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Tegumentary leishmaniasis and coinfections other than HIV

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20 **Abstract**

21 **Background.** Tegumentary leishmaniasis (TL) is a disease of skin and/or mucosal tissues caused by
22 *Leishmania* parasites. TL patients may concurrently carry other pathogens, which may influence the
23 clinical outcome of TL.

24 **Methodology/Principal findings.** This review focuses on the frequency of TL coinfections in human
25 populations, interactions between *Leishmania* and other pathogens in animal models and human
26 subjects, and implications of TL coinfections for clinical practice. For the purpose of this review, TL
27 is defined as all forms of cutaneous (localised, disseminated or diffuse) and mucocutaneous
28 leishmaniasis. HIV coinfection, superinfection with skin bacteria, and skin manifestations of visceral
29 leishmaniasis are not included. We searched MEDLINE and other databases and included 68
30 records: 21 experimental studies in animals, and 47 studies about human subjects (mainly cross-
31 sectional and case studies). Several reports describe the frequency of *Trypanosoma cruzi*
32 coinfection in TL patients in Argentina (about 41%), and the frequency of helminthiasis in TL
33 patients in Brazil (14% to 88%). Different hypotheses have been explored about mechanisms of
34 interaction between different microorganisms, but no clear answers emerge. Such interactions may
35 involve innate immunity coupled with regulatory networks that affect quality and quantity of
36 acquired immune responses. Diagnostic problems may occur when concurrent infections cause
37 similar lesions (e.g. TL and leprosy), when different pathogens are present in the same lesions (e.g.
38 *Leishmania* and *Sporothrix schenckii*), or when similarities between phylogenetically close
39 pathogens affect accuracy of diagnostic tests (e.g. serology for leishmaniasis and Chagas disease).
40 Some coinfections (e.g. helminthiasis) appear to reduce the effectiveness of antileishmanial
41 treatment, and drug combinations may cause cumulative adverse effects.

42 **Conclusions/Significance.** In patients with TL, coinfection is frequent, it can lead to diagnostic
43 errors and delays, and it can influence the effectiveness and safety of treatment. More research is
44 needed to unravel how coinfections interfere with the pathogenesis of TL.

45

46 **Author summary**

47 Infectious diseases are often studied one by one, but people can have more than one
48 infection at the same time. This is likely to happen when different microorganisms are linked to
49 specific geographical regions or living conditions. In this paper, we summarise the literature about
50 infections occurring together with tegumentary leishmaniasis, a disease of skin and mucosal tissues
51 that is caused by *Leishmania* parasites. We found that in Latin America, patients with tegumentary
52 leishmaniasis are often also infected with helminths or with *Trypanosoma cruzi* (the parasite that
53 causes Chagas disease). Information from other parts of the world is scarce. Animal studies and
54 observations in humans show that one infection can change the course of another infection, but
55 how this happens is not well understood. When different infections affect the same patient at the
56 same time, the diagnosis can be difficult, especially when different microorganisms are biologically
57 similar, when they cause similar lesions, or when they are present in the same lesions. Treatment
58 can also be difficult because some coinfections reduce the efficacy of the treatment against
59 *Leishmania*, and because some drug combinations can lead to cumulative adverse effects.

60

61 Introduction

62 Tegumentary leishmaniasis (TL) is a disease of the skin and mucosal tissues caused by
63 several species of the genus *Leishmania* (Protozoa, Trypanosomatida, Trypanosomatidae) that are
64 transmitted by the bite of phlebotomine sandflies [1]. Parasites belonging to the sub-genus
65 *Leishmania* are found in the Old and the New World, whereas those of the sub-genus *Viannia* are
66 restricted to the New World [1-3]. *Leishmania* parasites produce a wide spectrum of clinical
67 manifestations in humans and other mammals, ranging from asymptomatic infection to life-
68 threatening disease [1-3]. Yearly, an estimated one million people develop TL, mainly in Bolivia,
69 Brazil, Colombia, Peru, Algeria, Tunisia, Saudi Arabia, Syria, Iran, Afghanistan, and Pakistan [4].

70 The overlapping geographical distribution of TL with many highly prevalent (e.g.
71 helminthiasis) [5] and some less common (e.g. leprosy) [6] infectious diseases, as well as
72 experimental studies [7], together indicate the importance of understanding how coinfections may
73 alter the outcome of TL and *vice versa*. Indeed, several infectious diseases linked to poverty,
74 housing conditions, hygiene, or to vectors that thrive in similar circumstances tend to affect the
75 same populations [8-12]. It is, therefore, likely that in the tropical and temperate regions where TL
76 occurs, many people carry more than one pathogen at once, although the epidemiology of such
77 coinfections is not well known. Furthermore, the clinical outcome of *Leishmania* infection depends
78 on characteristics of both the *Leishmania* parasite and the human host immune response [13-16].
79 Pathogens other than *Leishmania* may modulate this host immune response and consequently,
80 influence the natural history of TL as well as the response to anti-leishmanial treatment [12,16].

81 The most frequently studied coinfection is that between *Leishmania* and human
82 immunodeficiency virus (HIV), where the natural history of each of the two infections is modified by
83 the presence of the other [17]. HIV increases the risk of severe and disseminated TL, and some HIV-

84 infected patients develop visceral leishmaniasis in the presence of *Leishmania* species that are
85 usually only dermatotropic [17-19]. HIV also increases the risk of TL recurrence and treatment failure
86 [18,19]. On the other hand, leishmaniasis interferes with monocyte and macrophage function in
87 such a way that it facilitates HIV progression [20]. Interactions between TL and infections other
88 than HIV have not been comprehensively reviewed before.

89 The objectives of the present review are to summarise the evidence about the (i) frequency
90 of TL and coinfections other than HIV in human populations, (ii) interactions between *Leishmania*
91 and other pathogens in animal models and human subjects, and (iii) implications of TL coinfections
92 for clinical practice.

93

94 **Methods**

95 **Eligibility criteria**

96 We searched the medical literature to identify publications about TL and coinfections. For
97 the purpose of this review, we defined TL as all forms of cutaneous (localised, disseminated or
98 diffuse) and mucocutaneous leishmaniasis. Records about the skin manifestations caused by *L.*
99 *donovani* and *L. infantum/L. chagasi* (such as post-kala-azar dermal leishmaniasis) were not
100 included because the main clinical outcome of these infections is visceral leishmaniasis, which is
101 outside the scope of this review.

102 Records about HIV/AIDS and TL were not included because this topic has already been
103 extensively reviewed elsewhere [17-19]. Records about the contamination or superinfection of TL
104 lesions with Gram-positive or Gram-negative bacteria of the skin such as *Staphylococcus aureus* or

105 *Streptococcus pyogenes* were also excluded. Review papers were not included. We did not restrict
106 the search by geographical region, study design, language of publication or publication date.

107

108 **Information sources and search**

109 The databases MEDLINE, Embase, LILACS, Scielo, Cochrane, African Index Medicus, as well
110 as local library databases, searched in August 2017, were the information sources for this review.
111 We used search terms indicating (groups of) infections, pathogens, and diseases caused by these
112 pathogens. The detailed search strategy for MEDLINE is given in S1 File. We also reviewed the
113 reference lists of selected articles.

114

115 **Data collection and synthesis**

116 Two reviewers extracted the data from the included records; any doubts and discordances
117 were resolved through discussion. Specific points of interest while reading and summarising the
118 articles were: (i) frequency of coinfection in humans; (ii) mechanisms of interaction and effect of
119 coinfection on TL progression; and (iii) potential implications for clinical management. We
120 described the information the same way the authors of the original publications did, using mainly
121 counts, proportions and medians.

