Health-seeking behaviour, diagnostics and transmission dynamics in the control of visceral leishmaniasis in the Indian subcontinent

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Countries in the Indian subcontinent have committed to reducing the incidence of kala-azar, a clinical manifestation of visceral leishmaniasis, to below 1 in 10,000 by 2020. We address the role of timing of use and accuracy of diagnostics in kala-azar control and elimination. We use empirical data on health-seeking behaviour and health-system performance from the Indian state of Bihar, Bangladesh and Nepal to parameterize a mathematical model. Diagnosis of cases is key to case management, control and surveillance. Treatment of cases prevents onward transmission, and we show that the differences in time to diagnosis in these three settings explain the observed differences in incidence. Shortening the time from health-care seeking to diagnosis is likely to lead to dramatic reductions in incidence in Bihar, bringing the incidence down to the levels seen in Bangladesh and Nepal. The results emphasize the importance of maintaining population and health-system awareness, particularly as transmission and disease incidence decline. We explore the possibility of diagnosing patients before the onset of clinical kala-azar (before 14 days fever), and show that this could have a marked impact on incidence, even for a moderately sensitive test. However, limited specificity (that results in false positives) is a major barrier to such a strategy. Diagnostic tests of high specificity used at an early stage of active infection, even if sensitivity is only moderate, could have a key role in the control of kala-azar, and prevent its resurgence when paired with the passive health-care system and tests of high sensitivity, such as the test for rK39 antibody response.

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the target product profile (TPP) of a diagnostic test that could identify less severe or even asymptomatic cases has not yet been defined. We considered the effect of such an intervention and the role of the specificity.

Within villages, cases of kala-azar tend to be clustered around index cases, suggesting that the drivers of local epidemics are individuals with kala-azar\(^a\). Most infected people are asymptomatic, but may still contribute to transmission at low levels\(^b\). Patients with post-kala-azar dermal leishmaniasis (PKDL) are known to harbour parasites, often in the dermal region, and are assumed to be infectious to sand flies\(^c\). The relative role of people with kala-azar, asymptomatic individuals and people with PKDL in sustaining transmission has not been measured directly and is unknown\(^d\). Some of this uncertainty will hopefully be addressed in the coming years, but at present more indirect methods are required to understand the dynamics of transmission and control. If kala-azar cases contribute to most of transmission, then early diagnosis and treatment is likely to be a highly effective intervention.

Very few modelling studies have been undertaken to help disentangle the interactions between individual, population and system processes for visceral leishmaniasis. This is partly because of a lack of quantitative information on the natural history of the disease\(^e\). The approach we present is to use a single model to compare information from three different endemic areas. From this we can infer the rates of progression through different clinical states, largely based on the fact that health seeking and health care have different outcomes in these areas. We then extend this core health-seeking model to account for transmission, using a simple, parsimonious framework to investigate the impact of changes in diagnosis on transmission dynamics.

We consider two interventions: reducing diagnostic delays in individuals who already fulfil the kala-azar definition, and introducing novel diagnostics to enable diagnosis of those who do not, or are yet to, fulfil the clinical definition of 14 days of fever and splenomegaly. We consider the dynamic consequences of these interventions, and highlight the potential for rebound epidemics as population (herd) immunity is curtailed. Finally, we consider the profile of a diagnostic required for diagnosis and treatment prior to full kala-azar, and emphasise that specificity, rather than sensitivity, is the limiting factor.

