Chapter 11
Visceral and Tegumentary Leishmaniasis

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Abstract Visceral and tegumentary leishmaniasis are neglected tropical diseases caused by the protozoan parasite *Leishmania.* In this chapter, we discuss the causative organisms and the different clinical manifestations, their global and endemic distribution, and methods of vector and human-to-human transmission. We also explore current drug treatment regimens for both diseases and present a brief introduction to vaccine development.

Keywords Visceral · Tegumentary · Leishmaniasis · Neglected tropical disease Treatment · Drugs · Vaccine

11.1 Introduction

Leishmaniasis is a complex neglected tropical disease caused by protozoan parasites of the genus *Leishmania.* In this chapter, we describe the different clinical presentations of leishmaniasis, the global distribution of the disease complex, and current treatment regimens and briefly introduce the concept of vaccination to protect against infection and disease.

11.2 What Are Visceral Leishmaniasis and Tegumentary Leishmaniasis?

Visceral leishmaniasis (VL), also locally called dum-dum fever or kala-azar [1, 2] is a disease that affects the entire human system and is caused by a protozoan parasite transmitted through the bites of the *Phlebotomus papatasi* phlebotomine sandflies

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[3]. It is caused by *Leishmania* species such as *Leishmania donovani* complex, *L. donovani* sensu stricto as the major protozoan in East Africa and the Indian subcontinent, and *L. infantum* in Europe, North Africa, and South America [1, 4, 5]. There exist two forms of VL with different characteristics of transmission: (1) anthropozoonotic VL occurs when the protozoan is transmitted from animal to vector to human, with humans serving as occasional hosts and dogs as the parasite's reservoir host, and (2) anthroponotic VL, in which the transmission cycle is from infected human to vector to human [6].

There are two forms of the *L. donovani* parasite in the transmission cycle: the promastigote flagellar form, which is peculiarly found in the gut of the phlebotomine arthropod vector, and the amastigote form, which develops in mammalian host cells [3, 7]. This transmission cycle is only made possible through the bite of female phlebotomine sandflies, which become infected when they ingest the amastigotes during a blood meal. Multiplication starts in the insect midgut, and amastigotes transform into small promastigotes that block the gut of the insect and are seen in the gullet, pharynx, and buccal cavity, from where they can be introduced into a new host via insect bite [1, 7, 8]. Inside the mammalian host, promastigotes are engulfed by dendritic cells and macrophages and transform into amastigotes by losing their flagella [3]. Through complex host-parasite interactions, they multiply and possibly survive in the phagolysosomes [9, 10]. The amastigotes escape dead macrophages and are engulfed by other viable macrophages and cause severe damage to the reticuloendothelial system [1], attacking the bone marrow, enlarging the liver and spleen and sometimes the lymph nodes [3].

Despite the fact that sandflies are the main vector for parasite and disease transmission, other routes of possible transmission have been reported, including via blood transfusion [11–13], organ transplantation [11], needle sharing [14], congenital [15], vertical, and sexual [12]. These routes of transmission are important as they can play a notable epidemiological role in sustaining and spreading the disease where the invertebrate vector is absent [16]. Mescouto-Borges and colleagues [15] reported two cases of congenital transmission of VL in the city of Palmas, Tocantins, Brazil. The presence of the parasite was detected with a polymerase chain reaction (PCR) test for the presence of *Leishmania* kDNA in bone marrow aspirates taken from the newborns. Sexual transmission of VL in humans was first reported in the UK, where no record of autochthonous leishmaniasis nor vector presence exists. This was reported in a woman who had not traveled out of the country but showed genital papule with intralesional *Leishmania* sp., and it was believed that she had been infected by her husband who had been diagnosed with VL many years before [17]. Although uncommon, there are also reports of genital lesions due to VL in human patients, including testicular infection detected in an immunocompromised boy with leukemia [18] and nodular ulcerative sore accompanied by intralesional *L. infantum* in the prepuce/foreskin of an adult man [19].