122 We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
123 statement [21] to prepare this review, but it was not possible to follow all the recommendations
124 because PRISMA mainly focuses on the evaluation of health care interventions and our focus was
125 broader than that. The PRISMA checklist is given in S2 List.

126

127 **Results**

128 **Study selection and characteristics**

129 The MEDLINE search retrieved 669 records and searching other databases yielded 348
130 additional records. After reading titles or abstracts or both, we removed 79 duplicates and
131 discarded 841 records because they were not relevant (Fig 1). The most frequent reason for
132 dropping records was that while leishmaniasis and another infection were mentioned in the same
133 text, the publication was not about coinfection (e.g. a paper about different infections occurring in
134 the same region but not affecting the same persons). We assessed the remaining 97 full-text
135 records for eligibility and retained 73 for the present review (Fig 1).

136 **Fig 1. Flow diagram of record search and selection.**

137 The 73 articles included in this review had different study designs (Table 1). There were 21
138 original research papers about experimental studies of coinfection in animal models, and 52 original
139 research papers about coinfection in human patients. The 52 studies about human subjects
140 included 1 clinical trial, 2 cohort studies, 13 cross-sectional or prevalence studies, 7 studies on the
141 development or performance of diagnostic tests, 24 case series or case reports with a clinical focus,
142 and 5 case series or reports with an immunological focus. The coinfecting pathogens for which we
143 found the highest number of records were *Trypanosoma cruzi* (n=18), *Mycobacterium leprae*
144 (n=14), helminths (n=12), and *Mycobacterium tuberculosis* (n=9). Two records addressed
145 coinfection of *Leishmania* with more than one pathogen (Table 1).

146 **Table 1. Overview of all studies about tegumentary leishmaniasis and coinfections included in this review**

Coinfecting pathogen	Study design	Number of studies	Number of human cases with coinfection	References to included studies
Helminths				
<i>Ancylostoma duodenale</i> , <i>Ascaris lumbricoides</i> , <i>Schistosoma mansoni</i> , <i>Strongyloides stercoralis</i> , and/or <i>Trichuris trichiura</i>	Randomised clinical trial	1	90	[22]
<i>Ancylostoma duodenale</i> , <i>Ascaris lumbricoides</i> , <i>Schistosoma mansoni</i> , <i>Strongyloides stercoralis</i> , and/or <i>Trichuris trichiura</i>	Cohort study	2	122	[5,12]
<i>Litomosoides sigmodontis</i> , <i>Nippostrongylus braziliensis</i> , <i>Schistosoma mansoni</i> , <i>Strongyloides ratti</i> or <i>Taenia crassiceps</i>	Experimental study in animals	8	Not applicable	[7,23-29]
Protozoa				

<i>Trypanosoma cruzi</i>	Cross-sectional study in general population	1	11	[30]
<i>Trypanosoma cruzi</i>	Cross-sectional study in TL patients ^a	7	211 ^a	[31-37]
<i>Trypanosoma cruzi</i>	Study about diagnostic tests ^a	6	74 ^a	[38-43]
<i>Trypanosoma cruzi</i>	Immunological study in humans	1	16	[44]
<i>Trypanosoma cruzi</i>	Case report/series	1	1	[45]
<i>Trypanosoma cruzi</i>	Experimental study in animals	2	Not applicable	[46,47]
<i>Trypanosoma brucei</i>	Experimental study in animals	2	Not applicable	[48,49]
<i>Toxoplasma gondii</i>	Cross-sectional study in TL patients	1	2	[37]
<i>Toxoplasma gondii</i>	Immunological study in humans	1	16	[50]
<i>Toxoplasma gondii</i>	Experimental study in animals	2	Not applicable	[51,52]
<i>Plasmodium sp.</i>	Experimental study in animals	7	Not applicable	[53-59]
Fungi				

<i>Sporothrix schenckii</i>	Case report/series	2	4	[60,61]
<i>Sporothrix schenckii</i>	Study about diagnostic tests	1	0	[62]
<i>Paracoccidioides braziliensis</i>	Cross-sectional study in TL patients	1	2	[37]
<i>Paracoccidioides braziliensis</i>	Cross-sectional study in patients with paracoccidioidomycosis	1	10	[63]
<i>Coccidioides posadasii</i>	Cross-sectional study in TL patients	1	1	[37]
<i>Cryptococcus laurentii</i>	Case report/series	1	1	[64]
Mycobacteria				
<i>Mycobacterium tuberculosis</i>	Cross-sectional study in TL patients	1	3	[37]
<i>Mycobacterium tuberculosis</i>	Case report/series	8	9	[65-72]
<i>Mycobacterium leprae</i>	Case report/series	12	25	[6,70,73-82]
<i>Mycobacterium leprae</i>	Case report/series of leprosy patients immunised with live <i>Leishmania tropica</i>	2	0	[83,84]

<i>Mycobacterium ulcerans</i>	Case report/series	1	1	[85]
Other bacteria				
<i>Treponema pallidum</i>	Cross-sectional study in TL patients	1	4	[37]
<i>Burkholderia pseudomallei</i>	Case report/series	1	1	[86]
Viruses				
HTLV-1	Cross-sectional study in TL patients	3	2	[87-89]
HTLV-1	Cross-sectional study in HTLV-1-infected subjects	1	8	[90]

147 TL: tegumentary leishmaniasis; HTLV-1; human T-lymphotropic virus 1

148 ^aSome overlap is possible because several papers come from the same research group.

149 **Frequency of TL coinfections in human populations**

150 The studies providing information about the frequency of coinfection in human populations
151 are summarised below and in Table 1.

152

153 ***Leishmania* and helminths.** Two Brazilian cohort studies describe the frequency of helminth
154 infections in patients with TL [5,12]. The first study recruited 120 patients with TL in a village health
155 post in a rural area of Bahia state [5]. Only patients with cutaneous forms of leishmaniasis were
156 included (maximum four lesions on maximum two body regions). The *Leishmania* species was not
157 determined, but the predominant species in this region is known to be *L. braziliensis*. Study
158 participants provided three stool samples for parasitological assays (sedimentation, Baermann, and
159 Kato-Katz methods). One hundred six (88%) of the 120 patients with TL were diagnosed with a
160 helminth infection. Seventy-three percent of the study participants were infected with more than
161 one helminth species at the same time. The most common helminths in this study were
162 *Ancylostoma duodenale*, *Trichuris trichiura*, *Ascaris lumbricoides*, *Schistosoma mansoni*, and
163 *Strongyloides stercoralis*.

164 The second study was done in an urban area in the state of Rio de Janeiro [12]. This was a
165 retrospective cohort study of 109 TL patients who received antimony therapy in a referral centre
166 between 2004 and 2006: there were 99 cases of cutaneous and 10 of mucocutaneous
167 leishmaniasis. All included patients had a parasitologically confirmed diagnosis of leishmaniasis. The
168 species was typed in samples from 47 patients; they were all *L. braziliensis*. Parasitological
169 examination of stool samples using sedimentation, Kato-Katz and Baermann-Moraes methods was
170 routinely performed during the study period. Fifteen (14%) out of 109 TL patients had helminth

171 infections. The most frequent helminths were Ancylostomidae, *Ascaris lumbricoides*, *Strongyloides*
172 *stercoralis*, *Schistosoma mansoni*, and *Trichuris trichiura* [12].

