Strong association between serological status and probability of progression to clinical visceral leishmaniasis in prospective cohort studies in India and Nepal. *PLoS Negl. Trop. Dis.* 8, e2657
7 Huda, M.M. *et al.* (2012) Active case detection in national visceral leishmaniasis elimination programs in Bangladesh, India, and Nepal: feasibility, performance and costs. *BMC Public Health* 12, 1001
8 Mondal, D. *et al.* (2009) Visceral leishmaniasis elimination programme in India, Bangladesh, and Nepal: reshaping the case finding/case management strategy. *PLoS Negl. Trop. Dis.* 3, e355
9 Joshi, A.B. *et al.* (2009) Chemical and environmental vector control as a contribution to the elimination of visceral leishmaniasis on the Indian subcontinent: cluster randomized controlled trials in Bangladesh, India and Nepal. *BMC Med.* 7, 54
10 Stauch, A. *et al.* (2011) Visceral leishmaniasis in the Indian subcontinent: modelling epidemiology and control. *PLoS Negl. Trop. Dis.* 5, e1405
11 Stauch, A. *et al.* (2014) Model-based investigations of different vector-related intervention strategies to eliminate visceral leishmaniasis on the Indian subcontinent. *PLoS Negl. Trop. Dis.* 8, e2810
12 Stauch, A. *et al.* (2012) Treatment of visceral leishmaniasis: model-based analyses on the spread of antimony-resistant *L. donovani* in Bihar. *India. PLoS Negl. Trop. Dis.* 6, e1973
13 Mubayi, A. *et al.* (2010) Transmission dynamics and underreporting of kala-azar in the Indian state of Bihar. *J. Theor. Biol.* 262, 177–185
14 Hartemink, N. *et al.* (2011) Integrated mapping of establishment risk for emerging vector-borne infections: a case study of canine leishmaniasis in southwest France. *PLoS ONE* 6, e20817
15 ELmojtaba, I.M. *et al.* (2012) Vaccination model for visceral leishmaniasis with infective immigrants. *Math. Methods Appl. Sci.* 36, 216–226
16 Dye, C. and Wolpert, D.M. (1988) Earthquakes, influenza and cycles of Indian kala-azar. *Trans. R. Soc. Trop. Med. Hyg.* 82, 843–850
17 Lee, B.Y. *et al.* (2012) The economic value of a visceral leishmaniasis vaccine in Bihar state, India. *Am. J. Trop. Med. Hyg.* 86, 417–425
18 Das, V.N.R. *et al.* (2011) Asymptomatic infection of visceral leishmaniasis in hyperendemic areas of Vaishali district, Bihar, India: a challenge to kala-azar elimination programmes. *Trans. R. Soc. Trop. Med. Hyg* 105, 661–666
19 Patole, S. *et al.* (2014) Multiple relapses of visceral leishmaniasis in a patient with HIV in India: a treatment challenge. *Int. J. Infect. Dis.* 25, 204–206
20 Burza, S. *et al.* (2014) HIV and visceral leishmaniasis co-infection in Bihar, India: an under-recognised and under-diagnosed threat against elimination. *Clin. Infect. Dis.* 59, 552–555
21 Zijlstra, E.E. *et al.* (1994) Endemic kala-azar in Eastern Sudan: a longitudinal study on the incidence of clinical and subclinical infection and post-kala-azar demal leishmaniasis. *Am. J. Trop. Med. Hyg.* 51, 826–836
22 Zijlstra, E.E. *et al.* (2000) Post-kala-azar dermal leishmaniasis in the Sudan: clinical presentation and differential diagnosis. *Br. J. Dermatol.* 143, 136–143
23 Rahman, K.M. *et al.* (2010) Increasing incidence of post-kala-azar dermal leishmaniasis in a population-based study in Bangladesh. *Clin. Infect. Dis.* 50, 73–76
24 Cunningham, J. *et al.* (2012) A global comparative evaluation of commercial immunochromatographic rapid diagnostic tests for visceral leishmaniasis. *Clin. Infect. Dis.* 55, 1312–1319

25 Boelaert, M. *et al.* (2014) Rapid tests for the diagnosis of visceral leishmaniasis in patients with suspected disease. *Cochrane Database Syst. Rev.* 2014, CD009135

26 de Ruiter, C.M. *et al.* (2014) Molecular tools for diagnosis of visceral leishmaniasis: systematic review and meta-analysis of diagnostic test accuracy. *J. Clin. Microbiol.* 52, 3147–3155