**METHODS**

**Empirical data.** The data that inform the model are from studies on self-report ed time from symptoms to health seeking and eventual diagnosis of kala-azar (Fig. 1a). In Nepal and Bihar, 92 patients with kala-azar who had experienced 103 kala-azar episodes were interviewed. Patients waited for 30 days (95% confidence interval (CI) = 18–42) in Nepal before seeking health care, 3.75 times longer than in Bihar where patients waited 8 days (95% CI = 4–12). Conversely, the lag time from seeking health care to receiving a kala-azar diagnosis was 90 days (95% CI = 68–113) in Bihar compared with 25 days (95% CI = 13–38) in Nepal. The time span between diagnosis and treatment was short in both countries. In Bangladesh, a 2007 cross-sectional study in Godagari Up zila, Rajshahi, Bangladesh by the International Centre for Diarrhoeal Disease Research, of the knowledge of, attitude to, and practice surrounding kala-azar by 5,000 dipstick test individuals who had had fever for more than 2 weeks. Around 5,000 households were surveyed, of these, 500 randomly selected household heads were interviewed, and indicated that it took 4 days

The model was parameterized to each locale. Each locale has two observations: the time from onset to health seeking (entry into $F_1$, and the time from health seeking to diagnosis ($K_a$ to $D$). These periods were expressed as functions of the four model parameters. Unique values of the parameters cannot be estimated, so we generated parameter sets of $a$, $b$, $c$ and $d$ that reproduce the observed times. We assumed that individuals with full kala-azar are more likely to seek health care than those with non-specific symptoms (c $> b$). A grid of all possible integer values for durations in each

**Table 1 |** Current diagnostic tests with sensitivity and specificity data taken from the Indian subcontinent where possible.

| Diagnostic test | Sensitivity | Specificity |
|-----------------|-------------|-------------|
| rk39 RDT\(^a\)  | 97.0% (95% CI = 90.0–99.5) | 90.2% (95% CI = 76.1–97.7) |
| DAT\(^a\)       | 97.1% (95% CI = 94.9–98.4) | 95.7% (95% CI = 88.1–98.5) |
| Parasitology spleen\(^a\) | $>95\%$ | 100% |
| Parasitology bone marrow\(^a\) | 60–85% | 100% |
| Antigen (KAtex)\(^a\) | 68–100% | 98% |
| PCR\(^a\)       | 92.3% (95% CI = 88.4–94.9) | 63.3 (95% CI = 53.9–71.8) |

CI, confidence interval; DAT, direct agglutination test; PCR, polymerase chain reaction; RDT, rapid diagnostic test.

**Figure 1 |** Data and model on delays in diagnosis. a, Time from onset of symptoms (defined as fever) to health-seeking and then diagnosis, for Bihar, Nepal\(^d\) and Bangladesh (D. Mondal, personal communication). b, Flow diagram of model. Open boxes show the behaviour model with progression post-infection through fever and full kala-azar (KA) (vertical flow), and from non-health-seeking to health-seeking (horizontal flow) behaviour. The shaded boxes and grey arrows indicate the extra states required for the transmission model.
state was compared with the observed outcomes. Parameter combinations that reproduce the observed times were retained, thus generating locale-specific combinations of parameters that produced results consistent with the data. The values of the parameters within the sets were correlated. For example, to reproduce the observed time to diagnosis, a shorter period spent health seeking is combined with a longer time waiting for diagnosis. Therefore, the parameters were retained as groups of appropriate parameters rather than ranges of possible values.

The model was then extended to include transmission dynamics (Fig. 1b). The extended model includes an incidence of infection and a latent class to account for delays between infection and onset of symptoms. Most latently infected individuals recover directly to the dormant stage without progressing to symptoms leading to kala-azar. The instantaneous rate of infection is calculated as the weighted sum of the force of infection from the various potentially infectious states: latent, fever, kala-azar and dormant. The equations, including analytical solution for the basic reproduction number, $R_0$, and equilibrium state, are given in the Supplementary Information. The basic reproduction number, $R_0$, is defined as the average number of onward infections caused by a single infectious individual in a wholly susceptible population throughout the infectious period of that individual. $R_0$ is a combination of the number of infections generated in each infection stage, which in turn is determined by the duration and infectiousness of the stage. For an endemic disease such as visceral leishmaniasis, populations are not wholly susceptible, and the number of onward transmissions will be reduced by potential contacts that are already infected or immune.