Clinical manifestation of VL ranges from asymptomatic to fully developed kala-azar [1]. Initially, it begins with symptoms such as fever, weakness, loss of appetite, and weight loss, which is followed later by anemia and enlargement of the lymph nodes, liver, and spleen [1, 3, 20, 21] that causes the archetypical protrusion/

swelling of the abdomen [1]. Other symptoms accompanying the disease condition include swelling of the face, malabsorption, diarrhea, bleeding of the mucous membranes, and nasal ulcers that cause breathing difficulties. There is also the possibility of secondary infection [1, 2]. VL is marked with a skin condition known as kala-azar, which means "black sickness," with the skin becoming earth-gray in color and presenting with diffused nodular lesions. Kala-azar is common [2].

Tegumentary leishmaniasis (TL) is a virulent, zoonotic, noncontagious disease affecting millions of people globally [1]. It is a NTD associated with poverty, and infection produces blisters or ulcers on the skin, which become difficult to heal and scar and sometimes extend to mucous membranes of the mouth, larynx, and nose [2]. Transmission to humans from wild and domesticated animals occurs via the bites of infected female phlebotomine sandflies, with *Lutzomyia* spp. as the commonest vector [1, 4, 6]. The *Leishmania* species responsible for TL are *Leishmania (Viannia) braziliensis*, *L. mexicana*, *L. (Leishmania) amazonensis*, and *L. (Viannia) guyanensis*, [7–11] as the main species in the New World [7, 8]; *L. major*, *L. aethiopica*, and *L. tropica* as the main species in the Old World [7, 8]; and *L. (Viannia) panamensis* in the New World [12, 13].

Four transmission cycle patterns have been described for TL, especially in Argentina; these are (1) transmission occurring in primary vegetation known as the wild cycle, (2) transmission associated with wild or secondary vegetation alterations described as possible peridomestic transmission, (3) peridomestic transmission in homes or settlements close to unused vegetation, (4) peridomestic transmission cycle occurring in rural or urban-rural links [14]. According to Kawa and Sabtoza [15], TL occurs in three primary ecological patterns, namely, the (1) sylvatic or rain forest where people actively involved in activities such as gathering are affected, (2) agricultural areas that have farmers affected in primary forests, and (3) peri-urban areas, where the inhabitants of the outskirts of cities are affected.

The transmission of *Leishmania* species that are responsible for TL begins when flagellated promastigotes are injected into humans through bites of infected female sandflies. Inside the human host and especially in the macrophage phagolysosomal compartment, these promastigotes transform into non-flagellated amastigotes characterized by their round shapes [16, 17]. Clinical manifestations of TL are often characterized by tendencies such as persistency, inactivity, and spread [18]. Symptoms range from self-healing cutaneous lesions to persistent sores/lesions and mucosal lesions throughout the skin that occur when parasites are spread through the blood and lymphatic systems [19–23]. Manifestation of symptoms is dependent on immunity of the individual and the *Leishmania* species involved [20].

11.3 The Global Distribution of VL and TL

Occurrence of VL is global and widely distributed on all continents, with the exception of Oceania [22]. The pattern of disease transmission has significantly changed from an initial predominantly rural distribution to the vector now invading

peri-urban and large urban areas [23, 24]. Regions of the world with predominant cases of VL include Africa, the Americas, and Southeast Asia [25]. Burza and colleagues [11] estimated new cases of the disease to be at ~700,000 to one million per annum, with well over 50,000 deaths. However, both figures are probably underestimates, as most cases of VL are either unidentified or not recorded [26, 27]. Most cases of VL are reported specifically in six countries, namely, Bangladesh, Nepal, Ethiopia, India, Brazil, and the Sudan [3, 25]. Leading factors contributing to increasing cases of VL include inadequate control measures, movement of people across continents, and co-infection of HIV with VL [28, 29]. Recently, the World Health Organization (WHO) [30] reported high burden cases of VL in 14 countries, including Bangladesh, Brazil, China, Ethiopia, Georgia, India, Kenya, Nepal, Paraguay, Somalia, South Sudan, Spain, the Sudan, and Uganda. However, there is currently a reduction in the number of reported cases of the disease, which has been attributed to a decline in cases in South Asia, where reported cases dropped from ~50,000 to 6746 during 2007 to 2016. Factors that accounted for this decline include improved living conditions, successful campaigns for elimination, and natural alternating trends of prevalence. This situation currently leaves Eastern Africa as the region with the highest burden of the disease globally with Ethiopia, the Sudan, Uganda, South Sudan, and Somalia recording the most observed number of cases. Bangladesh has now been replaced by Somalia in the top six countries with cases of VL [30]. Figures 11.1 and 11.2 show the status of endemic VL and the number of cases reported between 2005 and 2019 are also reported in Table 11.1.