173

174 ***Leishmania* and other Trypanosomatidae.** The existence of coinfection with *Trypanosoma cruzi*
175 was proven in Argentina in 1996 [33]. Seven (58%) out of twelve patients with TL were diagnosed
176 with *T. cruzi* infection based on specific serological tests. In three of the seven coinfecting patients,
177 the presence of *T. cruzi* could be proven with a direct parasitological technique (i.e. xenodiagnosis
178 using *Triatoma infestans* nymphs). Six additional studies confirmed, based on specific serological
179 and molecular techniques that *T. cruzi* coinfection is frequent in TL patients from Salta, northern
180 Argentina [31, 34-37,43], where the seroprevalence of *T. cruzi* in rural populations is estimated to
181 range between 4% and 30% [31,91]. In all these studies, the coinfecting patients had clinical TL but
182 no signs of cardiac abnormalities typical of Chagas disease at the time of recruitment. The largest
183 study included 330 patients with TL caused by *L. braziliensis* or *L. amazonensis* and found
184 coinfection with *T. cruzi* in 135 (41%) of them [36].

185 Coinfection with *T. cruzi* has also been found in other Latin American countries
186 [30,32,39,40]. One study in a hospital in Los Yungas in Bolivia recruited 28 patients with TL caused
187 by *L. braziliensis* complex, *L. mexicana* complex, or both and obtained positive PCR results for *T.*
188 *cruzi* in 22 (79%) [32]. In Paraguay, 8 (8%) out of 101 patients with clinical TL coming from the
189 Caazapá and Alto Paraná departments were suspected of carrying *T. cruzi* [39].

190 The largest prevalence study was done in Brazil and reported on the frequency of
191 coinfection of *L. braziliensis*, *L. infantum* (syn. *L. chagasi*), and *T. cruzi* in a sample of 1100
192 apparently healthy people living in fast-growing villages in the outskirts of São Luiz City, the capital

193 of Maranhão State [30]. Diagnosis of *Leishmania* and *Trypanosoma* infections was based on
194 serology and molecular testing of blood samples. Forty-one subjects (4%) were diagnosed with *L.*
195 *braziliensis* infection only, 35 (3%) with *T. cruzi* only, 50 (5%) with *L. chagasi* only, 17 (2%) had *L.*
196 *braziliensis* together with *L. chagasi*, 7 (1%) had *L. chagasi* together with *T. cruzi*, and 11 (1%) had *L.*
197 *braziliensis* together with *T. cruzi*. None of the study participants had signs of past or present TL,
198 visceral leishmaniasis or Chagas disease.

199

200 ***Leishmania* and human T-lymphotropic virus 1 (HTLV-1).** Three small studies in Colombia, Peru,
201 and Iran reported a low frequency of HTLV-1 infection in patients with TL. The number of study
202 participants with TL ranged from 4 to 92 and the frequency of HTLV-1 infection ranged from 0% to
203 4% in subgroups with different forms of TL (subclinical or clinical, acute or chronic) [87-89]. A
204 fourth study, from Mashhad in Iran also failed to confirm a clear link between these two infections.
205 These authors reported that 8 out of 100 HTLV-1-infected candidate blood donors mentioned a
206 history of cutaneous leishmaniasis, which was not significantly different from the frequency
207 reported by 100 HTLV-1-negative candidate blood donors [90].

208

209 ***Leishmania* and other pathogens.** One study from Salta in northern Argentina looked into several
210 coinfections at the same time [37]. In a series of 93 patients with parasitologically confirmed
211 cutaneous (n=50) or mucocutaneous (n=43) leishmaniasis, 37% had one or more coinfection, i.e.
212 intestinal parasites (n=2), *T. cruzi* (n=25), *Toxoplasma gondii* (n=2), *Paracoccidioides brasiliensis*
213 (n=2), *Coccidioides posadasii* (n=1), *Mycobacterium tuberculosis* (n=3), and/or *Treponema pallidum*

214 (n=4). The authors described that the frequency of coinfections was higher in patients with mucosal
215 forms of leishmaniasis than in those with cutaneous leishmaniasis [37].

216 Our search retrieved no studies on the frequency of other coinfecting pathogens in TL
217 patients or the general population, although there were some case reports and series. Therefore,
218 we can only report on the absolute number of human cases with coinfection mentioned in the
219 literature. We found reports of 16 cases of concurrent coinfection of *Leishmania* with *Toxoplasma*
220 *gondii*, 4 with *Sporothrix schenckii*, 10 with *Paracoccidioides brasiliensis*, 1 with *Cryptococcus*
221 *laurentii*, 9 with *Mycobacterium tuberculosis*, 25 with *Mycobacterium leprae*, 1 with *Mycobacterium*
222 *ulcerans*, and 1 with *Burkholderia pseudomallei* (Table 1).

223

224 **Interactions between *Leishmania* and other pathogens in animal models and human subjects**

225 **Types of interaction.** Coinfections may influence the immune response during TL in several
226 different ways: through actions on local phagocytes, innate immune mechanisms, the balance
227 between effector and regulatory T-cell subsets, and the capacity of macrophages to kill *Leishmania*
228 amastigotes (Fig 2).

229 **Fig 2. Immune responses during tegumentary leishmaniasis and the potential for interference**

230 **through coinfection: a means to focus new research.** Panel A. *Leishmania* parasite transmission
231 during sandfly bite initiates TL. Local phagocyte function (including neutrophils, macrophages, and
232 dendritic cells) may be affected by coinfections affecting skin homeostasis. Furthermore,
233 coinfection may affect the nature of pre-existing immunity to sandfly saliva and/or the local
234 response to sandfly/parasite proteins. Panel B. Innate immune mechanisms regulated by stromal
235 cells, dendritic cells, and innate lymphoid cells may all be influenced by the microenvironment

236 created by local or systemic coinfection. Panel C. Changes to innate immunity or immunological
237 cross-reactivity may influence the balance between effector (Th1, Th2 and Th17) and regulatory (R)
238 T-cell subsets, leading to altered control of parasite load and/or altered immunopathology. Panel D.
239 Coinfections may directly or indirectly alter macrophage intracellular signalling, affecting the
240 intracellular survival of *Leishmania* independently of any effects on the specific T-cell response.

241 There is considerable evidence supporting the roles of various key phagocyte populations
242 (dermal macrophages, monocyte-derived macrophages and dendritic cells, and neutrophils) in the
243 establishment of infection and first-line defence against *Leishmania* [92]. There is also a growing
244 body of literature indicating that the functional attributes of these phagocytes can be influenced by
245 products introduced during transmission (e.g. sandfly salivary proteins or parasite-derived
246 immunomodulators) [93-95] or by changes in skin homeostasis (e.g. driven by pathologic
247 coinfection or changes to the commensal microbiota) [96,97]. One study in mice showed that
248 resident skin commensals were critical to promoting protective effector T-cell responses to *L. major*
249 [98], and thus act as potent immunomodulatory coinfections necessary for the control of TL.
250 However, specific publications about how phagocytes engaged in TL control may be affected by
251 other pathogens or skin microbiota are currently lacking. Likewise, coinfection-associated changes
252 in the function of innate lymphoid cells or mesenchymal stromal cells, although readily predicted
253 from the literature, have yet to be shown to be relevant in established models of TL.