The duration of the latent stage, relative infectiousness of different stages and $R_0$ cannot be measured with current diagnostics and available epidemiological data. Consequently, we chose values that are consistent with current understanding, that reproduce patterns consistent with general observations, and so that the equilibrium state of the model in the three settings was consistent with relative epidemiological patterns. All of the biological parameters were the same across all three settings, so differences between settings were due to the differences in health-seeking behaviour and healthcare response (see Supplementary Information).

**RESULTS**

**Estimated pathways to diagnosis.** The parameter sets that are consistent with the data are shown in Figure 2. There are 526 unique parameter combinations ($a$, $b$, $c$, $d$) for Bihar, 2,320 for Nepal and 312 for Bangladesh. The time between fever onset and progression to clinical kala-azar is 33 days $< a < 55$ days. In Nepal, individuals develop the disease faster than they seek health care, so that the typical path for an individual is fever to kala-azar to seeking diagnosis, with most individuals diagnosed and treated within the first few weeks of symptoms. In Bihar and Bangladesh, health seeking starts much earlier, but diagnosis is slower so that individuals enter the health system, but then remain in the symptomatic state without treatment. The major difference between Nepal and the other two regions is that kala-azar cases in Nepal most frequently first present to health-care services as clinical kala-azar, whereas in Bihar and Bangladesh people first present with non-specific symptoms. Consequently, in Bihar, patients are likely to be diagnosed and treated for more common infections (such as bacterial infection) owing to presentation of non-specific symptoms. There is a risk that treatment failure, rather than misdiagnosis, is blamed, leading to repeat treatments for the wrong diagnosis. In addition, many patients present to unqualified practitioners or the private health-care system, delaying correct diagnosis.
Transmission dynamics. As with all transmission models, incidence of diagnosed cases increases non-linearly with the basic reproduction number, $R_0$, for all values of the transmission parameters (Fig. 3). At equilibrium, as long as individuals with kala-azar provide most infection to vectors, the transmission potential is higher in Bihar than Nepal (the average number of onward transmissions per infected individual, $R_0$, will be different). Only when transmission rates are high (Fig. 3), and therefore the number of onward infections, $R_0$ is also high, are the incidences of disease in all settings similar. At this level of transmission, the diagnostic differences are masked by the high infectiousness of latent, fever and dormant cases and variation between parameter sets and settings is obliterated. In reality, the transmission dynamics are not at equilibrium, and incidences are reducing in all locations due, at least in part, to reductions in $R_0$. Consequently, differences in incidence between settings can be explained by the differences in diagnostic delays that are consistent with the observed durations (Fig. 2). This suggests that variability in health-care seeking and diagnostic delays between different settings, and the resulting distribution of times with non-specific and specific symptoms are likely to have an impact on transmission patterns, particularly if there is differential infectivity at these different stages of infection.

Dynamic consequences of interventions. Owing to a lack of further information, we set the relative transmission parameters to be those in the central panel of Figure 3 (see Table 1 for parameter values). At these values, the equilibrium for Bihar is between 4 and 5 cases per 10,000 people per year.

We consider two interventions that shorten the period of high infectiousness and transmission potential. The impact of these interventions on the dynamics of diagnoses is similar (Fig. 4). First, we switched the delay in diagnosis seen in Bihar (43–63 days) to the average delay in Nepal (10 days, added to the 14 days of fever to become a clinical suspect; Fig. 4a). A reduction in time to diagnosis shows an initial large peak in cases, as the cases that are ‘waiting’ to be diagnosed are found. This leads to a rapid reduction in transmission, which then leads to a decline in incidence. For a setting with an incidence of 5 per 10,000 people per year, elimination would be achieved with this change in the current model. Whether or not elimination would be achieved in reality depends on, among other things, the details of transmission from asymptomatic infections and spatial heterogeneities. If diagnostic delay is returned to its previous length after 4 years, then there is a rebound epidemic, but this is much slower and occurs over several years. Note that the predicted patterns are similar for all the parameter sets fitted to the Bihar situation.