27 Zijlstra, E.E. and Alvar, J., (eds) (2012) *The Post Kala-azar Dermal Leishmaniasis (PKDL) Atlas*, WHO

28 ELmojtaba, I.M. *et al.* (2010) Mathematical analysis of the dynamics of visceral leishmaniasis in the Sudan. *Appl. Math. Comput.* 217, 2567–2578

29 ELmojtaba, I.M. *et al.* (2010) Modelling the role of cross-immunity between two different strains of *Leishmania. Nonlinear Anal. Real World Appl.* 11, 2175–2189

30 Boelaert, M. (2005) Efficacy, acceptability and cost-effectiveness of long lasting insecticide nets (LLIN) in the prevention of kala azar (KALANET) European Commission

31 Ostyn, B. *et al.* (2011) Incidence of symptomatic and asymptomatic *Leishmania donovani* infections in high-endemic foci in India and Nepal: a prospective study. *PLoS Negl. Trop. Dis.* 5, e1284

32 Matlashewski, G. *et al.* (2014) Research priorities for elimination of visceral leishmaniasis. *Lancet Global Health* 2, e683–e684

33 Kaye, P.M. and Aebischer, T. (2011) Visceral leishmaniasis: immunology and prospects for a vaccine. *Clin. Microbiol. Infect.* 17, 1462–1470

34 Verma, S. *et al.* (2010) Quantification of parasite load in clinical samples of leishmaniasis patients: IL-10 level correlates with parasite load in visceral leishmaniasis. *PLoS ONE* 5, e10107

35 Mondal, D. *et al.* (2014) Challenges for management of post kala-azar dermal leishmaniasis and future directions. *Res. Rep. Trop. Med.* 5, 105–111

36 Singh, R.P. *et al.* (2012) Post-kala-azar dermal leishmaniasis in visceral leishmaniasis-endemic communities in Bihar, India. *Trop. Med. Int. Health* 17, 1345–1348

37 WHO (2010) *Control of the Leishmaniasis*, WHO

38 Mondal, D. *et al.* (2010) Enhanced case detection and improved diagnosis of PKDL in a kala-azar-endemic area of Bangladesh. *PLoS Negl. Trop. Dis.* 4, e832

39 Bousema, T. *et al.* (2014) Asymptomatic malaria infections: detectability, transmissibility and public health relevance. *Nat. Rev. Microbiol.* 12, 833–840

40 Salah, A.B. *et al.* (1994) Development of a mathematical model on the dynamics of canine leishmaniasis transmission. *Archives de l'Institut Pasteur de Tunis* 71, 431–438

41 Quinnell, R.J. *et al.* (1997) The epidemiology of canine leishmaniasis: transmission rates estimated from a cohort study in Amazonian Brazil. *Parasitology* 115, 143–156

42 Mejhed, H. *et al.* (2009) Development of mathematical models predicting the density of vectors: case of sandflies vectors of leishmaniasis. In *Proceedings of the 10th WSEAS International Conference on Mathematics and Computers in Biology and Chemistry*, pp. 62–67 World Scientific and Engineering Academy and Society (WSEAS)

43 Dye, C. and Williams, B.G. (1995) Non-linearities in the dynamics of indirectly-transmitted infections (or, Does having a vector make a difference?). In *Ecology of Infectious Diseases in Natural Populations* (Grenfell, B.T. and Dobson, A.P., eds), pp. 260–279, Cambridge University Press

44 Stockdale, L. and Newton, R. (2013) A review of preventative methods against human leishmaniasis infection. *PLoS Negl. Trop. Dis.* 7, e2278

45 Uranw, S. *et al.* (2011) Post-kala-azar dermal leishmaniasis in Nepal: a retrospective cohort study (2000–2010). *PLoS Negl. Trop. Dis.* 5, e1433

46 Matlashewski, G. *et al.* (2011) Visceral leishmaniasis: elimination with existing interventions. *Lancet Infect. Dis.* 11, 322–325

47 Joshi, S. *et al.* (2014) Visceral leishmaniasis: advancements in vaccine development via classical an molecular approaches. *Front. Immunol.* 5, 1–18

48 Picado, A. *et al.* (2010) Longlasting insecticidal nets for prevention of *Leishmania donovani* infection in India and Nepal: paired cluster randomised trial. *BMJ* 341, c6760

49 Picado, A. *et al.* (2010) Effect of village-wide use of long-lasting insecticidal nets on visceral leishmaniasis vectors in India and Nepal: a cluster randomized trial. *PLoS Negl. Trop. Dis.* 4, e587

