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When discovery meets neglect: rethinking disease emergence in cutaneous leishmaniasis and other neglected tropical diseases

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Recent reports of *Leishmania donovani* causing cutaneous leishmaniasis (CL) in Nepal have revived a key question in disease ecology: when does a disease truly emerge, and when is it simply newly recognized? Apparent emergence likely reflects underdiagnosis rather than parasite evolution. These cases have likely gone unnoticed because surveillance programs and clinical awareness have historically centered on VL in this *L. donovani*–endemic region. As leishmaniasis expands into previously non-endemic areas, physicians encountering unfamiliar lesions are prompted to investigate and identify the etiological agent, revealing not a new parasite variant, but the geographic and diagnostic expansion of a known one previously unrecognized by the healthcare system. Epidemiological "emergence," in this context, stems less from parasite evolution than from the intersection of changing disease ecology, improved diagnostics, and shifting clinical attention. We hypothesize that cutaneous leishmaniasis due to *L. donovani* in Nepal represents a detection-driven phenomenon rather than a novel biological event.

KEYWORDS

cutaneous leishmaniasis, emergence, epidemiology, *Leishmania donovani*, Nepal, surveillance, tissue tropism, visceral leishmaniasis

Introduction: when "new" does not always mean emerging

Nepal provides a unique context for examining the difference between biological emergence and detection-driven recognition. Recent genomic studies in Nepal have reignited a debate in parasitic-disease epidemiology: when is an outbreak truly emergent, and when does it simply reveal what was already present but previously overlooked? Reports of *Leishmania donovani* isolated from CL patients (1, 2) challenge traditional assumptions about parasite tropism. In Nepal, where national control programs and diagnostic protocols have long prioritized VL, cutaneous manifestations are likely to have been missed, self-treated, or classified under other dermatoses. As transmission extends into previously unaffected areas, clinicians encountering unusual skin lesions are prompted to identify the causative agent. This shift in clinical vigilance, combined with broader molecular tools, creates the appearance of novelty. Thus, what seems to be the emergence of a new disease may in fact represent the recognition of an existing parasite in new geographic or ecological contexts. This corresponds primarily to detection-driven emergence, occasionally combined with epidemiological emergence when transmission truly expands into new foci.

Cutaneous lesions caused by visceral *Leishmania* species: diagnostic ambiguity and epidemiological visibility

Cutaneous lesions caused by traditionally visceral *Leishmania* species such as *L. donovani* and *L. infantum* pose a diagnostic paradox; clinically, these infections often present as chronic, non-ulcerative, or nodular lesions with low parasite density, features that can easily be confused with other dermatological conditions, including lupus vulgaris, sarcoidosis, or fungal infections (3, 4). Histopathological findings are typically nonspecific, showing granulomatous inflammation with scant amastigotes, which complicates diagnosis in the absence of molecular confirmation (5). In endemic regions where surveillance and diagnostic protocols are primarily focused on VL, these atypical cutaneous forms are often misdiagnosed, self-treated, or never sampled for parasitological testing (6).

When such atypical lesions arise in regions historically regarded as leishmaniasis-free, they tend to prompt closer clinical scrutiny and subsequent etiological assessment. In these situations, apparent "novelty" reflects increased diagnostic vigilance and the use of more sensitive molecular assays rather than the emergence of new genotypes. Similar cutaneous presentations of *L. infantum* have long been reported in southern Europe and North Africa, typically in VL-endemic regions, underscoring that both clinical forms can coexist within the same transmission cycle (3, 7).

Molecular blind spots: the limitations of ITS1

Most studies in Nepal rely on ITS1 sequencing for species identification. Although useful for species-level classification, ITS1 lacks the resolution to detect genomic differences associated with tissue tropism, virulence or ecological adaptation. ITS2, 28S-D2/D3, and kDNA suffer similar limitations, evolving too slowly or inconsistently to capture intra-specific diversity (7–9).