Second, we introduce the diagnosis and treatment of patients while they are health seeking with non-specific febrile symptoms, before they develop kala-azar (before they have passed 14 days of fever and have splenomegaly; Fig. 4b). The dynamic response is similar to the dynamics of reducing diagnostic delays for those who have kala-azar, but without the immediate diagnostic spike. The modelled intervention (30% of kala-azar cases are diagnosed during non-specific fever) is insufficient to eliminate infection. Consequently, there is an epidemic while the intervention is in place, owing to the build-up of individuals with increased susceptibility to infection who were previously protected by the reduction in transmission. If the intervention is kept in place, then incidence eventually returns to a low level. When the intervention is removed, the second epidemic is a consequence of the increase in transmission owing to the longer infectious period when screening of fever cases is stopped.

In both interventions, the supply of full clinical kala-azar diagnoses is curtailed, transmission is reduced and there is a reduction of population (herd) immunity that leads to a bounce back of cases if the intervention is stopped. The speed at which the subsequent epidemic occurs is dependent on the success of the intervention — better curtailment of transmission results in a longer period to the next epidemic. The slow build-up means that there will be no obvious link between lengthening diagnosis delay and incidence, with clear implications for monitoring efficiency of diagnosis and treatment. In particular, if this intervention were implemented, then potentially there would be a reduction in clinical awareness of visceral leishmaniasis, resulting in a
lengthening of diagnostic delays. We suggest that although reducing diagnosis delay through special efforts is likely to be an effective means to short-term reduction in cases, it is, depending on the epidemiological setting (baseline prevalence and biting rates), unlikely to be a sustainable route to long-term elimination. The quantitative details depend on specific parameter values and model structure, but this general pattern will be observed if those with kala-azar contribute most of the infection to vectors and onward transmission, and if there is sufficient (concomitant) immunity to kala-azar.

Impact of sensitivity of a novel diagnostic. We also consider the consequences of differing diagnostic sensitivities for diagnosis during the non-specific symptom phase in terms of its impact on equilibrium and short-term incidence of diagnoses (Fig. 5). Increased sensitivity will result in a larger proportion of cases being diagnosed earlier. At equilibrium, as the proportion of cases diagnosed increases, the incidence of diagnosis during the fever stage increases, but total diagnoses fall owing to reduced transmission (Fig. 5a). Elimination of transmission is possible even with relatively moderate sensitivity. If most transmission is from kala-azar cases, then halving the numbers progressing to this state will halve $R_0$. However, achieving equilibrium incidence in such models takes many decades and is mainly of theoretical interest. Consequently, we also consider the impact on the numbers of cases expected over the 5 years that follow the introduction of the intervention (Fig. 5b). Clearly, the dramatic fall in cases (Fig. 4b) occurs for low values of sensitivity, and over the short-term there is little extra to be gained from diagnosing more than 25–30% of cases before kala-azar.

Profile of the diagnostic. We profiled the diagnostic required for early case detection in terms of both sensitivity and specificity (Fig. 6). The size of the false-positive problem is determined by the frequency of fever cases (visceral leishmaniasis and non-visceral leishmaniasis) being tested for kala-azar, the specificity of the test and the proportion of fever cases that are due to visceral leishmaniasis. We, therefore, modelled a scenario in which there is a background rate of non-visceral leishmaniasis cases that present for diagnosis, and, to account for the possibility of multiple testing owing to the long duration of the fever stage for kala-azar (a known phenomenon), we include a frequency of testing for health-seeking kala-azar cases with fever. If each person who seeks health care presents once, then the proportion of true cases diagnosed is the sensitivity (Fig. 5). However, if people are tested at multiple consultations, then there are multiple opportunities for a correct, true-positive result, and a lack in sensitivity can be overcome by more frequent testing (Fig. 6a,b). However, as the number of testing occasions increases, the rate at which false positives are found increases, and increasing specificity linearly decreases the false positives (Fig. 6c). Holding the test frequency constant, the average positive predictive value (proportion of positives that are true positives) is shown in Fig. 6d as a function of sensitivity and specificity. There are likely to be many hundreds to thousands of false positives for every true positive identified unless the diagnostic, or diagnostic combination, is more than 99% specific. This problem is amplified by a decreasing prevalence of true infection, as witnessed in any elimination setting.