254 A well-known paradigm in immunity relates to the opposing effects of interferon-gamma
255 (IFN γ) and interleukin-4 (IL-4) with regard to control of *L. major* lesion development in mice
256 [99,100]. Whereas C57BL/6 mice self-heal under the control of IFN γ , BALB/c mice succumb to
257 *Leishmania* infection in an IL-4-dependent manner. These counter-acting cytokines were identified
258 as the products of different subsets of CD4⁺ T helper cells (Th1 and Th2). The finding that these Th

259 subsets/cytokines have different roles in the control of helminth *versus Leishmania* infection led to
260 the notion that differing infections may skew T-cell immunity in polarised directions [100,101].

261 The included studies that contribute information about the interactions between
262 *Leishmania* and specific other pathogens are summarised below per coinfecting agent. Most of
263 these reports are based on research in animal models (n=22), while only a few (n=5) provide an
264 extensive immunological characterisation of human coinfection. Most of the possible interaction
265 mechanisms outlined in figure 2 have not been covered yet by the specific literature about TL and
266 coinfections included in this review.

267

268 **Helminths.** The effect of helminth coinfection on the course of TL has been studied in mice models
269 [7,23-29] and described in human patients [5,12,22], with mixed findings. Some of the studies in
270 mice concluded that in the presence of helminth infection, the time between experimental
271 infection with *Leishmania* and development of skin lesions increased [26,27], while others found
272 that this pre-patent period decreased [23] or remained unchanged [28]. The conclusions were also
273 divided about the size of the TL lesions, finding larger [7], smaller [27], or similar lesions [25,28] in
274 mice with helminth coinfection. One study with extended follow-up (16 weeks) showed that the
275 impact of helminth coinfection on lesion growth was time-dependent [26]. These divergent findings
276 may be partly due to the parasites used in the experiments (*Schistosoma mansoni* or *Litomosoides*
277 *sigmodontis*, with *L. mexicana* or *L. major*) and the time between the two experimental infections
278 [23,26,27].

279 When it comes to explaining the effects of helminth coinfection on the course of TL, one
280 experimental study suggested that the Th2 responses induced by helminth infection had systemic

281 effects that down-regulated the initial, local Th1 response to *Leishmania* [26]. In contrast, several
282 other studies found that helminth infection did not interfere with the generation of *Leishmania*-
283 specific Th1-type responses [24,25,27-29]. Furthermore, two groups used *in vitro* models to show
284 that macrophages from helminth-infected mice were impaired in their ability to kill *Leishmania*
285 [7,26]. Three studies in mice also evaluated whether TL altered the course of helminth infections,
286 but no measurable effect was reported [24,26,28].

287 Two cohort studies in Brazil compared the characteristics of TL in patients with and without
288 helminthiasis [5,12]. The studies were conducted in Rio de Janeiro and Bahia, where *L. braziliensis* is
289 predominant and pentavalent antimony is the recommended treatment. The study in Bahia
290 enrolled 120 patients with cutaneous forms of TL (including 106 (88%) with helminthiasis) and the
291 study in Rio de Janeiro enrolled 109 patients with cutaneous and mucocutaneous forms of TL
292 (including 16 (15%) with helminthiasis). The helminths detected were *Ancylostoma duodenale*,
293 *Trichuris trichiura*, *Ascaris lumbricoides*, *Schistosoma mansoni* and *Strongyloides stercoralis*. Both
294 studies reported that the time to heal under pentavalent antimony treatment was longer for
295 patients with TL and helminth infection than for patients with TL only [5,12]. The study in Rio de
296 Janeiro also found significant associations of helminth coinfection with mucosal leishmaniasis and
297 poor response to treatment [12].

298

299 ***Trypanosoma***. Four experimental studies (in mice or squirrel monkeys) and one observational study
300 in humans addressed the effect of *Trypanosoma* coinfection (*T. brucei* or *T. cruzi*) on TL [46-49].
301 Experimental Chagas disease did not protect against leishmaniasis and *vice versa* [46], although
302 there were elements of immune cross-reactivity [47]. For the studies evaluating the impact of
303 *Trypanosoma* on time until *Leishmania* lesion development [46-49], the main finding was a

304 reduction in lesion growth rate in coinfecting animals. In some cases, protection from ulceration
305 was reported [46,48,49]. Normal lesion growth returned once the *Trypanosoma* infection was
306 treated [48]. In one study in squirrel monkeys, *L. braziliensis* coinfection was shown to block the
307 increase in QRS interval, i.e. the depolarisation time of the cardiac ventricles, that is normally
308 associated with *T. cruzi* infection. This finding led the authors to suggest that prior infection with
309 *Leishmania* parasites might provide some protection against Chagas-related cardiopathy [46]. One
310 human immunological study focused on T-cell responses and showed that TL patients coinfecting
311 with *T. cruzi* had a higher T-cell differentiation profile than patients with TL only [44].

312

313 **Toxoplasma.** Experimental studies in mice suggest that toxoplasmosis affects the course of
314 leishmaniasis and *vice versa* [51,52]. Albino mice that were infected first with *L. major* and 30 to 70
315 days later with *Toxoplasma gondii* developed more severe forms of leishmaniasis than mice
316 infected with *L. major* alone [51]. By contrast, the course of toxoplasmosis was more benign in
317 coinfecting mice than in those infected with *Toxoplasma* alone [51]. Another study showed a
318 different type of interaction. Here, BALB/c mice were experimentally infected first with *T. gondii*
319 and five days later with *L. major*. The acute toxoplasmosis induced a strong Th1 response, and the
320 BALB/c mice that are normally susceptible to leishmaniasis developed a level of resistance
321 comparable to that of C57BL/6 mice [52]. In human patients, such positive or negative interactions
322 between toxoplasmosis and TL have not been reported yet, although one *in vitro* study found that
323 *T. gondii*-specific T cells are recruited into *L. braziliensis* lesions and could influence TL pathogenesis
324 locally [50].

325

326 **Plasmodium.** Seven experimental studies assessed *Plasmodium* coinfection and TL [53-59]. In
327 coinfection models of *P. yoelii* or *P. berghei* together with *L. enrietti*, *L. mexicana* or *L. amazonensis*
328 in hamsters, C57BL/6 mice, and BALB/c mice, the coinfecting animals had larger lesions than the
329 animals with *Leishmania* infection only. There was also an adverse effect of leishmaniasis on the
330 course of malaria, as coinfecting animals had increased parasitaemia and mortality compared to
331 animals with *Plasmodium* infection only [53-58]. These effects may vary according to the
332 *Leishmania* species, because one study of *P. yoelii* in BALB/c mice reported different findings for *L.*
333 *amazonensis* and *L. braziliensis* [59].

334

335 **Sporothrix.** Coinfection with *Sporothrix* may occur when fungal spores are inoculated in a TL lesion.
336 In Colombia, it was suggested that such inoculations occur when people lance their TL lesions using
337 *Sporothrix*-contaminated thorns [60]. There is also a case report linking coinfection with *Sporothrix*
338 to traumatic injury and TL reactivation (Koebner phenomenon) [61].

339

340 **Mycobacterium tuberculosis.** We found nine studies (eight case reports and one cross-sectional
341 study) describing 12 human patients with concurrent tuberculosis and TL (table 1). Five out of these
342 twelve patients had mucosal forms of TL and four had other, non-localised forms; the type of TL
343 was not described in three patients. Results of leishmanin skin tests (arguably an *in vivo* correlate of
344 Th1 responses) were available for six coinfecting patients: five were positive or strongly positive.
345 More detailed analyses of T-cell responses were not performed. Some authors hypothesised that an
346 episode of tuberculosis can trigger reactivation of latent leishmaniasis [65,67-69]. Others suggested
347 that an underlying immune defect could lead to the development of several infectious diseases at

348 the same time [70]. This was based on the study of one patient who had lepromatous leprosy,
349 several leishmaniasis lesions, and miliary tuberculosis, and in whom a reduced responsiveness to IL-
350 12 was found [70].

