Leishmaniasis, conflict, and political terror: A spatio-temporal analysis

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A R T I C L E   I N F O

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A B S T R A C T

Background: Leishmaniasis has been estimated to cause the ninth largest burden amongst global infectious diseases. Occurrence of the disease has been anecdotally associated with periods of conflict, leading to its referral as a disease of ‘guerrilla warfare.’ Despite this, there have been few studies that quantitatively investigate the extent to which leishmaniasis coincides with conflict or political terror.

Methodology: This study employed a longitudinal approach to empirically test for an association between cutaneous and visceral leishmaniasis incidence with occurrence of conflict and political terror at the national level, annually for 15 years (1995–2010). Leishmaniasis incidence data were collected for 54 countries, and combined with UCDP/PRIO Armed Conflict and Amnesty International political terror datasets. Mixed effects negative binomial regression models clustered at the country-level were constructed to evaluate the incidence rate ratios against the predictors, while controlling for wealth. Additionally, to understand how and why conflict-terror may be associated with leishmaniasis incidence, we conducted a historical analysis. We identify and discuss posited causal mechanisms in the literature, and critically assessed pathways by which leishmaniasis might occur in places and times of conflict-terror.

Results: There was a significant dose-response relationship for disease incidence based on increasing levels of conflict and terror. Country-years experiencing very high levels of conflict-terror were associated with a 2.38 times higher [95% CI: 1.40–4.05] and 6.02 times higher [95% CI: 2.39–15.15] incidence of cutaneous and visceral leishmaniasis, respectively. Historical analysis indicated that conflict and terror contribute to—or coincide with—leishmaniasis incidence through processes of population displacement and health system deterioration.

Conclusions: This research highlights the potentially increased risks for cutaneous and visceral leishmaniasis incidence in areas of high conflict-terror. Notably, conflict-terror may act as an empirical proxy for indirect and concomitant processes of social breakdown, migration, and instability, which emerge as the dominant processes associated with disease incidence.

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1. Introduction

Leishmaniasis, a vector-borne protozoan parasitic diseases endemic to 88 countries worldwide, is a source of significant public health concern (Alvar et al., 2012; WHO, 2014a; Desjeux, 2001a). With a prevalence of approximately 12 million cases, leishmaniasis causes the ninth largest burden amongst global infectious diseases (Alvar et al., 2012; Desjeux, 2001a). Additionally, it is the leading cause of morbidity and mortality amongst the World Health Organization’s neglected tropical diseases (NTDs) group (WHO, 2014b). Leishmaniasis is transmitted by sandfly vectors (Phlebotomus spp.), and its subtypes are caused by various leishmania species that, if left untreated, can be fatal (Palatnik-de-Sousa and Day, 2011). Despite its global endemicity, over two thirds of the approximately one million new annual cases of cutaneous leishmaniasis (CL) occur in only ten countries: Afghanistan, Algeria, Brazil, Colombia, Costa Rica, Ethiopia, Iran, Peru, Syria and Sudan (Alvar et al., 2012; WHO, 2014a). Similarly, 90% of the annual 300,000 global cases of visceral leishmaniasis (VL) occur within six countries: Bangladesh, Brazil, Ethiopia, India, Sudan and South Sudan (Alvar et al., 2012). Despite leishmaniasis prevention and treatment strategies— including vector abatement, bed-net usage, and anti-microbial dispersal (Jacobson, 2011; Hotez et al., 2012)— leishmaniasis transmission persists, with the most severe
outbreaks often occurring in high conflict areas (Hotez, 2014). This correlation has led to its referral in media sources as a disease of guerrilla warfare (Beyrer et al., 2007).

In recent years, the literature has begun to recognize the impacts of conflict on global health outcomes and infectious disease emergence (Beyrer et al., 2007; Garfield and Neugut, 1991; Gobarah et al., 2004; Guha-Sapir and Panhuis, 2004; Iqbal, 2006; Kerridge et al., 2012; Spiegel et al., 2007; Berrang-Ford et al., 2011). Communicable diseases may be propagated in conflict zones as a result of various social and healthcare system breakdowns, including: susceptible population movement, compromised health programs, shortages in medical care, and the destruction of health-related infrastructure (Iqbal, 2006; Kerridge et al., 2012; Leaning and Guha-Sapir, 2013). These conditions are further exacerbated by the frequent diversion of public and private investment from health to military expenditure (Kerridge et al., 2013). Vector borne diseases, such as leishmaniasis, may be particularly impacted by armed conflict due to the introduction of immuno-compromised populations into areas with limited vector control and surveillance programs (Berrang-Ford et al., 2011). Political terror [PT] and one-sided violence, which do not necessitate armed conflict, have also been associated with destabilizing public health systems (Kerridge et al., 2012; Berrang-Ford et al., 2011; Hoddie and Smith, 2009). However, dissociation between this type of violence and armed conflict can be difficult given that they often occur simultaneously in unstable regions (Kerridge et al., 2013; Eck and Hultman, 2007).