DISCUSSION
Our principal conclusion is that earlier diagnosis and prompt therapy have the potential to reduce ongoing transmission to elimination or near-elimination levels. This is indeed one of the pillars of the current elimination campaign, and, although this is likely to have already affected transmission in Nepal and Bangladesh, there is a large potential gain in Bihar, given that the diagnostic delays in this area are longer. We have also highlighted that curtailing transmission is likely to decrease population immunity in the long-term, so that there is a potential for large epidemics if vigilance is not maintained and diagnostic delays are allowed to increase. If diagnostic delays lengthen either the stage of health-care seeking or the ability of the system to recognise kala-azar, then subsequent epidemics are predicted to have a long lead time, and will not be immediately recognized. We have shown that the introduction of novel diagnostics on non-specific fever cases (before full kala-azar) can be effective even if sensitivity is relatively low, but that their introduction is prevented at present by less than ideal specificity, given the issues of delivery, safety and...
cost of treatments. The paucity of data available to fit more complex models means that our results rely as much on understanding of infectious-disease epidemiology as on our simple model. Nonetheless, we believe that these conclusions are supported by current understanding, and, if nothing else, are valid, strong hypotheses.

We studied two mechanisms by which earlier diagnosis could occur in highly endemic settings, such as Bihar. The first is improving the health system to reduce delays in treatment. At present, differences in the time to diagnosis between countries are assumed to be because of differing time spent in the private health-care system where knowledge of kala-azar is relatively poor. Potentially, patients present with less-specific symptoms and enter a different diagnostic algorithm, and kala-azar is only suspected later. A study in Bihar using accredited social health activists (community health workers in India) to identify and refer suspected kala-azar cases showed that the time from onset of fever to seeking treatment and diagnosis at peripheral health facilities could be reduced to 32–50 days in total46. Our modelling reinforces the observation that reducing the time to diagnosis is an effective intervention, but as prevalence decreases it will be more difficult to maintain the necessary knowledge and infrastructure to sustain this. Intriguingly, the efficiency of the diagnostic process may have a natural equilibrium, depending on the frequency of diagnosis. We have also shown that resurgence in cases will occur after several years if transmission is reduced and not halted, and that the peak of the resurgence may well be higher than the pre-intervention. Typically, local kala-azar outbreaks occur regularly — 3 peaks have occurred in India 14–15 years apart over the past 40 years31.

The second mechanism to reduce the time to diagnosis in highly endemic areas such as Bihar is to identify active infection before kala-azar onset. Specificity becomes important when designing a test that targets early case detection (before 14 days of fever). Only a test with very high specificity will allow patients to be treated, given the limited range of treatments available (toxicity, cost, administration or adherence, depending on the treatment). Nonetheless, if specificity is high enough to consider treating patients before they have 14 days of fever and become a clinical suspect, then patients could be tested and treated much earlier than is possible with the current diagnostic algorithm. This would eliminate a pool of patients that transmit visceral leishmaniasis to their local community, thereby substantially reducing future cases. Our analysis demonstrates that sensitivity of early testing for visceral leishmaniasis is not the main problem. Even a moderately sensitive test (30%) can have dramatic affect on kala-azar transmission alongside the current testing algorithm of passive surveillance with rk39. The challenge to testing earlier in the course of the disease, with the intention of treating, is avoiding a large number of false positives. However, as prevalence decreases, the positive predictive value of all tests will fall as more patients are false positives than true positives, but the resultant gain in sustainable elimination (if such a test were to be implemented) is significant.