In Nepal, where *L. donovani* predominates, this limitation has important consequences. Routine diagnostics and the national surveillance system long targeted VL exclusively, leaving cutaneous infections undetected. However, when CL cases began appearing in new ecological zones, it was perceived as a novelty, prompting clinicians to use molecular tests that revealed *L. donovani*, creating an impression of emergence rather than rediscovery.

Examples from other regions highlight this issue. In Sri Lanka, for example, CL cases caused by *L. donovani* were long considered unusual until whole-genome sequencing (WGS) revealed distinct genomic clusters and reduced A2 gene copy number, a signature of attenuated visceral virulence (10, 11). Comparable studies from East Africa and the Mediterranean have shown that multilocus sequence typing (MLST) and WGS uncover population structures invisible to ribosomal or kDNA markers (12, 13). These examples underscore how limited molecular tools and low diagnostic visibility can obscure the true diversity of *Leishmania* and the clinical spectrum of *Leishmania* infections, that can coexist in endemic areas.

Importantly, parasite genomics is only one determinant of tissue tropism. Host factors also shape whether infection manifests as a cutaneous or visceral disease. Strong localized Th1 responses tend to restrict parasites to the skin, whereas systemic immunosuppression or dysregulated cytokine signaling can favor visceral dissemination (3, 13). These immunological influences further underscore the complexity of interpreting tissue tropism from limited molecular markers.

Ecological transitions and diagnostic asymmetries

The ecological context further complicates interpretation. Both Nepalese studies identified *Phlebotomus argentipes*, the proven vector of *L. donovani*, as the likely transmitter of CL. This overlap strongly supports a shared transmission cycle between CL and VL. However, reports of CL from higher altitudes (14) raise questions about shifting sandfly distributions, potentially driven by environmental or anthropogenic change. While the entire area lies within the geographic range of sand flies, higher elevations (above 600 m) were considered unsuitable for *P. argentipes* due to cooler temperatures. Yet, in recent years, sand flies have been reported at much higher altitudes in India and Nepal, up to 4,460 m. Concurrent detection of VL and occasional CL caused by *L. donovani* suggests an upward expansion of both vector and parasite (15–17). Modeling studies suggest that climate change, land-use modification, and urbanization all contribute to sand fly range expansion across continents and likely influence Asian foci as well (18). Such global environmental shifts may amplify the ecological reach of *Leishmania* vectors, contributing indirectly to the apparent emergence of CL in new areas.

At the same time, diagnostic systems remain strongly biased toward VL. While VL is a notifiable and often lethal disease that attracts surveillance resources, CL cases are frequently unreported, self-treated, or misdiagnosed as other dermatoses. In many endemic regions, the incidence of CL is likely underestimated because reporting is not mandatory and surveillance systems are fragmented (3). According to the European Centre for Disease

Prevention and Control (ECDC), notification of human leishmaniasis is mandatory in all endemic countries except France, Egypt, and Serbia; however, this typically refers to visceral forms and not always to CL, contributing to under recognition across regions (19). Unfortunately, detailed operational data on CL diagnostic effort, such as the annual number of skin smears, biopsies, or PCR tests performed, are not publicly available in Nepal. Neither the national kala-azar elimination program nor WHO country reports currently disaggregate CL from VL diagnostic activities (19, 20). Our interpretation therefore relies on qualitative proxy indicators of diagnostic attention rather than formal time-series data. These include the progressive accumulation of case reports, small clinical series, targeted molecular investigations, and policy changes documented over the past two decades. See Box 1 for a chronological overview of CL recognition and diagnostic milestones in Nepal.

Taken together, these ecological and diagnostic patterns highlight the need to distinguish between two forms of emergence. The detection of new CL foci due to *L. donovani* likely reflects geographical or epidemiological expansion likely driven by environmental change, population mobility, or improved clinical recognition, rather than the evolution of novel dermotropic lineages. Current evidence from Nepal thus supports a detection-driven and ecological emergence scenario rather than true biological innovation within the parasite population.