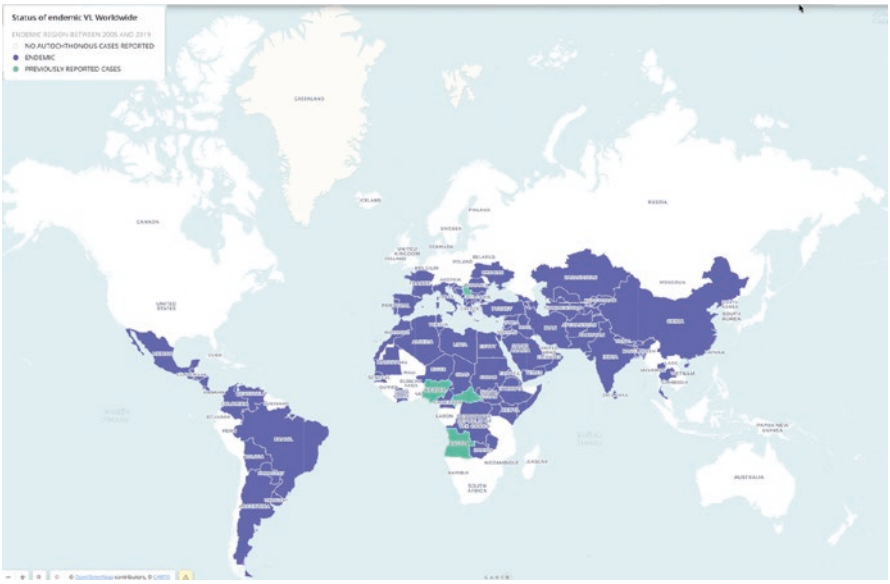

Fig. 11.1 Status of endemic VL between 2005 and 2019. (Map [31], data source [32])

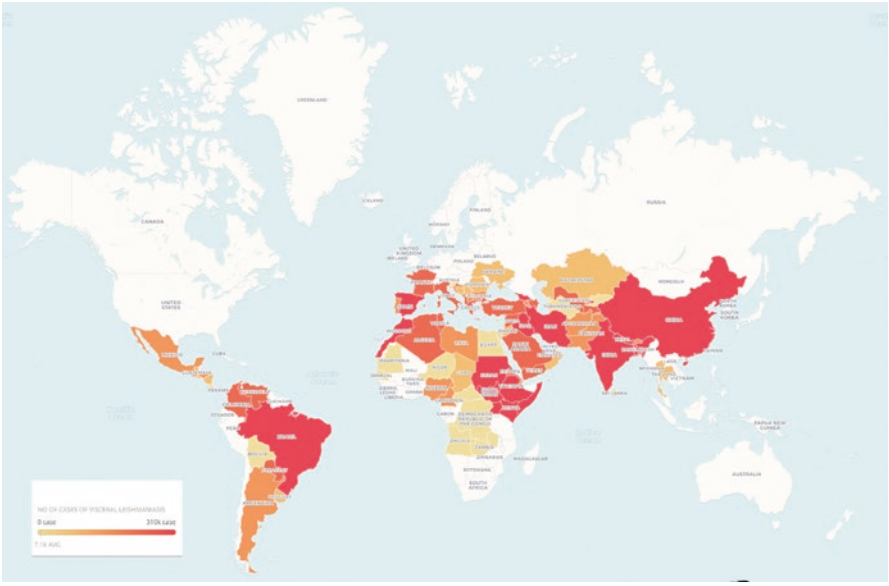

Fig. 11.2 The number of cases of VL reported between 2005 and 2019. (Map [33], data source [34])