Amongst infectious diseases, conflict and political violence have been associated with concomitant increases in HIV/AIDS, malaria and tuberculosis, suggesting a dose-response relationship where greater, or more intense, conflict is associated with higher incidence (Gobarah et al., 2004; Li and Wen, 2005). Additionally, high conflict and terror levels have been found to induce prolonged impacts, known as ‘lag effects,’ for diseases such as human African trypanosomiasis (Berrang-Ford et al., 2011). Similar results are seen in cases of leishmaniasis—for instance, Collin et al. (2004) note significantly greater VL incidence among combatant and civilian populations during and following periods of civil conflict and unrest in Sudan and South Sudan. It has also been suggested that regional conflicts and their associated population movements can complicate leishmaniasis clinical and vector program management, as well as impede surveillance and knowledge sharing efforts (Jacobson, 2011; Hotez et al., 2012; Collin et al., 2004). These conflict associated impacts, which endure past the initial period of active warfare, are important but poorly researched determinants of health.

Despite anecdotal associations, research investigating leishmaniasis in conflict zones has been limited, with case-studies focused on Sudan, South Sudan and parts of the Middle East (Jacobson, 2011; Hotez et al., 2012; Collin et al., 2004; Reyburn et al., 2003; Rowland et al., 1999; Seaman et al., 1996; Zijlstra et al., 1994; Salam et al., 2014). To our knowledge, there have been neither multi-country nor multi-year studies assessing evidence that incidence systematically coincides with conflict over space and through time. We herein employ a longitudinal analysis to empirically test for an association between the global incidence of CL and VL, and occurrence of conflict and political terror at the national level, annually over a 15-year period (1995–2010). Additionally, to understand how and why conflict and/or terror may be associated with—or proxy determinants of—leishmaniasis incidence, we conduct a historical analysis. We identify and discuss posited causal mechanisms in the literature, and critically assess the most likely pathways by which leishmaniasis might occur. Herein, our objectives include (1) quantitatively assess the association between conflict and political terror with regards to CL and VL, and (2) evaluate the processes by which conflict-terror contributes to—or coincidences with—leishmaniasis incidence.

2. Methods

2.1. Data sources [Table 1]

CL and VL incidence data were obtained from national annual case reports collected by the World Health Organization Leishmaniasis Control Team (Alvar et al., 2012). The dataset, which reports the adjusted incidence (i.e. includes the estimated underreporting rates by country and year), is the most comprehensive collection of leishmaniasis incidence available globally. The surveillance and acquisition processes for the dataset’s development are described in detail by Alvar et al. (2012). Given the lack of systematic reports, common with NTDs, only countries with at least 10-years of data between 1995 and 2010 were included in our analysis. The exception to this criterion was the inclusion of the previously mentioned 10 and 6 countries known to have the highest CL and VL incidences, respectively. In total we evaluated data from 39 countries for CL and 38 countries for VL, both for 15 years [see also Supporting Information]. Sub-national data on leishmaniasis incidence by Pigott et al. (2014), were considered; however, these were only available as binary disease occurrences (i.e. no incidence or prevalence estimates) and were therefore not suitable for our analysis. Population data, used to standardize the estimated leishmaniasis incidence per capita, were obtained from the United Nations Department of Economic and Social Affairs (UN DESA, 2013).

Armed conflict and political terror data were collected for all countries in our dataset between the years 1985 and 2010. The inclusion of data up to 10-years prior to leishmaniasis incidence reports was considered to allow for the possibility of lag periods (i.e. number of years between conflict-terror exposure and leishmaniasis incidence) (Berrang-Ford et al., 2011). Conflict data were collected at the national level from the UCDP/PRIO Armed Conflict Dataset, which defines conflict as “any contested incompatibility that concerns government and/or territory where the use of armed force between two parties, of which at least one is the government of a state, results in at least 25 battle-related deaths” (Upssala Conflict Database Program, 2013). Not all conflicts at sub-regional levels are captured by UCDP/PRIO, thus the dataset is biased against countries with frequent—but smaller—conflicts. We include only domestic conflict (i.e. excluded participation in conflicts outside of national borders) to ensure spatial coincidence of determinants and outcomes within national boundaries. Political terror data were obtained from the Political Terror Scale database coded by Amnesty International and the US State Department (Gibney et al., 2013), and were included to capture violence-related outcomes not reflected by armed conflict. The PT measure is based on a five-level terror scale (Table 1), which evaluates the integrity of human rights observed by a country’s government, including: incidents of state induced disappearances, imprisonment, torture and/or death in a given year. The national level resolution of the PT variable is also biased against smaller conflicts, such as those within the Balkans, which are not captured in the dataset.

It is plausible—and likely—that associations between conflict or terror and leishmaniasis incidence may be partially attributable to confounding by national wealth. For instance, conflict and terror are more frequent in poorer countries, conflict in developing regions can be a drain on national resources, and poorer nations may have fewer resources for healthcare (Kerridge et al., 2013). We thus included national wealth as a control variable in all models. Data for the gross domestic product (GDP) per capita in International were retrieved from the World Bank [see also Supporting Information].
between con-

visually evaluate time-variant trends. To assess spatial associations

aggregated average incidences of CL and VL were generated to

at-risk population (Berrang-Ford et al., 2011). Subsequently,

year metric to evaluate leishmaniasis incidence as compared to the

some countries. Descriptive statistics included generating a people-

country-years); however, there were missing data for some years in

were also generated at the country level.

modelled as outcome measures, with armed con-
terror as predictors and controlling for wealth. Due to collinearity

between the two predictors, combined con-
terror levels were

determined to be the most comprehensive score for each country (Gibney et al., 2013).

was retained as a control in the models.

proxies for national wealth (World Bank, 2014).