The illusion of emergence: lessons from other regions

Global experience supports a more conservative interpretation. *Leishmania infantum*, the canonical visceral species in Europe and North Africa, has long been recognized to cause CL, yet it was not argued that it represents an "emerging" parasite species (1, 27). Similarly, in Sudan, CL caused by *L. donovani* are reported in sympatry with VL caused by *L. donovani* (28–30). Comparable patterns occur elsewhere: *L. infantum* has produced CL in Latin America, from Brazil to Costa Rica, often in immunocompetent hosts (31, 32), and both *L. infantum* and *L. donovani* cause co-endemic CL and VL in East Africa (33). In Sri Lanka, dermotropic *L. donovani* strains show reduced A2 gene copy number but remain phylogenetically close to *L. donovani* strains responsible for visceral disease (11).

The Nepalese scenario may therefore fit a broader pattern of underrecognition rather than *de novo* emergence. What changes is not necessarily the parasite's genome, but rather our incomplete and fragmented understanding of *Leishmania* diversity and its clinical manifestations, both globally and regionally. The apparent novelty of CL cases often reflects improved diagnostic sensitivity and broader epidemiological reach rather than genuine biological innovation, but it may also point to evolving disease dynamics and the identification of dermotropic variants accompanying the spread of leishmaniasis into newly endemic zones. These variants might represent early signals of shifting epidemiology, particularly in Nepal, where ecological and climatic transitions could be reshaping parasite–vector–host interactions. Similar dynamics have been reported beyond South Asia.

In Kabylie, northern Algeria, a region historically dominated by *L. infantum*, cutaneous lesions had long been attributed exclusively to this species. The recent molecular detection of autochthonous *L. major* was therefore unexpected. Yet this finding almost certainly reflects long-standing underdiagnosis rather than the introduction of a new parasite. Because clinicians assumed that all CL in the region was due to *L. infantum*, *L. major* infections went unrecognized for decades. In this context, the apparent "emergence" of *L. major* represents the unveiling of previously overlooked transmission, amplified by ecological shifts and the recent adoption of species-level diagnostics (34).

BOX 1 Timeline of cutaneous leishmaniasis (CL) recognition and diagnostic effort in Nepal (1998–2025).

Year/Period	Key Milestones and Diagnostic Context
Before 2000	Nepal considered endemic only for VL due to *L. donovani*; no CL diagnostics; VL-focused surveillance.
1998–2006	First CL-like lesions noted; first confirmed CL case in a Nepalese patient (21).
2006–2015	Occasional case reports (including *L. major* infection); but no routine CL diagnostics and CL absent from national reporting (22). Diagnostics remain VL-centered.
2016–2019	Cluster of 42 autocthonous CL cases described as "emergence" (23, 24), mostly in central and western Nepal. dermatology units and research groups begin systematic sampling.
2019 — Policy inflection	*National Guideline on Kala-azar Elimination* revised to include CL and PKDL surveillance and diagnostic recommendations (25).
2020–2022	Increasing use of molecular tools (PCR, ITS1 sequencing) in clinical studies; CL still absent from national notifiable-disease statistics.
2023 — Diagnostic expansion	Molecular confirmation of *L. donovani* and *L. major* in CL lesions (2); CL cited as a "public concern" in western Nepal; detection at higher altitudes (26).
2025-Current interpretation	Rise in CL detection aligns diagnostic expansion and policy inclusion, suggesting detection-driven emergence.

Toward robust interpretation: integrating data streams and defining emergence

Distinguishing between "underdiagnosed" and "truly emerging" infections requires integration of genomic, ecological, and epidemiological data. Whole-genome sequencing (WGS) and comparative genomics should become routine to detect gene-copy variation, aneuploidy, and virulence-associated loci that influence tissue tropism. Entomological and ecological mapping have documented *Phlebotomus argentipes* distribution across altitudes done by Roy et al. (35), would have to be complemented by molecular xenomonitoring to detect mixed or cryptic infections. Coordinating these datasets under a One Health framework will clarify whether cutaneous infections contribute to visceral transmission cycles and whether new ecological foci represent real transmission expansion or simply improved detection (26). Only when genetic, ecological, and epidemiological signals coincide can emergence be considered biological; otherwise, what appears "new" is more plausibly diagnostic rediscovery.