351

352 ***Mycobacterium leprae***. The search retrieved 12 case reports/series of human patients with
353 concurrent leprosy and TL, but none of them contained evidence of a significant interaction
354 between the two infections. Leprosy and TL are both caused by obligate intracellular organisms and
355 involve a broad spectrum of clinical, histopathological, and immunological manifestations [6,70,73-
356 83]. The paucibacillary/pauciparasitic type of disease (tuberculoid leprosy and localised cutaneous
357 leishmaniasis) is at one pole of the spectrum and reflects effective T-cell immunity. At the other
358 pole of the spectrum is the multibacillary/multiparasitic type of disease (lepromatous leprosy and
359 diffuse cutaneous leishmaniasis), which occurs when the antigen-specific T-cell response is
360 depressed [70,82-83].

361 We found descriptions of five patients with lepromatous leprosy and localised TL [74,75,77-
362 79]. In one of these cases, a man with lepromatous leprosy and mucosal leishmaniasis, skin reaction
363 and IFN γ production against *Leishmania* antigens were strong whereas the responses against *M.*
364 *leprae* antigens were almost absent [78,79]. Therefore, despite the similarities in the pathogenesis
365 of TL and leprosy, patients can have a divergent T-cell response to each pathogen, indicating a
366 degree of compartmentalisation of T-cell immunity. Nonetheless, follow-up of one patient
367 suggested that IL-10-mediated regulatory responses induced during leprosy may help control the
368 immunopathology of mucosal leishmaniasis [78,79]. Twenty other patients described in the
369 literature had disease manifestations of leprosy and TL that were not that far apart on the disease
370 spectrum [6,70,73,74,76,80-82].

371 In addition to these naturally occurring combinations of TL and leprosy, we found
372 descriptions of artificially induced coinfection [83,84]. In the 1950s and 1960s, it was common
373 practice in some *Leishmania*-endemic areas to immunise people against leishmaniasis by the
374 inoculation of live *L. tropica* parasites (“leishmanisation”). Two papers report on the clinical and
375 histopathological evolution of 24 Israeli patients with lepromatous leprosy who received a
376 vaccination with living *Leishmania* parasites. Twenty-three patients showed the classical clinical
377 progression of cutaneous leishmaniasis at the site of inoculation. The authors suggested that this
378 clinical response to vaccination was similar to that of people without leprosy [83]. One additional
379 patient with lepromatous leprosy, described in a separate report, developed diffuse leishmaniasis
380 after vaccination, but also in this person, the lesions healed spontaneously. These observations also
381 suggest that leprosy does not alter the course of TL or *vice versa* [84].

382

383 **Implications of TL coinfections for clinical practice**

384 **Clinical similarities complicating diagnosis.** A first diagnostic challenge occurs when there are
385 clinical similarities between the lesions caused by *Leishmania* and some other pathogens. When
386 one aetiological diagnosis is well established, a clinician may be tempted to attribute all the
387 patient’s lesions to this one infection and stop examining the patient for symptoms and signs of
388 other diseases. This may happen for instance in patients with concurrent leprosy and leishmaniasis,
389 particularly when patients have many skin lesions [82]. Furthermore, two case reports describe a
390 year-long delay in the diagnosis of mucosal leishmaniasis because nasal symptoms were first
391 attributed to leprosy [77,78]. Mucosal leishmaniasis can also be confused with mucosal
392 manifestations of tuberculosis. Several authors have emphasised the importance of examining
393 multiple samples from different skin lesions when coinfection is suspected [73-75,82]. Diagnosis of

394 coinfection can become particularly challenging when more than one pathogen is present within
395 the same lesion. *Leishmania* parasites have been found in skin or mucosal lesions together with
396 *Sporothrix schenckii*, *Cryptococcus laurentii*, *Mycobacterium tuberculosis*, *Mycobacterium leprae*
397 and *Mycobacterium ulcerans* [6,60,61,64,65,85].

398

399 **Biological similarities complicating diagnosis.** A second diagnostic challenge stems from the
400 biological similarities between *Leishmania* parasites and other pathogens. This problem is well
401 documented for *Leishmania* and *T. cruzi*, which are both kinetoplastid protozoa with antigenic
402 similarities. When conventional serological tests are used for the diagnosis of Chagas disease, there
403 is a problem of cross-reactivity with *Leishmania*. There have been several attempts to develop
404 serological tests that differentiate *Leishmania* from *T. cruzi* infections [38,39,41,42] and to evaluate
405 their diagnostic performance in settings where both pathogens are endemic [42,43]. Tests using
406 purified or recombinant specific antigens of *T. cruzi*, such as Ag163B6, Ag162B6/cruzipain, or shed
407 acute phase antigen (SAPA) proved to be useful to identify true coinfections [41,42].

408

409 **Issues with the interpretation of diagnostic test results.** One Brazilian study found that 52 out of
410 107 patients with a definite diagnosis of sporothrichosis also had one or more positive
411 immunological test results for leishmaniasis (leishmanin skin test, ELISA or indirect
412 immunofluorescence test) [62]. The diagnosis of TL could not be confirmed in this study, as
413 parasitological confirmation tests were negative (n=24) or not done (n=28). It was, therefore, not
414 possible to distinguish between true coinfections, serological cross-reactions, or false-positive
415 results of the leishmanin skin test due to an allergy to the diluent [62]. The authors emphasise that

416 in such a setting, incorrect diagnoses of TL are possible in patients with sporotrichosis, and that
417 even in the presence of suggestive clinical and epidemiological arguments together with positive
418 immunological test results for TL, parasitological confirmation is still needed before patients are
419 exposed to a toxic and possibly unnecessary TL treatment [62].

420

421 **Treatment sequence.** The first therapeutic challenge in patients with coinfection is to determine
422 the best sequence of the different treatments. As helminth coinfection appears to increase the time
423 to healing in patients with cutaneous leishmaniasis [5,12], it seems logical to assume that prompt
424 diagnosis and treatment of helminth infections may improve the outcome of TL treatment. One
425 randomised, double-blind, placebo-controlled trial in Bahia, Brazil, examined early *versus* deferred
426 treatment of helminth coinfection [22]. This trial enrolled 90 patients with cutaneous leishmaniasis
427 (most probably caused by *L. braziliensis*) and helminth coinfection (mainly hookworms, *Trichuris*
428 *trichiura*, *Ascaris lumbricoides*, *Schistosoma mansoni* and *Strongyloides stercoralis*). All participants
429 were treated with intravenous antimony at 20 mg/kg/day for 20 days. The treatment group also
430 received triple antihelminthic therapy with albendazole, ivermectin and praziquantel at days 0 and
431 30, and placebo at day 60. The control group received placebo at days 0 and 30, and specific
432 antihelminthic therapy based on stool test results on day 60. There was no significant difference
433 between the two groups in the time to healing of the skin lesions: the median time to cure was 98
434 days in the treatment group and 88 days in the control group [22].

435

436 **Treatment side effects.** When two infections are treated at the same time, the drug combinations
437 may lead to increased intolerance or adverse effects. The combination of antimony with

438 antituberculous drugs is feared, and we found a description of death due to renal failure that was
439 attributed to the combined treatment [67]. The combination treatment for TL (with pentavalent
440 antimony) and leprosy (with diaminodiphenyl sulfone + rifampicin + clofazimine) may also produce
441 considerable side effects [6]. Furthermore, several authors have raised concerns about the use of
442 antimonial treatment for TL in patients with Chagas disease [40,45]. Pentavalent antimony drugs
443 are known to prolong QT time and cause arrhythmia; they are therefore contraindicated in patients
444 with known heart disease. On the one hand, cardiomyopathy is a well-known clinical manifestation
445 of Chagas disease, and therefore, prudence is called for in patients with *Leishmania-Trypanosoma*
446 coinfection [40,45].