A WHO report [35] on country-specific data on worldwide distribution of VL in 2016 recorded the following reported cases for various countries across continents and regions. Ethiopia and South Sudan recorded the highest numbers in Africa with 1593 and 4175 cases, respectively. In Southeast Asia, cases recorded included 255 for Bangladesh, 6249 for India and 242 for Nepal. In the Americas, Brazil, Paraguay, Colombia, and Venezuela reported figures of 3200, 64, 37, and 33, respectively. In the East Mediterranean, the Sudan recorded the highest number of VL cases with reported figures as 3810. European countries such as Georgia (60), Greece (57), Italy (49), Azerbaijan (44), and Uzbekistan (38), though having comparatively low figures, had the highest number of cases on the continent [35]

In Algeria, cases of VL reported from 48 provinces between 1998 and 2008 were 1562, an average of 142 cases annually, and an annual average incidence of 0.45 cases per 100,000 inhabitants, with 45 out of 48 provinces in the country reporting at least 1 case of the disease [36]. VL in Ethiopia occurs mostly in arid and semiarid regions, although recent reports suggest spread of the disease to previously non-endemic highland areas [37–40]. The estimated annual burden of the disease in this country is between 4500 and 5000 cases [37, 41, 42]. The Ministry of Health in Brazil in its 25-year notification on VL from 1990 to 2014 reported total cases of the disease at 78,444, with the northeastern region of the country accounting for ~67% of them. The annual mean number of cases in Brazil within this period was 3137 cases, an incidence of 2 cases per 100,000 inhabitants [43]. In Bangladesh, 45 out of the 64 districts in the country are endemic to VL [44]. Cases of the disease reported from 1998 to 2014 were 78,530 [45], with the disease usually affecting the

Table 11.1 Breakdown of cases of visceral leishmaniasis per country from 2005 to 2019

Country	Year															Total all years
	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	
Afghanistan	20	23	14	9	8	12	16	24	21	11	nd	nd	nd	nd	nd	158
Albania	nd	45	22	15	15	33	54	53	52	60	62	75	108	117	136	847
Algeria	46	40	34	74	38	30	54	53	89	87	84	84	112	147	112	1084
Angola	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Argentina	9	2	9	11	8	11	6	24	15	21	18	19	17	2	0	172
Armenia	17	17	17	17	18	9	7	8	7	9	nd	14	9	5	3	157
Azerbaijan	61	40	51	44	28	6	14	22	15	32	16	35	32	23	24	443
Bangladesh	97	124	210	258	544	650	1103	1902	2874	3800	4293	4840	4932	9379	6892	41,898
Bhutan	1	3	1	nd	nd	nd	4	2	4	6	2	0	0	7	nd	30
Bolivia	1	0	0	0	0	0	0	0	0	0	nd	nd	nd	nd	nd	1
Bosnia and Herzegovina	nd	nd	0	0	0	2	1	0	0	1	1	0	2	0	1	8
Brazil	2529	3466	4103	3127	3223	3453	3253	2770	3894	3716	3693	3852	3604	3651	3597	51,931
Bulgaria	nd	1	0	3	5	12	13	2	3	4	6	2	6	6	12	75
Cameroon	28	nd	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	28
Central African Republic	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Chad	nd	2	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	2
China	166	180	190	321	514	292	120	218	293	402	539	529	382	294	335	4775
Colombia	11	16	29	37	21	31	13	9	11	34	54	33	54	44	66	463
Costa Rica	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Côte d'Ivoire	nd	nd	0	nd	nd	nd	nd	nd	nd	nd	nd	0	0	0	0	0
Croatia	0	0	nd	0	nd	nd	2	0	0	nd	1	4	4	6	7	24
Cyprus	0	2	1	1	0	nd	0	0	1	1	nd	0	0	2	nd	8