Accurate differentiation between CL and VL also depends on diagnostic specificity. Microscopy and serology, though suitable for VL, often fail for CL, particularly for dermotropic *L. donovani* or *L. infantum* producing pauciparasitic lesions. Incorporating PCR-based assays, loop-mediated amplification, and point-of-care molecular tests in endemic and newly affected areas would markedly improve case detection and avoid misclassification (3, 5). Artificial-intelligence (AI)–assisted diagnostic platforms, already validated for general dermatology and amastigote recognition (36–42), could assist clinicians with limited CL experience by recognizing lesions earlier, standardizing documentation, and strengthening epidemiological visibility. Together, these tools transform diagnostic progress into an explicit analytical dimension of emergence rather than an artefact.

Strengthening diagnostic networks and synthesizing dispersed case reports through systematic reviews and field-based diagnostic surveillance will further clarify how different emergence mechanisms operate in neglected-disease settings such as Nepal. This integrated evidence base supports not only better interpretation but also targeted public-health response.

Redefining "emergence" in parasitology to address the realities of neglected tropical diseases

Interpreting apparent novelty in parasitic diseases requires conceptual precision. In case detection can arise from multiple mechanisms: biological, ecological, diagnostic, or merely observational. Yet the term « emergence » is routinely applied without distinguishing among these fundamentally different processes, leading to confusion in scientific interpretation and misdirection in public-health response.

To clarify these distinctions, we propose a four-part framework that separates true evolutionary innovation from ecological expansion, and both from purely diagnostic phenomena. This framework recognizes that circulation, detection, and recognition do not occur on the same timescale, and that neglected diseases are especially vulnerable to interpretive errors because surveillance, molecular tools, and clinical awareness are structurally uneven.

Box 2 summarizes these four forms of emergence, each defined by its dominant driver and expected empirical signature. Applying this framework to the Nepal situation suggests that CL due to *L. donovani* is best explained by a combination of detection-driven emergence and epidemiological expansion, not by biological innovation.

Across parasitology, many apparent "emergences" reflect improved visibility rather than biological innovation. The detection of *S. haematobium*–*S. bovis* hybrids (43, 44), *Strongyloides stercoralis* rediscovery (45), or the molecular reclassification of *Cryptosporidium* and *Entamoeba* species (46–48) exemplify how advances in detection reshape our

BOX 2 Four distinct forms of "emergence" in parasitic diseases.

Type of Emergence	Definition (sharpened)	What It Looks Like in Practice	Illustrative Examples
Biological emergence	Appearance of a new or genetically altered lineage with changes in virulence, host range, vector preference, or tissue tropism.	New hybrid, mutant, recombinant, or host/vector-shifted parasite with altered biological properties.	*Schistosoma haematobium* × *S. bovis* hybrids.
Epidemiological emergence	A measurable increase in incidence, geographic range, or transmission intensity of an existing parasite due to ecological, climatic, demographic, or behavioral shifts.	Expansion into new ecological zones; increasing incidence without genetic innovation.	Sand fly range expansion with climate change; northward spread of CL leishmaniasis in North Africa.
Detection-driven emergence	An apparent rise in cases resulting from improved diagnostics, surveillance, new technologies, or increased clinical awareness. Infections existed previously but were undetected.	New molecular tools, clinician awareness, or surveillance uncover cases that were always present.	CL due to *L. donovani* in Nepal; recognition of *Leishmania* (*Mundinia*) species via molecular diagnostics.
Illusion of emergence	Temporal delay between true parasite circulation and its recognition by the health system, often due to diagnostic blind spots or misclassification.	Long-standing infections discovered only after retrospective correction of diagnostic gaps.	*Strongyloides stercoralis* rediscovery; misclassified *Cryptosporidium*/*Entamoeba* species.