447

448 **Unexpected responses to treatment.** Some case reports discussed unexpected benefits of one
449 treatment on two infections. For example, there was a report about a patient with chagasic
450 cardiomyopathy and TL [45]. Amiodarone was used to control the patient's ventricular arrhythmia
451 and seemed to promote the healing of TL. The authors considered that amiodarone could have had
452 an antileishmanial effect although they could not rule out the possibility that the use of amiodarone
453 coincided with the healing of TL by chance [45].

454 Another interesting case was reported in Colombia [69]. A patient diagnosed with
455 mucocutaneous leishmaniasis and pulmonary tuberculosis first received treatment for tuberculosis
456 with rifampin, isoniazid, streptomycin and pyrazinamide, over a period of seven months. The
457 antimonial treatment was deferred because of concerns about the adverse effects of the
458 combination of antituberculous and antimonial drugs. Despite the lack of specific antileishmanial
459 treatment, when assessed three months after the end of antituberculous therapy, the mucosal
460 lesions were fibrosed, scar tissue was evident, and the patient was biopsy culture-negative. A

461 similar observation was reported in Brazil, where the lesions of a patient with diffuse cutaneous
462 leishmaniasis temporarily improved while receiving antituberculous therapy [66]. Some studies
463 have suggested that streptomycin, isoniazid, and rifampin may have direct antileishmanial activity
464 [66]. Alternatively, this response might reflect an interaction between TL and tuberculosis. For
465 example, reduction of mycobacterial burden may release regulatory pressure within the immune
466 system that also favours resolution of mucosal lesions, or anti-tuberculous treatment may
467 (re)activate host protective mycobacteria-specific T cells that cross-react with *Leishmania* antigens.

468

469 **Discussion**

470 **Summary of main findings**

471 This is the first comprehensive review of the literature about TL and coinfections other than
472 HIV. Coinfection adds to the complexity of TL: the outcome of a single *Leishmania* infection in
473 humans is difficult to predict and the impact of coinfection on the course of TL is even more
474 puzzling. Nevertheless, coinfection is clinically relevant, as it is frequent, it can lead to diagnostic
475 errors and delays, and it can influence the effectiveness of treatment and drug side effects.
476 Therefore, it is crucial to gain a better understanding of the interaction between TL and other
477 infectious diseases.

478 The frequency of coinfections has been studied mostly in Latin-America so far. There is
479 relatively good evidence about *Trypanosoma cruzi* infection in Argentina (an estimated 41% of TL
480 patients also carry *T. cruzi*) [36] and about helminthiasis in Brazil (an estimated 14% to 88% of TL
481 patients also carry helminths) [5,12].

482 Several hypotheses have been explored about the mechanisms of interaction between the
483 different microorganisms, but no clear answers emerge so far from a literature that is scattered and
484 still developing. Such interactions may involve one or all components of innate immunity coupled
485 with the complexity of regulatory networks that affect the quality and quantity of the acquired
486 immune responses (e.g. T-cell subset bias or regulatory cytokine production). Given that TL
487 pathology is fundamentally an immunopathology reaction, coinfections could paradoxically lead to
488 exacerbated TL disease by enhancing immune responses against *Leishmania* parasites in lesions.
489 The impact of *Plasmodium* coinfection on TL in animal models is clearly detrimental; the impact of
490 all other coinfections in animal models or human studies is less clear or less consistent.

491 Diagnostic problems occur when concurrent infections cause similar lesions (e.g. TL and
492 leprosy), when different pathogens are present in the same lesions (e.g. *Leishmania* and *Sporothrix*
493 *schenckii*), or when crossreactions induced by phylogenetically close pathogens affect the accuracy
494 of diagnostic tests (e.g. serology for leishmaniasis and Chagas disease). Regarding treatment, some
495 coinfections seem to reduce the efficacy of antileishmanial drugs (i.e. helminthiasis), and there may
496 be cumulative adverse effects caused by drugs or drug combinations (e.g. antimonial treatment in
497 patients with chagasic cardiomyopathy, and combinations of antileishmanial and antimycobacterial
498 drugs).

499

500 **Strengths and limitations**

501 The strengths of this review are the broad search of the literature and the fact that the
502 reporting follows PRISMA guidelines [21]. On the other hand, because the search strategy had few
503 restrictions, we retrieved information in heterogeneous formats. As a consequence, we could not

504 systematically assess the risk of bias in the individual records and decided to include all the
505 available information. Most animal studies pre-date the introduction of the ARRIVE (Animals in
506 Research: Reporting *In Vivo* Experiments) guidelines for reporting animal research [102]; hence,
507 issues related to experimental design and the avoidance of bias may not have been explicitly
508 recorded in the publications reviewed.

509 Despite the broad search including several databases other than MEDLINE, the retrieved
510 information was fragmented, and the evidence was insufficient to give firm answers to all the
511 review questions. For example, all the evidence about TL and malaria came from animal studies
512 without validation in humans. By contrast, all the information about tuberculosis came from human
513 case reports with limited information about pathogenesis. In total, only 3 out of the 73 included
514 records were cohort studies or clinical trials specifically designed to investigate the impact of
515 coinfection on the course of TL in humans. Furthermore, there was not enough information
516 available to look into the effect of coinfections on different clinical forms of TL (i.e. localised,
517 diffuse, disseminated, and mucosal) separately. This is an important limitation because the host
518 immune responses underlying these different forms of TL are contrasting and may be differentially
519 modified by coinfections. For example, coinfections that induce a strong pro-inflammatory
520 response could be beneficial in early cutaneous but detrimental in mucosal leishmaniasis. Finally,
521 there was almost no information about coinfection in human subjects from Africa or Asia.

522 Several factors may have contributed to the lack of evidence about coinfections. First,
523 coinfections tend to get less attention than single infections. Second, TL, as well as many of the
524 relevant coinfections, are neglected diseases that affect poor populations and are typically under-
525 researched and under-reported. Finally, the complexity of TL together with other infections may

526 lead to negative results or findings that are difficult to explain, which may reduce the chance of
527 publication.

528

529 **Implications for future research**

530 From a clinical point of view, several questions remain to be resolved. Even if the
531 interactions between pathogens are complex, these clinical questions are fairly straightforward. For
532 each of the coinfecting microorganisms, we need to better document: (i) how frequent it is among
533 patients with TL in different settings, (ii) whether TL patients with the coinfection fare better or
534 worse than patients without it, (iii) whether the presence of the coinfection affects the accuracy of
535 diagnostic tests, and (iv) what is the best way to treat the coinfecting patient. With advances in the
536 development of vaccines for leishmaniasis, including TL, an understanding of how vaccine
537 responses might be modulated due to coinfection also becomes a question of some significance.

538 With regard to the interaction between pathogens, additional mechanisms, unexplored in
539 the literature to date in relation to TL, are worthy of consideration. First, metabolic disturbances
540 resulting from coinfection may alter the capacity of the immune system to appropriately respond
541 during TL or *vice versa* [103,104]. Second, coinfections, in particular with helminths, may lead to a
542 dysbiosis (i.e. alterations in the development or composition of the microbiota) that consequently
543 impacts on immune health [97,104,105]. Hence, the answer to how the clinical outcome differs
544 between single and co-infected patients may not lie in understanding how two specific sets of
545 immune responses interact, but rather in how these responses are linked via complex regulatory
546 circuits established and maintained by our commensal microbiota.