Democratic Republic of the Congo	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Djibouti	1	12	34	9	10	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	66
Egypt	0	0	0	0	0	0	0	0	0	nd	nd	1	nd	nd	nd	1
El Salvador	0	3	2	0	0	0	1	0	1	0	0	0	1	0	0	8
Eritrea	514	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	104	129	131	129	1007
Ethiopia	1360	1828	1490	1593	1990	2705	1732	2381	2032	1936	1083	1356	1579	2375	2585	28,025
France	nd	17	12	8	8	11	8	10	25	5	14	17	22	16	19	192
Gambia	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Georgia	47	52	38	49	64	55	117	106	123	141	169	171	182	174	160	1648
Greece	nd	51	83	57	64	82	75	47	41	28	28	30	48	35	48	717
Guatemala	1	4	2	2	2	0	1	0	2	0	1	1	nd	nd	nd	16
Honduras	3	8	8	7	6	2	3	0	7	7	3	3	4	9	7	77
India	2822	4360	5758	6249	8500	9241	13,851	20,572	33,155	28,382	24,213	33,598	44,533	39,173	32,803	307,210
Iran	72	67	60	61	59	26	81	94	90	91	94	125	153	139	133	1345
Iraq	170	259	172	183	427	362	575	1045	1167	1843	1549	1041	836	1434	2028	13,091
Israel	nd	1	nd	1	3	1	5	1	0	1	0	2	2	2	3	22
Italy	nd	72	nd	49	55	63	62	81	62	71	72	72	104	113	152	1028
Jordan	1	1	0	0	0	0	0	0	0	nd	nd	nd	nd	nd	nd	2
Kazakhstan	0	0	0	0	1	nd	0	0	2	nd	nd	0	0	2	0	5
Kenya	1247	891	950	692	894	880	181	457	406	nd	85	258	35	195	150	7321
Kyrgyzstan	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Lebanon	0	0	0	0	0	0	2	0	0	nd	0	nd	nd	nd	nd	2

(continued)

Table 11.1 (continued)

Country	Year															Total all years
	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	
Libya	28	34	18	10	0	1	12	nd	nd	nd	3	3	2	nd	nd	111
Malta	0	2	5	0	nd	nd	0	3	2	nd	nd	nd	nd	nd	4	16
Mauritania	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Mexico	1	0	1	0	1	0	4	4	0	9	7	9	9	9	3	57
Monaco	nd	1	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	1
Montenegro	nd	nd	4	6	5	3	4	nd	nd	1	3	3	1	4	2	36
Morocco	91	106	106	92	81	85	111	113	107	139	134	163	160	170	114	1772
Nepal	185	208	244	237	217	311	325	575	886	708	824	1371	1433	1531	1463	10,518
Nicaragua	0	0	0	0	0	0	0	0	0	1	1	4	1	1	1	9
Niger	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Nigeria	nd	nd	0	0	0	0	0	57	0	0	0	0	1	0	2	60
Oman	0	0	nd	nd	1	0	nd	1	0	1	1	0	1	0	2	7
Pakistan	nd	nd	nd	nd	nd	7	7	14	10	nd	nd	nd	nd	nd	nd	38
Paraguay	22	19	34	64	92	118	107	76	114	144	82	54	70	66	21	1083
Portugal	nd	5	nd	nd	0	0	8	5	13	17	11	14	23	10	13	119
North Macedonia	nd	12	9	5	4	11	20	13	2	12	4	7	7	9	7	122
Romania	nd	0	1	1	1	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	3
Saudi Arabia	0	1	4	4	3	10	5	8	7	8	17	32	41	31	31	202
Senegal	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Serbia	nd	nd	0	0	0	nd	2	1	2	nd	nd	nd	nd	nd	nd	5
Slovenia	nd	0	0	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Somalia	293	413	857	734	1165	1045	936	394	290	nd	507	583	nd	nd	nd	7217
South Sudan	1013	1867	3567	4285	2840	7472	2364	5012 4353	11,862 10,468	9166	1907	582	758	1117	3141	40,079
Spain	nd	nd	196	176	nd	106	276	213	235	153	179	193	255	246	199	2427