2.2. Data analysis

The total CL analysis included 39 countries (n = 510 country-

years) and the VL analysis included 38 countries (n = 507 country-years); however, there were missing data for some years in

some countries. Descriptive statistics included generating a people-

eyear metric to evaluate leishmaniasis incidence as compared to the

at-risk population (Berrang-Ford et al., 2011). Subsequently,

aggregated average incidences of CL and VL were generated to

visually evaluate time-variant trends. To assess spatial associations

between conflict and terror with CL and VL, average incidences

were also generated at the country level.

In our models, the CL and VL incidences per 1000 people were

modelled as outcome measures, with armed conflict and political

terror as predictors and controlling for wealth. Due to collinearity

between the two predictors, combined conflict-terror levels were

created by grouping categories by natural breaks. The combined

categories—divided into five levels—were based on combinations

of conflict-terror that descriptively showed similar clusters of cases

(Table 2) [see also Supporting Information]. The multivariable

model used multi-level mixed effects negative binomial regression,

clustered at the country-level. The mixed effects model with a

random intercept clustering at the country level was chosen to

account for the violation of model independence from repeated
country-year measures. Negative binomial specification with a log- link function was selected to account for over-dispersion of leish-
mansiasis incidence data (i.e. a large number of country-years with

no or few cases). Poisson and zero-inflated models were also tested,

and not found to be a better fit than the negative binomial distri-
bution. Given that the lag period between exposure to conflict and

incidence differs by disease (Berrang-Ford et al., 2011), we tested

our model at varying lag periods (i.e. conflict-terror at t−1, t−2

… t−10) to identify the most significant period for leishmaniasis. The

strongest association was found at t−1, thus all final models used

conflict-terror levels lagged one year behind leishmaniasis data. To

adjust for misspecification and within-country correlation, the

models used Huber-White Robust SES clustered by country

(Formula (1)).

\[
\ln \{E(y_{ij} \mid X_j)\} = \beta_0 + \beta_1 X_1_{ij} + \beta_2 X_2_{ij} + \epsilon_{ij}
\]

\ y \sim \text{nbinomial} \\
X_1 \text{ is the conflict-terror predictor for country } i \text{ at time } j, \text{ where } j \text{ is } t-1 \\
X_2 \text{ is the wealth (control variable) of country } i \text{ at time } j, \text{ where } j \text{ is } t

Table 2

Composite conflict-terror categories.

<table>
<thead>
<tr>
<th>Combined Conflict-terror levels*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1: Very low</td>
<td>Countries with no armed conflict and low political terror (levels 1–3).</td>
</tr>
<tr>
<td>Level 2: Low</td>
<td>Countries with no armed conflict and high political terror (levels 4–5).</td>
</tr>
<tr>
<td>Level 3: Medium</td>
<td>Minor conflict and low political terror (levels 1–3) as well as major conflict and low political terror (levels 1–3).</td>
</tr>
<tr>
<td>Level 4: High</td>
<td>Minor conflict and high political terror (levels 4–5).</td>
</tr>
<tr>
<td>Level 5: Very high</td>
<td>Major conflict and high political terror (level 4–5).</td>
</tr>
</tbody>
</table>

* See Supporting Information Figs. 2 and 3 for details on natural breaks of case clusters used to descriptively create categories.
Incidence Rate Ratios [IRRs] with 95% confidence-level intervals are reported for all models.

To verify the statistical power and stability of the models, we conducted post-estimation tests and sensitivity analyses. Model diagnostics were assessed by visually examining the assumptions conducted post-estimation tests and sensitivity analyses. Model are reported for all models.

3. Results

3.1. Descriptive statistics

Over 8 million CL and 3 million VL cases were recorded in the dataset between 1995 and 2010 (Table 3). VL incidence was highly focalized in countries and during years (country-years) experiencing high conflict—terror. Approximately 65% of all VL cases occurred in country-years within the high and very high conflict-terror levels, and only 10% occurred in the low and least conflict-terror levels. The proportion of cases occurring in the higher levels was greater than would be expected, given the at-risk population (44%) measured by the people-year distribution. CL indicated a weaker relationship, with country-years in the very high conflict-terror level containing 17% of cases and the second highest level containing 16%. As compared to the at-risk people-years, there was higher incidence at lower conflict-terror levels (37%) than would be expected (28%). This suggests that as compared to VL, the association between CL and conflict-terror is less clear. Temporally, both subtypes followed similar trends in annual incidence rates (Fig. 1). In general, incidence increased for both CL and VL over the study period, with fluctuations in the late 1990s and mid-2000s, followed by substantial increases towards the end of the study period. The spatial distribution of VL (Fig. 2) indicates that incidence—and in particular high magnitudes of incidence—coincide with regions experiencing higher levels of conflict-terror. Spatial coincidence of CL incidence and conflict-terror is also evident, but to a lesser extent (Fig. 3).