547 Several elements of the design of future experimental research deserve consideration. First,
548 it is important to clarify what the outcomes of interest are, i.e. the risk of symptomatic disease, the
549 time between infection and lesion appearance, the size of the lesion, time to healing, response to
550 treatment, or risk of metastasis and comorbidities. The impact of coinfections on these different
551 clinical outcomes may vary. Second, the species, the infective doses, and the timing of *Leishmania*
552 and coinfection may also matter. Finally, animal models differ from each other, and they do not
553 always represent what happens in human coinfection.

554

555 **Conclusion**

556 In patients with TL, coinfection with other pathogens may be the rule rather than the
557 exception. More research is needed to unravel how other infections interfere with the
558 pathogenesis of TL. It is important that clinicians bear in mind the possibility of coinfection because
559 this can complicate diagnosis and treatment.

560

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855

856 **Supporting information**

857 **S1 File. Command used to search MEDLINE via PubMed.**

858 **S1 List. PRISMA checklist.**

859

PRISMA checklist for the manuscript “Tegumentary leishmaniasis and coinfections other than HIV” by Martínez DY *et al.*

The checklist is taken from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097. More information is available from www.prisma-statement.org.

The 27 PRISMA items are copied using *italic font*, the way in which we have been addressed each of these items in our manuscript is described using regular, not-italic font.

1. *TITLE - Identify the report as a systematic review, meta-analysis, or both.*

We do not claim that this manuscript is a systematic review because our focus was broad (more than one review question) and because the available information was diverse (e.g. different types of coinfection and divergent study designs). Nevertheless, as described below, we took a systematic approach to searching literature, selecting records and obtaining information from the included records. The title of the manuscript is “Tegumentary leishmaniasis and coinfections other than HIV”. The fact that the manuscript is a review is mentioned early in the abstract.

2. *ABSTRACT - Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.*

Applicable elements are included in the abstract; the review protocol was not registered.

3. *INTRODUCTION - Describe the rationale for the review in the context of what is already known.*

People infected with *Leishmania* may carry other pathogens as well. These other pathogens may alter the host immune response against *Leishmania* infection and hence the clinical course of leishmaniasis. The interaction between tegumentary leishmaniasis and HIV is well established and has been reviewed before. This is the first comprehensive review of tegumentary leishmaniasis and coinfections with pathogens other than HIV.

4. *INTRODUCTION - Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).*

The focus of this review is explained in the last paragraph of the introduction: “The objectives of the present review are to summarise the evidence about the (i) frequency of tegumentary leishmaniasis (TL) and coinfections other than HIV in human populations, (ii) interactions between *Leishmania* and other pathogens in animal models and human subjects, and (iii) implications of TL coinfections for clinical practice.”

5. *METHODS - Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.*

No protocol has been registered for this review.

6. *METHODS - Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.*

We searched the medical literature to identify publications about TL and coinfections. To identify coinfections, we used search terms indicating (groups of) infections, pathogens, and diseases caused by these pathogens. For the purpose of this review, we defined TL as all forms of cutaneous (localised, disseminated or diffuse) and mucocutaneous leishmaniasis. Records about the skin manifestations caused by *L. donovani* and *L. infantum/L. chagasi* were not included because the main clinical outcome of these infections is visceral leishmaniasis, which is outside the scope of this review. Records about HIV/AIDS and TL were not included because this topic has already been extensively reviewed elsewhere. Records about the contamination or superinfection of TL lesions with Gram-positive or Gram-negative bacteria of the skin such as *Staphylococcus aureus* or *Streptococcus pyogenes* were also excluded. Review papers were not included. We did not restrict the search by geographical region, study design, language of publication or publication date.

7. *METHODS - Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.*

Information for this review was identified in August 2017 by searches of MEDLINE, Embase, LILACS, Scielo, Cochrane, African Index Medicus, as well as local library databases. We also reviewed the reference lists of selected articles.

8. *METHODS - Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.*

The detailed search strategy for MEDLINE is given in S1 File.

9. *METHODS - State the process for selecting studies (i.e., screening, eligibility, included in the systematic review, and, if applicable, included in the meta-analysis).*

One reviewer (DYM) screened titles and abstracts, and two reviewers (DYM and KV) assessed the eligibility of the full-text papers using the eligibility criteria outlined above (item 6). Doubts and discordances were resolved through discussion.

10. *METHODS - Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.*

Two reviewers (DYM and KV) read and summarised the included records. Doubts and discordances were resolved through discussion. We did not contact investigators to obtain additional information or to confirm data.

11. *METHODS - List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.*

Specific points of interest while reading and summarising the articles were: (i) frequency of coinfection in humans; (ii) mechanisms of interaction and effect of coinfection on TL progression; and (iii) potential implications for clinical management.

12. *METHODS - Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.*

Our search did not include restrictions in study design and retrieved information in various formats. As a consequence, we did not formally assess the risk of bias of individual studies but described the different study designs instead.

13. *METHODS - State the principal summary measures (e.g., risk ratio, difference in means).*

The information was found in heterogeneous formats. We described the information the same way the authors of the original publications did, using counts, proportions and medians.

14. *METHODS - Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I²) for each meta-analysis.*

This review does not include a meta-analysis.

15. *METHODS - Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).*

Not done

16. *METHODS - Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.*

Not done

17. *RESULTS - Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.*

The MEDLINE search retrieved 3014 records and searching other databases yielded 348 additional records. After reading titles or abstracts or both, we removed 382 duplicates and discarded 2853 records because they were not relevant (Fig 1). The most frequent reason for dropping records was that while leishmaniasis and another infection were mentioned in the same text, the publication was not about coinfection (e.g. a paper about different infections occurring in the same region but not affecting the same persons). We assessed the remaining 127 full-text records for eligibility and retained 71 for the present review (Fig 1).

18. *RESULTS - For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.*

Table 1 gives an overview of all the included studies. This table describes according to the coinfecting pathogen and the study design: the number of included studies, the number of human cases with coinfection, and the citations.

19. *RESULTS - Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).*

Study design is described instead of risk of bias: the 71 articles included in this review had different study designs. There were 21 original research papers about experimental studies of coinfection in animals, and 50 original research papers about coinfection in human patients. The 50 studies about human subjects included 1 clinical trial, 2 cohort studies, 13 cross-sectional or prevalence studies, 7 studies on the development or performance of diagnostic tests, 22 case series or case reports with a clinical focus, and 5 case series or reports with an immunological focus.

20. *RESULTS - For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.*

Main findings are summarised following a different structure: frequency of TL coinfections in human populations; interactions between *Leishmania* and other pathogens, and Implications of TL coinfections for clinical practice.

21. *RESULTS - Present results of each meta-analysis done, including confidence intervals and measures of consistency.*

Not done

22. *RESULTS - Present results of any assessment of risk of bias across studies (see Item 15).*

Not done

23. *RESULTS - Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).*

Not done

24. *DISCUSSION - Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).*

The discussion contains a specific section entitled 'summary of main findings'.

25. *DISCUSSION - Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).*

The discussion contains a specific section entitled 'strengths and limitations'.

26. *DISCUSSION - Provide a general interpretation of the results in the context of other evidence, and implications for future research.*

The discussion contains a specific section entitled 'implications for future research'.