Sri Lanka	nd	nd	nd	nd	0	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
The Sudan	2563	2584	3894	3810	2829	3415	2389	5153	7418	6957	4880	3310	2788	1827	3713	57,530
Syrian Arab Republic	47	38	55	25	20	36	30	17	18	19	16	17	11	3	19	371
Tajikistan	15	32	23	25	26	47	63	46	25	40	53	15	14	19	14	457
Thailand	0	1	2	1	1	0	2	5	1	2	1	4	2	1	nd	23
Tunisia	27	19	23	17	30	44	38	37	55	36	55	63	100	121	120	785
Turkey	nd	nd	nd	23	23	22	33	13	30	36	23	13	41	20	32	309
Turkmenistan	0	0	0	1	0	0	0	0	0	nd	nd	nd	nd	nd	nd	1
Uganda	101	29	31	35	34	32	141	86	77	78	72	200	38	0	504	1458
Ukraine	0	nd	0	1	0	0	0	2	1	1	nd	2	3	3	1	14
Uruguay	3	1	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	4
Uzbekistan	41	34	49	38	34	42	37	38	28	25	26	13	5	1	6	417
Venezuela	23	43	40	33	37	9	7	9	15	15	15	18	17	41	58	380
Yemen	132	56	44	nd	5	15	nd	nd	0	nd	0	nd	nd	nd	nd	252
Zambia	nd	nd	0	0	0	0	0	0	0	nd	nd	nd	nd	nd	nd	0
Total per year	13,809	17,092	22,497	22,500	23,954	30,800	28,275	46,129	76,058	58,257	44,901	52,939	62,671	62,711	58,872	606,644

nd no data

poorest people living in remote rural areas in the country [46]. Reported cases of VL in Nepal are restricted mainly to 13 districts, which are located southeast of the Terai region in the country bordering the districts of Bihar state in India that has endemic disease [47]. Between 1980 and 2007, total reported cases in Nepal was 23,368 [47], with reported endemicity in poor rural areas [48]. From 1995 to 2010, reported cases of VL in Georgia was 1919 of which 1052 cases were from Tbilisi [49] where urban transmission appeared to be encouraged by the shape of the city, which is outstretched along banks of river Mtkvari, mostly in areas near forests and hills. Wild animals such as jackals and foxes frequently appear from here, facilitating synanthropic association with stray dogs and domesticated dogs [49], which are reservoirs of *Leishmania* parasite [50].

VL in India is usually a disease of the rural poor [51] and occurs generally in deprived/indigent communities living on the peripheries or suburbs of villages where more accessibility to sandfly vectors is provided [52, 53]. Most reported cases are from the state of Bihar [52]. Movement of the disease from southern parts of India occurred in the first 50 years of the C20th, with endemic reports in eastern states of Bengal, Assam, and Bihar [53]. Recent epidemiology of the disease in the country shifted from east to west, recording new foci in eastern Uttar Pradesh [54], Himachal Pradesh [55], and Uttarakhand [56], all of which have currently become endemic for the disease [57].