3.2. Statistical modelling

Incidence of leishmaniasis—especially visceral leishmaniasis—was significantly greater in country-years with very high levels of conflict-terror (Table 4). The incidence of CL/1000 people was 2.38 times greater [IRR = 2.32—15.17 and IRR = 6.02, 95% CI: 2.39—15.15] than for country-years at the lowest level. These associations persisted even when controlling for wealth; unadjusted IRRs excluding wealth ranged from 2.23 [95% CI: 1.18—4.19] for CL to 8.22 [95% CI: 2.73—24.72] for VL at Very High conflict-terror levels [see also Supporting Information]. This indicates that wealth may account for some—but not all—of the association between conflict-terror and leishmaniasis.

Additionally, we evaluated IRRs by conflict-terror lagged by up to 10 years. Incidences for both CL and VL were strongest at conflict-terror lagged by only one year. Values decreased in both effect size and significance at longer lag periods, suggesting that the impacts of conflict-terror on leishmaniasis are more immediate. Pearson residuals indicate that there are a small number of countries that contain a very high number of cases (namely Sudan and South Sudan), thus residuals >1.5 and <-1.5 were removed for sensitivity analyses. Model IRRs remained stable and were not significantly affected by outliers. The robustness of the model was also tested to climatic assumptions using country latitudes as a proxy (Tuite et al., 2013); this was not found to significantly affect the outcomes. Post-estimation diagnostics identified no concerns with model fit.

4. Discussion

Conflict-terror—particularly Very High levels—may be a risk factor for leishmaniasis; indeed incidence rate ratios of greater than 2 (for CL) and 6 (for VL) indicate substantial spatio-temporal
association. Although occurrence of conflict-terror and leishmaniasis incidence in the same geographic location is not well studied, these results are consistent with the growing body of literature identifying conflict and terror as determinants for infectious disease (Ghobarah et al., 2004; Guha-Sapir and Panhuis, 2004; Iqbal, 2006; Kerridge et al., 2012; Spiegel et al., 2007; Elston, 2003). Because we controlled for national wealth, it is unlikely that the outcomes owed solely to economic confounding.

The significance of the results and the magnitude of association between conflict-terror levels are greater for VL than for CL. This variation in disease subtype may be due to different transmission pathways, which are likely responding differently to conflict-terror influences (Chappuis et al., 2007). CL can infect a variety of hosts including: small rodents, marsupials, domestic dogs, and humans; however, VL primarily follows an anthropotonic (i.e. highly human-dependent) transmission cycle (Pigott et al., 2014; Reithinger et al., 2007a). An anthropotonic transmission cycle suggests that conflict-terror conditions, which are known to correspond with crowding, migration, population displacement and poor housing, may be particularly significant in propagating disease within human populations (Beyrer et al., 2007). In contrast, the less direct and more complex mechanisms by which conflict-terror influences non-anthropotonic disease transmission, may explain the inconsistent results for CL incidence. The association between the extremely high incidence rate and high conflict-terror within Sudan, South Sudan and Ethiopia may also contribute to the observed results. These countries account for the three highest VL incidence per capita within our dataset, and they were consistently at a High or Very High conflict-terror level; neither of these countries met criteria for inclusion in the CL analysis. Their higher residual values, which suggest that the model under-predicted incidence, may indicate that the IRRs were subject to the influence of a relatively small number of countries. Notably, however, our analysis controls for temporal clustering by country—through multi-level modelling and robust clustered errors—indicating that even within these high incidence countries, VL rates are associated with changing magnitudes of conflict-terror between years.

4.1. Limitations

The significant variation in CL and VL incidence rates across space and through time demonstrates the value of evaluating the disease burden between countries. The model identifies a high degree of differentiation between countries of high and low conflict-terror. However, it is limited in its ability to detect temporal variation within a country, especially when the country consistently experienced high conflict-terror. Although these nations have peaks of incidence within the study period, they are not well explained within the model given the consistent conflict. Sub-national level data for both CL/VL incidence and conflict-terror could better explain within country variation and avoid assumptions of spatial homogeneity (Berrang-Ford et al., 2011). Finer data resolution could be useful in overcoming bias against smaller or less frequent conflicts, such as notable disputes within the Balkan
region during this period. Additionally, the definition of political terror as ‘state-induced’ does not adequately capture processes of terror induced by other groups such as in the cases of Boko Haram, ISIS or organized crime within Mexico and Brazil. Thus, more nuanced conflict-terror categories—especially at the higher levels—may identify within country variations, thereby elevating the statistical power of the model.