Limitations of this model and data gaps

There are few well-conducted studies to describe the natural history of visceral leishmaniasis, which is multifactorial30, and hence the risks for an infected individual to become diseased are not quantified. Owing to the localized epidemics that are seen surrounding index cases it is reasonable to assume that patients with kala-azar are the main reservoir of infection for sand flies. It is also thought that those with PKDL and asymptomatic individuals or those with a dormant infection can also be infectious to sand flies, but the evidence base for this relies on anecdotal studies. Only one experimental study46 has been published whereby sand flies were allowed to feed on four people with PKDL. Of the 400 fed flies, 104 became infected. In our analysis we have assumed that asymptomatic individuals and those with PKDL are, on average across the population, considerably less infectious than symptomatic cases46. Should asymptomatic individuals be more infectious than anticipated, the relative importance of kala-azar cases to R0 will decrease. This means that the period of infectiousness will increase, reducing the probability of elimination and necessitating lower overall transmission rates to maintain the levels of incidence in the 1–5 cases per 10,000 people per year. If people with kala-azar are less infectious than we have assumed, the impact of reduction in diagnostic delays will be reduced, but the effect of early, novel diagnostics will be enhanced (results not shown). Of course, diagnostics for asymptomatic cases and people with PKDL may be essential for elimination if these groups are shown to be involved in transmission of disease and maintain long-term infections.

Unfortunately, without more detailed data, the models we have described are only able to highlight the qualitative patterns, although they are robust across a large range of biologically plausible parameters. The health-seeking behaviour data are informative about ranges of parameters, including the duration of non-specific symptoms, a parameter that has not been previously estimated. The data would be greatly improved by systematically sampling a population in which incidence was also estimated.

In addition to the uncertainties on the human side of transmission, we also know little of sand-fly behaviour, life expectancy and range. Clearly, these vector dynamics will have an important role in the transmission cycle and in the design of effective interventions against transmission.

Diagnostics of the future

Diagnostics play a crucial part in the control and elimination of kala-azar and are a research priority45. We argue that one avenue to revolutionize the current control algorithm is to develop a highly specific test of active infection (whether symptomatic or asymptomatic), even if limited in sensitivity. There is currently no suitable antigen test capable of detecting active kala-azar. The only commercially available product, KATex, has challenges in utility and suboptimal sensitivity, although we would argue that low sensitivity should not necessarily be considered a barrier to implementation. Simplified molecular diagnostic tools that can be adapted for field situations are under development, including loop-mediated isothermal amplification48. These tests, along with standard polymerase chain reaction, are able to detect circulating DNA in the blood of individuals who are actively infected. Studies show that molecular tests are very sensitive, and although they have low specificity, it may be that these are infections that are below the limit of detection of the reference standard, and therefore in fact true positives.4 Diagnostics that are able to detect asymptomatic infection and PKDL may also be important, depending on the relative role of transmission in these groups.

Given the uncertainty in clinical progression of kala-azar and diagnostic performance, there is clearly a chance that some, possibly much, of the morbidity and mortality caused by Leishmania infection is being misclassified. The process of diagnosis of kala-azar provides both the clinical information for treatment, as well as the data on which surveillance is built. Consequently, it is inevitable that 100% of cases of kala-azar are diagnosed and treated, regardless of the performance of the health-care system or the health-seeking behaviour of the population. Ideally, surveillance would include information that is independent of clinical diagnosis. This is particularly needed as kala-azar becomes rarer, and it is likely that both clinical and patient awareness wanes. A diagnostic tool that enables population surveillance of infection and disease, independent of clinical diagnosis, is a crucial step in achieving, enforcing and demonstrating elimination.

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**SUPPLEMENTARY MATERIAL**

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**COMPETING FINANCIAL INTERESTS**

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**ADDITIONAL INFORMATION**

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