understanding of endemic infections. A particularly illustrative case of hybrid emergence is found in the *Leishmania (Mundinia)* subgenus. These species (*L. martiniquensis*, *L. orientalis*, *L. enriettii)*, among others represent a true biological emergence within the genus, forming a distinct phylogenetic lineage revealed by genomic and phylogenetic analyses (49, 50). Yet, their recognition as human pathogens was largely detection-driven, enabled by the advent of molecular diagnostics that disentangled them from morphologically indistinguishable *Leishmania* species. Thus, *Mundinia* illustrates how evolutionary novelty and diagnostic progress can converge to create a hybrid emergence, where taxonomic discovery and epidemiological visibility unfold simultaneously. These reinterpretations highlight that emergence is as much epistemological as biological. Without sustained surveillance, genomic baselines, and ecological mapping, the concept itself remains ambiguous. A paradigm shift is therefore needed, from fascination with novelty to commitment to completeness. Understanding CL in Nepal is less about discovering new strains than about recognizing what has always been there. Distinguishing among these categories is not a semantic exercise: each one implies different surveillance priorities, diagnostic investments, and research.

Why defining types of emergence matters

Clear conceptual boundaries between biological, epidemiological, and detection-driven emergence are essential for sound interpretation and policy.

Conceptual clarity

In parasitology, increases in disease detection are often mistaken for new pathogen evolution. Yet most "emerging" infections represent diagnostic rediscovery rather than genuine biological novelty. As Morse (51) and Smolinski et al. (52) emphasized, emergence may result from evolutionary, ecological, or observational change, processes that must be disentangled to avoid false alarms. In *L. donovani* cutaneous leishmaniasis (CL) in Nepal, apparent emergence reflects under-recognition within a visceral-leishmaniasis surveillance system. Comparable reinterpretations followed the introduction of molecular tools for *Strongyloides stercoralis* and *Cryptosporidium hominis* as discussed above. Recognizing these mechanisms prevents misdirected "novel-strain" investigations when the real issue is diagnostic visibility.

Guiding public-health response

Each emergence type demands distinct control strategies (53, 54), see Table 1.

Misclassifying detection-driven events as biological can divert resources to unnecessary genomic surveys. Global analyses confirm that most "emerging infections" are zoonoses whose apparent novelty stems from surveillance intensity or ecological encroachment rather than new pathogens (55).

Scientific credibility and communication

The term *emerging* has become inflated in parasitology. Gramiccia & Gradoni (56) showed that so-called "emerging" leishmaniases often reflect uneven surveillance or vector redistribution, while Diwon et al. (57) warned that molecular tools can convert long-standing infections into "newly detected" diseases. Restricting the term emergence to contexts with verified biological or ecological change maintains conceptual precision and scientific credibility.

Conclusion

Cutaneous leishmaniasis caused by *L. donovani* in Nepal challenges traditional notions of tissue tropism and disease emergence. Current evidence supports detection driven recognition rather than the evolution of new dermotropic variants. Confirming this requires integrated WGS-based surveillance, ecological mapping, clinical data harmonization, and sustained field diagnostics. Emerging AI-based image and microscopy analysis tools may further support early recognition of *Leishmania* CL lesions in both endemic and newly affected areas, reducing misdiagnosis and strengthening surveillance for these atypical presentations. Clarifying whether CL contributes to VL persistence is essential for achieving elimination targets. More broadly, distinguishing between biological, epidemiological, and detection driven emergence will prevent misallocation of resources and improve interpretation of parasitic disease dynamics, especially in neglected tropical disease settings.

TABLE 1 Types of emergence and priority response.

Type of emergence	Typical drivers	Priority response
Biological	Mutation, hybridization, host/vector shift	Genomic surveillance, virulence monitoring
Epidemiological	Environmental or demographic change	Vector and reservoir mapping, One-Health surveillance
Detection-driven	Diagnostic innovation, increased awareness, improved reporting	Training, diagnostic rollout, harmonized reporting

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: All data are available in the literature. Requests to access these datasets should be directed to denis.sereno@ird.fr.

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