Missing data and underreporting rates of CL and VL, which stem from the fact that leishmaniasis is an NTD, are another limitation. Although Alvar et al. (2012) attempt to account for underreporting rates, it is still widely accepted that leishmaniasis is poorly diagnosed and recorded (Alvar et al., 2012; Chappuis et al., 2007). These underreporting rates and missing data are further exacerbated given the focus of this study in conflict-terror zones, where healthcare capacities are particularly weak. For instance, our analysis indicates that Palestine has high incidence of CL throughout the study period, which coincides with high and very high levels of conflict-terror in the region; however, CL incidence for Israel was not included given missing data. As such these analyses do not account for reduced surveillance bias during times of conflict-terror, nor do they account for increased and advanced surveillance technologies through time. Although missing data is a critical issue within observational studies, these factors would be expected to bias towards the null, implying that the results presented here may be conservative.

### 4.2. Historical analysis

The empirical association between conflict-terror and leishmaniasis incidence cannot be presumed to imply a causal impact; data do not exist—and it is not feasible—to conduct robust quantitative causal modelling on this topic globally. Indeed the associations presented here may be confounded by other factors, and conflict-terror may act as a proxy for broader social processes. Thus, we conducted a historical literature analysis to qualitatively unpack the possible causal (or proxy) mechanisms underpinning our results. Using our multivariable model as an heuristic tool, we explored the potential processes by which conflict-terror has

<table>
<thead>
<tr>
<th>Predictor</th>
<th>IRR (95% confidence interval)</th>
<th>Cutaneous</th>
<th>Visceral</th>
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</thead>
<tbody>
<tr>
<td>Conflict-Terror level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level 1: Very low</td>
<td>Ref</td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Level 2: Low</td>
<td>1.35 (1.05–1.72)**</td>
<td>2.48 (0.83–7.37)</td>
<td></td>
</tr>
<tr>
<td>Level 3: Medium</td>
<td>1.05 (0.85–1.30)</td>
<td>3.49 (1.51–8.05)**</td>
<td></td>
</tr>
<tr>
<td>Level 4: High</td>
<td>1.23 (0.96–1.58)**</td>
<td>5.93 (2.32–15.17)**</td>
<td></td>
</tr>
<tr>
<td>Level 5: Very High</td>
<td>2.38 (1.40–4.05)**</td>
<td>6.02 (2.39–15.15)**</td>
<td></td>
</tr>
<tr>
<td>GDP per capita (International $)</td>
<td>0.99 (0.99–1.00)</td>
<td>0.99 (0.9997–0.999)**</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05.
** p < 0.01.

Fig. 3. Cutaneous leishmaniasis incidence (cases/100,000) for countries with at least 10-years of available data overlaid on mean conflict-terror, 1995–2010.
historically contributed to—or coincided with—notable leishmaniasis incidence clusters. We selected spatial and temporal hotspots of leishmaniasis from our dataset, and conducted focused literature reviews to investigate the mechanisms posited in the literature for increased incidence, with particular attention to consideration of conflict and terror (Table 5).

Many countries within our dataset have been linked to conflict or conflict-terror related events; this is specifically the case for Sudan, South Sudan and Ethiopia for VL (Fig. 4a), and Afghanistan, Iraq, and Colombia for CL (Fig. 4b). For instance, associations between the Sudanese Civil War (1983–2005) and VL incidence in Sudan and South Sudan is one of the leading explanations for the sustained epidemic (Zijlstra et al., 1994; Reithering et al., 2007b). In particular, conflict and conflict-terror conditions may capture processes of migration within the region, specifically the migration of vulnerable populations into dense or overcrowded areas (Beyrer et al., 2007; Aagaard-Hansen et al., 2010). Such population transitions not only strain vulnerable individuals—contributing to immune-compromised health status—but they can also increase human-vector interactions (Desjeux, 2001b). Our analysis indicates that South Sudan’s peaks in VL incidences occurred between 2002 and 2005, which coincides with the mass internal migrations that preceded its autonomy in 2005 (Kolaczinski et al., 2008). Additionally, the literature suggests that large influxes of refugees and displaced persons from this conflict may be associated with spill-over into neighboring Ethiopia, another area of high VL incidence (Desjeux, 2004). Migration and overcrowded conditions have also been found to occur in refugee camps or among displaced population routes. In Afghanistan, the largest CL outbreaks occurred in 2002 and 2007 within Kabul refugee camps (Reithering et al., 2010). Persistence of the disease in Kabul has been thought to be at least partially attributed to the continuous flow of migrants to overcrowded camps (Aagaard-Hansen et al., 2010).

Conflict-induced determinants may be further exacerbated by political terror, which captures the broader social instability and breakdown that can occur. Terror can result in the limiting of resources towards, and access to, vector-control programmes, treatment options, and surveillance capabilities (Jacobson, 2011). For instance, we identify Colombia as a severe CL disease cluster, and it was categorized within High or Very High conflict-terror levels for the entirety of the study period. Reports indicate that political violence and social unrest have escalated since the 1980s within the country (Bern et al., 2008), and there have been concomitant increases in military spending from 0.92% of the GDP in 1991 to 3.3% in 2005 (Beyrer et al., 2007). These funding reallocations could be associated with reductions in public health initiatives. With reduced access to CL treatment options or decreased vector surveillance, it is possible that infected individuals who may be subject to internal displacement are continuing to perpetuate the disease (Beyrer et al., 2007; Aagaard-Hansen et al., 2010). In Iraq, it is postulated that similar socio-political and economic processes may be occurring at the population level (Jacobson, 2011; Salam et al., 2014). These areas of persistent conflict, political instability, and leishmaniasis, suggest that conflict-terror may be a significant risk factor for disease incidence.