27. *FUNDING - Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.*

DYM received a PhD scholarship from the Belgian Directorate General for Development Cooperation (third framework agreement, project 95502). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Identification

Records identified through
database searching
(n=3014)

Additional records identified
through other sources
(n=348)

Screening

Records after duplicates removed
(n=2980)

Records screened
(n=2980)

2853 records excluded based on
screening of titles and abstracts

Eligibility

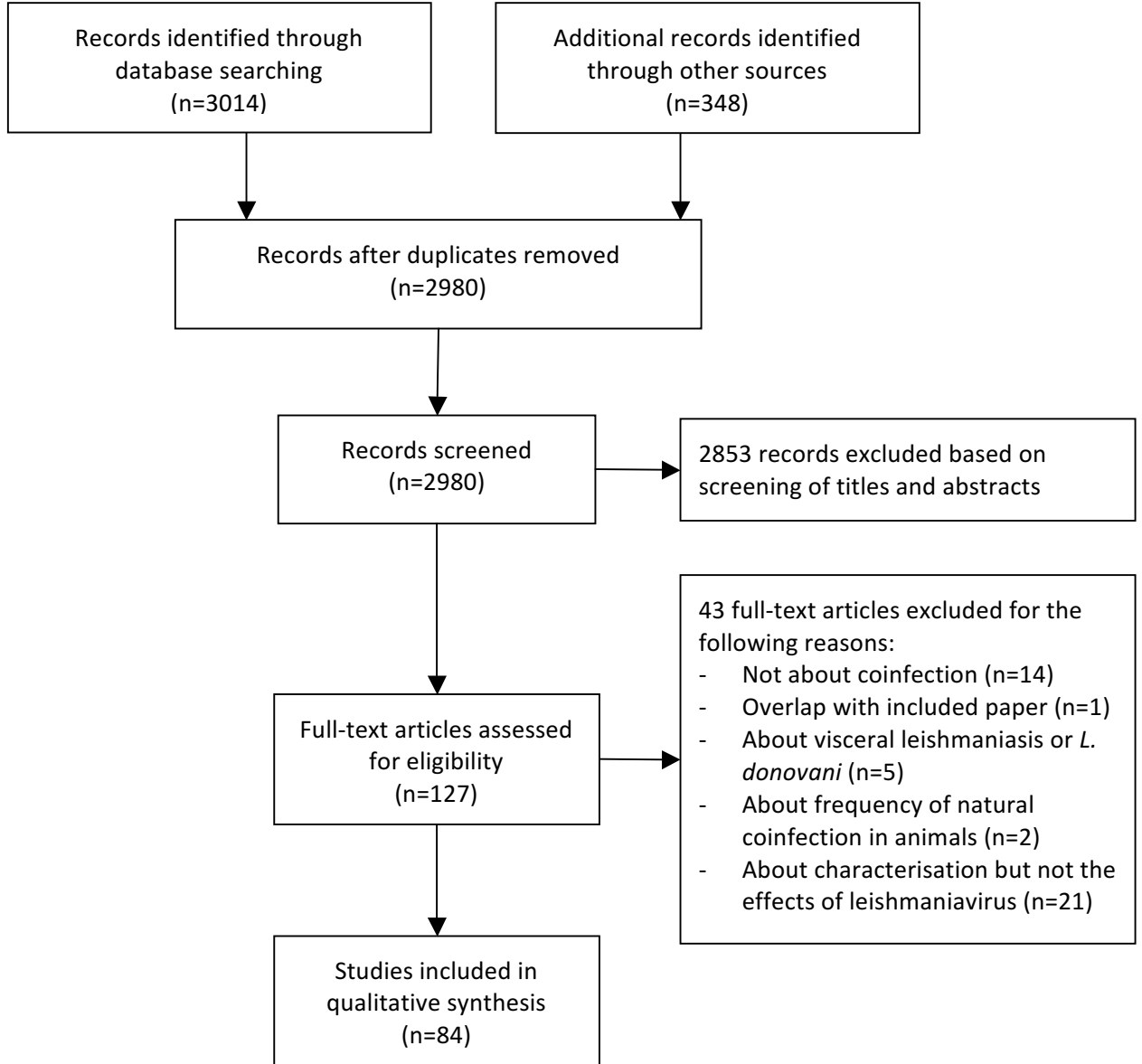
Full-text articles assessed
for eligibility
(n=127)

43 full-text articles excluded for the
following reasons:

- Not about coinfection (n=14)
- Overlap with included paper (n=1)
- About visceral leishmaniasis or *L. donovani* (n=5)
- About frequency of natural coinfection in animals (n=2)
- About characterisation but not the effects of leishmanivirus (n=21)

Included

Studies included in
qualitative synthesis
(n=84)



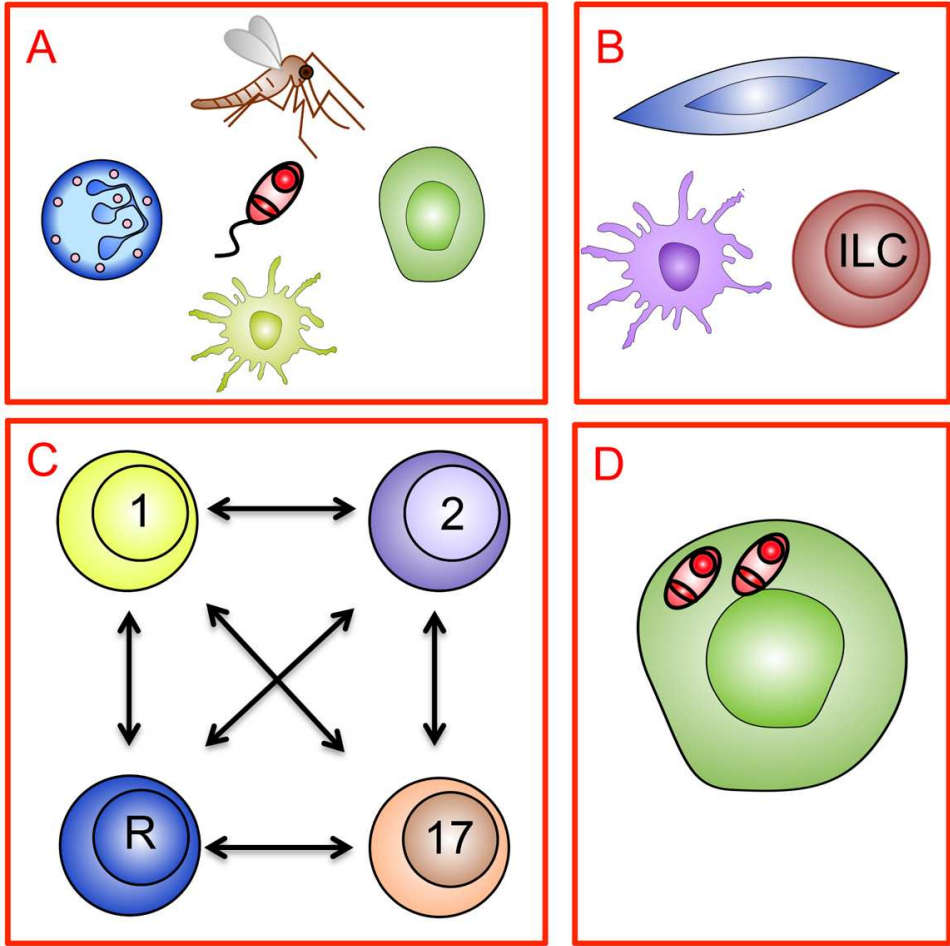


Figure 2