50 Coffeng, L.E. *et al.* (2014) Elimination of African onchocerciasis: modeling the impact of increasing the frequency of Ivermectin mass treatment. *PLoS ONE* 9, e115886

51 Stolk, W.A. *et al.* (2013) Modeling the impact and costs of semiannual mass drug administration for accelerated elimination of lymphatic filariasis. *PLoS Negl. Trop. Dis.* 7, e1984

52 Fischer, E.A.J. *et al.* (2011) The long term effect of current and new interventions on the new case detection of leprosy: a modeling study. *PLoS Negl. Trop. Dis.* 5, e1330

53 Anderson, R.M. *et al.* (1992) *Infectious Diseases of Humans: Dynamics and Control*, Oxford University Press

54 Leta, S. *et al.* (2014) Visceral leishmaniasis in Ethiopia: an evolving disease. *PLoS Negl. Trop. Dis.* 8, e3131

55 Hassan, M.M. *et al.* (2009) Role of the domestic dog as a reservoir host of *Leishmania donovani* in eastern Sudan. *Parasit. Vectors* 2, 26

56 Dereure, J. *et al.* (2000) Visceral leishmaniasis in Sudan: first identification of *Leishmania* from dogs. *Trans. R. Soc. Trop. Med. Hyg.* 94, 154–155

57 Hasibeder, G. *et al.* (1992) Mathematical modelling and theory for estimating the basic reproduction number of canine leishmaniasis. *Parasitology* 105, 43–53

58 Courtenay, O. *et al.* (2002) Infectiousness in a cohort of Brazilian dogs: why culling fails to control visceral leishmaniasis in areas of high transmission. *J. Infect. Dis.* 186, 1314–1320

59 Costa, D.N.C.C. *et al.* (2013) Culling dogs in scenarios of imperfect control: realistic impact on the prevalence of canine visceral leishmaniasis. *PLoS Negl. Trop. Dis.* 7, e2355

60 Courtenay, O. *et al.* (2014) Heterogeneities in *Leishmania infantum* infection: using skin parasite burdens to identify highly infectious dogs. *PLoS Negl. Trop. Dis.* 8, e2583

61 Boelaert, M. *et al.* (1999) Cost-effectiveness of competing diagnostic–therapeutic strategies for visceral leishmaniasis. *Bull. World Health Organ.* 77, 667–674

62 Meheus, F. *et al.* (2010) Cost-effectiveness analysis of combination therapies for visceral leishmaniasis in the Indian subcontinent. *PLoS Negl. Trop. Dis.* 4, e818

63 Dye, C. (1988) The epidemiology of canine visceral leishmaniasis in southern France: classical theory offers another explanation of the data. *Parasitology* 96, 19–24

64 Dye, C. (1996) The logic of visceral leishmaniasis control. *Am. J. Trop. Med. Hyg.* 55, 125–130

65 Williams, B.G. and Dye, C. (1997) Infectious disease persistence when transmission varies seasonally. *Math. Biosci.* 145, 7–88

66 Reithinger, R. *et al.* (2004) Are insecticide-impregnated dog collars a feasible alternative to dog culling as a strategy for controlling canine visceral leishmaniasis in Brazil? *Int. J. Parasitol.* 34, 55–62

67 Palatnik-de-Sousa, C.B. *et al.* (2004) Improving methods for epidemiological control of canine visceral leishmaniasis based on a mathematical model. Impact on the incidence of the canine and human disease. *Anias da Academia Brasileira de Ciencias* 76, 583–593

68 Ribas, L.M. *et al.* (2013) Estimating the optimal control of zoonotic visceral leishmaniasis by the use of a mathematical model. *Sci. World J.* 2013, 1–6

69 Knowles, R. *et al.* (1926) On a herpetomonas found in the gut of the sandfly *Phlebotomus argentipes*, fed on kala-azar patients: a preliminary note. *Ind. Med. Gaz.* 59, 593–597

70 Shortt, H.E. *et al.* (1926) Note on a massive infection of the pharynx of *Phlebotomus argentipes* with *Herpetomonas donovani. Ind. Med. Res. Mem.* 4, 441–444

71 Miller, E. *et al.* (2014) Quantifying the contribution of hosts with different parasite concentrations to the transmission of visceral leishmaniasis in Ethiopia. *PLoS Negl. Trop. Dis.* 8, e3288

72 Picado, A. *et al.* (2015) Long-lasting insecticidal nets to prevent visceral leishmaniasis in the Indian subcontinent; Methodological lessons learned from a cluster randomised controlled trial. *PLoS Negl. Trop. Dis.* 9, e3597