Alternatively—or concurrently—conflict-terror may be capturing larger social processes. Conflict-terror acts as an empirical proxy for social breakdown, migration, and instability beyond measures of wealth (Reithering et al., 2003; Bern et al., 2008; Hewitt et al., 1998). In countries where conflict-terror has been incited but population movement has been sustained, the processes may become conflated. For instance, Iran is considered a conflict/post-conflict hotspot and has reported high levels of internal migration, which could point to interactions between these dual processes and high leishmaniasis incidence (Hotez and Thompson, 2009). Even within this, analyses suggest that terror may be a more nuanced indicator of leishmaniasis incidence than armed conflict levels. This is likely compelled by severe leishmaniasis incidence in countries reporting no formal conflict, but high levels of political terror. Syria, for example, records no years of armed conflict between 1995 and 2010, but all years have a political terror level of 3 or 4. Within the country, CL is focalized in the city and peri-urban areas of Aleppo (Desjeux, 2004). Although we found no literature positing a relationship between conflict-terror and CL incidence within our study period, Syria’s political instability has been linked to internal migration and refugee movements (Hotez, 2014; Salam et al., 2014). In this case, political terror—as opposed to conflict—may more accurately capture changes affecting health services. In other words, it may not be the actual armed conflict per se that is associated with increased leishmaniasis incidence, but the larger socio-economic and political changes in a country’s ability to prevent and control disease during and proceeding conflict periods that is of primary concern (Berrang-Ford et al., 2011).

Within Latin America, and particularly Colombia, a literature predominantly indicates that social vulnerability and migration are major leishmaniasis determinants (Desjeux, 2004). Social vulnerability can be engendered through processes of unplanned or poorly structured migrations, which promote high population density, low sanitation and precarious living conditions (Desjeux, 2001a). Although generally considered a rural disease, these populated areas may foster leishmaniasis vector domestication and adaptation, in turn leading to increased transmission in urban and peri-urban areas (Bern et al., 2008). Stagnant water pools, which are essential for vector breeding and development, may also form in these peri-urban areas due to the construction of makeshift water sources for migrant populations (Aagaard-Hansen et al., 2010). Such processes may have been particularly relevant in the cases of Bolivia and Peru, where settlement schemes have been associated with mass rural-to-urban migrations (Alcais et al., 1997; Davies et al., 2000). Within Brazil this migration trend has been particularly linked with the formation of favelas (shanty towns), which are built at the edges of cities and close to forested areas (Aagaard-Hansen et al., 2010). These areas are characterized by limited medical access, high population density, organized crime, environmental degradation, and inadequate sewage disposal, all of which may capture the complexity of human-vector interactions for both leishmaniasis subtypes (Aagaard-Hansen et al., 2010; Desjeux, 2001b). Notably, Brazil reported no occurrence of armed conflict within the study period, but High (level 4) terror levels for 13 of the included years. As noted earlier, these overarching social and political processes may be captured within—or conflated with—the conflict, and particularly the terror dataset. In the event that migration and social vulnerability are dominant processes within favelas, they could propagate leishmaniasis in similar ways to its spread within refugee camps.

Populations with low economic capacity and its associated social vulnerability are also typically plagued by limited access to disease prevention, treatment, and general care (Spiegel et al., 2007). This may be the case for VL incidence within India, Nepal, and Bangladesh—where intense transmission is highly focalized in extremely poor communities. The increasing costs of caring for VL patients (an estimated US $80–120 in South Asia) has been highlighted as an economic barrier (Ahwar et al., 2006). Additionally, there are reports of large in-and-out migrations within the region (Desjeux, 2004). All three of these countries fall within the low or lower-middle income groupings according to World Bank
### Table 5

<table>
<thead>
<tr>
<th>Country</th>
<th>Significant sub-Sub-Type</th>
<th>Incidence/ 100,000 Peaks dates</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afghanistan</td>
<td>CL</td>
<td>638.6</td>
<td>1995, 2002, 2007–2010 The high incidence has been linked to the consistent conflict, socio-political instability, and foreign military intervention occurring in the 1990s. While the whole country is endemic, the highest incidence rates have been associated with refugee camps in Kabul in the years 1995, 2002, and 2007. In particular, these outbreaks have been associated with poor housing conditions, displacement and migration of people, as well as poor healthcare infrastructure (Reithinger et al., 2003; Reithinger et al., 2010; Aagaard-Hansen et al., 2010; Aagaard-Hansen and Chaignat, 2010).</td>
</tr>
<tr>
<td>Algeria</td>
<td>CL</td>
<td>29.2</td>
<td>2003 &amp; 2004 Although the country has experienced significant civil conflict and political terror, we were unable to identify published literature on determinants of CL outbreaks. However, the country was home to a civil war, which began in 1990 between the government and various rebel groups, and subsided in the early 2000s. Following this conflict, the country has faced significant political instability, particularly between 2002 and 2007 (Martinez, 2000).</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>VL</td>
<td>12.8</td>
<td>2006 Bangladesh has experienced recurrent epidemics and a progressive increase in VL incidence since the mid-1990s (Bern et al., 2008). However, the literature identifies socio-economic vulnerability as the dominant factor for increased transmission processes (Alvar et al., 2006). There appears to be no references to associations between conflict or terror and VL.</td>
</tr>
<tr>
<td>Bolivia</td>
<td>CL</td>
<td>95.4</td>
<td>2006 &amp; 2007 There is limited published evidence about leishmaniasis in Bolivia. It has been noted that the country has experienced high rates of internal migration since the 1980s thereby introducing susceptible populations into endemic regions (Alcayd et al., 1997; Desjeux, 2004).</td>
</tr>
<tr>
<td>Brazil</td>
<td>CL/VL</td>
<td>53.1/2.8</td>
<td>1995 &amp; 2000 Demographic and environmental factors have largely been linked to the persistent CL and VL incidences. The number of cases has been generally increasing since the 1990s, which is associated with rural-urban migration and subsequent increased population density, favelas, and precarious living conditions (Aagaard-Hansen et al., 2010; Bern et al., 2008; Desjeux, 2001b).</td>
</tr>
<tr>
<td>Colombia</td>
<td>CL</td>
<td>83.8</td>
<td>2004–2006 Leishmaniasis incidence coincides with the country’s high political violence, guerilla warfare, and social unrest, all of which have escalated since the 1980s. The highest incidence rates are known to have occurred among military personnel and insurgents, especially during uprisings in 2002 and 2006 (Bern et al., 2008). Additionally, the conflict-terror has led to the internal displacement of approximately 3.6 million Colombian citizens between the years 1985 and 2005 (Beyrer et al., 2007).</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>CL</td>
<td>112.2</td>
<td>2006 &amp; 2009 There is very little published evidence on CL incidence in Costa Rica, and we were not able to find information in regards to its specific determinants.</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>VL</td>
<td>102.5</td>
<td>2000 &amp; 2005 Aside from a significant period of civil war (1970–1991) and national disputes (1998–2000), evidence suggests that migrant workers and refugee populations from the bordering Sudan-South Sudan conflict spilled into Ethiopia (Desjeux, 2004). This may have contributed to the sustained leishmaniasis epidemics and limited healthcare capacity within the region.</td>
</tr>
<tr>
<td>Honduras</td>
<td>CL</td>
<td>70.5</td>
<td>2004 It has been suggested that the country’s history of military regimes and corruption within the military has exacerbated crime and furthered social vulnerability within the population (Geneva Academy, 2015). However, the literature regarding CL in Honduras is lacking.</td>
</tr>
<tr>
<td>India</td>
<td>VL</td>
<td>13.0</td>
<td>2006 &amp; 2007 Leishmaniasis incidence in this region stretches across northeast India, through the border into Nepal and central Bangladesh (Bern et al., 2008). Socio-economic and cultural factors have been identified as primary determinants for the persistence of the disease (Alvar et al., 2006; Desjeux, 2001b). Hostility, civil unrest and border disputes could also be potential explanations (Kujur, 2009).</td>
</tr>
<tr>
<td>Iran</td>
<td>CL</td>
<td>112.3</td>
<td>2004 Iran has been identified as a conflict/post-conflict hot spot (Hotez and Thompson, 2009), given the intermittent conflict that has been present since the 1960s. Notable conflicts include the 1991 Gulf War and the 2004 civil conflict (Jacobson, 2011). A particularly high resurgence of CL incidence following 2003 has been attributed to an earthquake in the Bam region, which destabilized health infrastructure (Sharifi et al., 2013).</td>
</tr>
<tr>
<td>Iraq</td>
<td>CL/VL</td>
<td>78.7/25.4</td>
<td>1995, 1996 &amp; 2009 The high incidences of both CL and VL have been linked to the persistent conflict and terror induced by the government and from abroad. Civilian cases re-surfaced in the mid 1990s following the Gulf War, and military cases started rising in 2003 and peaked in 2009. Additionally, this conflict has directly impacted population movements, sanitary conditions, health infrastructure, and the access to leishmaniasis treatment (Jacobson, 2011; Salam et al., 2014; Desjeux, 2001b; Hotez and Thompson, 2009).</td>
</tr>
<tr>
<td>Nepal</td>
<td>VL</td>
<td>19.7</td>
<td>2000–2003 Despite containing a significant VL caseload, there is very little published and publically available literature on its determinants in Nepal. The country is subject to continuous population movement between India and Bangladesh, and it has reported intermittent political instability between 1996 and 2006 (Bern et al., 2008; Desjeux, 2004; Desjeux, 2001b).</td>
</tr>
<tr>
<td>Panama</td>
<td>CL</td>
<td>254.9</td>
<td>2006 There is very little literature on CL incidence in Panama, and we found no evidence for specific processes or causal mechanisms.</td>
</tr>
<tr>
<td>Peru</td>
<td>CL</td>
<td>109.9</td>
<td>1996 &amp; 2007 The literature has noted the steadily increasing CL rate in the country since the 1980s, but has mainly attributed this to settlement schemes and population migration from high Andean plateaus to low tropical plains (Desjeux, 2004; Davies et al., 2000).</td>
</tr>
<tr>
<td>Tunisia</td>
<td>CL</td>
<td>209.5</td>
<td>2005 The key factors associated with spatio-temporal dynamics of leishmaniasis in the country are not well established in the literature. Potential associations have been made with geo-physical and environmental properties conducive to sandfly and rodent proliferation (Sahal et al., 2007). Additionally, Tunisia’s surrounding countries are areas of high conflict-terror, which could induce disease spill-over.</td>
</tr>
<tr>
<td>Sudan</td>
<td>VL</td>
<td>85.0</td>
<td>1999–2003 Consistent leishmaniasis incidence has been linked to the long Sudan-South Sudan civil war (1983–2005). In addition to population displacement, the high rates of leishmaniasis mortality could be due to food insecurity, population malnourishment, and limited medical access associated with the war (WHO, 2014a; Zijlstra et al., 1994; Aagaard-Hansen and Chaignat, 2010; Reithinger et al., 2007).</td>
</tr>
<tr>
<td>South Sudan</td>
<td>VL</td>
<td>200.4</td>
<td>2002–2005 Given that South Sudan’s official independence from Sudan only occurred in 2011, many of the same causal mechanisms are attributed to its high leishmaniasis incidence within our study period (Seaman et al., 1996). VL peaks have been particularly associated with the mass population displacements that occurred between 2002 and 2005, preceding the separation and autonomy of South Sudan (Kolaczinski et al., 2008).</td>
</tr>
<tr>
<td>Syria</td>
<td>CL</td>
<td>466.5</td>
<td>2009 &amp; 2010 Leishmaniasis is endemic in the region and its increased incidence rate since 1985 has been associated with political instability, rural-urban migration, high population density, poor housing and population displacements to refugee camps (Bern et al., 2008; Desjeux, 2004; Hayani et al., 2015). Syria has been indicated as a conflict/post-conflict hot spot in association with NTDs (Hotez and Thompson, 2009). Additionally, in recent years that are out of the scope of this paper, the high incidence rates of CL have been directly associated with conflict and its related health system breakdowns (Salam et al., 2014).</td>
</tr>
</tbody>
</table>

*We selected countries exceeding the global average incidences for CL and VL between 1995 and 2010, as well as all of the previously identified ten CL and six VL hotspots not already included [see also Supporting Information].
estimates, therefore suggesting that poverty and leishmaniasis may interact in a feedback loop that exacerbates disease burden (World Bank, 2014; Alvar et al., 2006). However, our aggregate model suggests that conflict-terror associations remain even when controlling for wealth. Within our dataset, both India and Nepal were categorized in high and very high conflict-terror levels. Although this may be a component of the elevated incidence rates—with Nepal indicating intermittent periods of civil conflict between 1996 and 2006 and India indicating resurgent border disputes in the Northwest with Pakistan, as well as unrest in the Northeast by Naxilites in Bihar (Uppsala Conflict Database Program, 2013; Gibney et al., 2013; Kujur, 2009)—this highlights the bias of our data's definitions of conflict and terror. In particular, the dataset may overgeneralize exposure due to aggregation at the national level and the pooling of spatial and temporal data. Given that only one conflict-terror level data point was assigned to each country-year, it is implied that regions within the country have homogeneous exposure and outcomes to conflict-terror processes. As such, where there is limited anecdotal association between leishmaniasis determinants and conflict, our analysis points to conflict-terror and leishmaniasis data to better target areas of intervention (Aagaard-Hansen et al., 2009). Health impact evaluations in leishmaniasis endemic areas, should also consider conflict and terror, particularly in the context of internal migration and displacement.

5. Conclusions

Our findings indicate that populations in countries with major conflict and high political terror are at significantly elevated risk for both cutaneous and visceral leishmaniasis, as compared to those in areas with no conflict and low terror. Through a historical analysis, we suggest that terror may be a more sensitive descriptor for the larger socio-economic and political processes that are associated with increased leishmaniasis incidence. However, further research is needed to better understand these associations while taking into account the important roles that environmental and other social determinants have on leishmaniasis incidence (Aagaard-Hansen et al., 2009). Modelling exercises, with specific parameters for temperature, rainfall and vegetation coverage in addition to our distal social factors may provide such insight. Sub-national analyses, which disaggregate conflict-terror and leishmaniasis data to more accurately reflect their uneven spatial distribution, are also necessary research avenues for understanding their epidemiology. Current interventions for leishmaniasis control and prevention presume stable social and political contexts for the delivery of services. However, these results highlight the need for explicit considerations and adaptations to these strategies within the context of instability. As such, it is recommended that leishmaniasis risk assessments consider integrating socio-political indices, such as conflict-terror and migration, into their statistical and spatial analyses to better target areas of intervention (Aagaard-Hansen et al., 2009).

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Appendix A. Supporting information

Supporting information related to this article can be found at http://dx.doi.org/10.1016/j.soscimed.2016.04.038.

References