Regions prone to TL are Africa (especially in Tunisia, Morocco, and Ethiopia), Latin America (mostly in Colombia, Ecuador, Brazil, Venezuela, Bolivia, and Peru), the Middle East (largely in Afghanistan, Pakistan, Iran, Iraq, Syria, and Saudi Arabia), the Mediterranean Basin, and Central Asia [19, 21, 24] (Table 11.2). Approximately 95% of TL cases are reported in the Americas, Central Asia, the Mediterranean basin, and Middle East [25]. Cases of TL are mainly reported in countries such as Pakistan, Brazil, Peru, Saudi Arabia, Afghanistan, Bolivia, Tunisia, Syria, Algeria, Iran, Colombia [26], Argentina [5, 27], Costa Rica, and the Sudan [28], with an estimated one million people developing the disease annually [25, 26, 28]. Brazil accounts for 38.9% of the TL cases reported in the Americas, with cases reported in all states of the country, which shows adaptation of both parasites and vectors to human environments [29, 30]. From 1990 to 2013, the total number of cases of TL reported was 635,399, with an average incidence of 15.7 cases per 100,000 inhabitants [31]. Although, officially, cases reported annually in the country does not exceed 30,000 [28]. In the state of Amazonas, which has the highest burden of TL [32], the southern part shares more concentration of the disease with wide distribution between urban and rural areas [33]. In Panama, TL is regarded as a serious health issue and among the most ubiquitous parasitic zoonosis, with an estimate of 3000 new cases per year. There are ~60–100 cases per 100,000 inhabitants, although this number is likely to be underestimated by 50% [34], and infection is concentrated among the marginalized population [34, 35]. The disease is endemic in rural Bolivia [36] where the number of cases reported in 2006 was 33 new cases per 100,000 inhabitants [37]. TL is endemic in 7 of the country's 9 administrative departments, with 2909 cases of the disease reported in three provinces that make up the Department of La Paz [38]. Konate et al. [39] reported 2608 cases of TL from

Table 11.2 Breakdown of cases of cutaneous (tegumentary) leishmaniasis per country from 2005 to 2019

Country	Year															Total all years
	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	
Afghanistan	55,225	38,407	32,065	34,912	29,392	19,065	23,621	33,894	31,293	32,145	32,937	24,585	30,319	19,689	12,752	450,301
Albania	nd	2	0	6	1	0	1	0	1	1	1	2	7	3	3	28
Algeria	10,293	10,847	13,106	10,678	7523	5423	6428	7418	11,742	10,173	10,666	8442	6764	14,379	30,227	164,109
Argentina	241	303	306	241	334	138	90	173	140	166	163	208	201	257	282	3243
Armenia	0	0	0	0	0	0	0	0	0	nd	nd	nd	nd	nd	nd	0
Azerbaijan	43	16	10	35	18	15	33	19	31	45	33	14	22	17	15	366
Belize	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Bhutan	1	0	2	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	3
Bolivia	2052	3127	2283	2222	2231	1683	2016	1767	1598	1440	1487	1650	3153	3152	2657	32,518
Bosnia and Herzegovina	nd	nd	0	0	0	0	0	0	0	nd	nd	nd	nd	nd	1	1
Brazil	15,484	16,432	17,528	12,690	19,395	20,418	18,226	23,547	21,395	22,397	21,989	20,123	21,530	22,397	26,685	300,236
Bulgaria	nd	0	nd	0	0	0	0	nd	nd	nd	nd	nd	nd	nd	nd	0
Burkina Faso	nd	615	712	1075	729	741	947	1134	1389	nd	nd	nd	nd	827	827	8996
Cameroon	nd	nd	51	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	51
Central African Republic	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Chad	82	46	8	nd	nd	nd	nd	nd	nd	nd	nd	nd	200	nd	nd	336
China	0	0	0	0	0	0	5	6	6	nd	nd	nd	nd	nd	nd	17
Colombia	5913	6362	7764	10,966	7541	11,586	9353	9757	9063	14,818	15,420	9595	13,331	16,241	18,043	165,753
Costa Rica	601	1247	2224	1148	1171	2150	1950	1453	1376	1143	2025	818	1807	1870	1676	22,659
Côte d'Ivoire	nd	nd	0	0	nd	nd	nd	0	0	0	0	0	0	0	1	1
Croatia	1	1	nd	0	4	nd	5	2	1	nd	nd	3	5	1	2	25
Cyprus	0	0	3	0	1	nd	0	5	0	nd	nd	0	0	4	nd	13

(continued)

Table 11.2 (continued)

Country	Year															Total all years
	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	
Democratic Republic of the Congo	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Djibouti	0	0	0	0	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Dominican Republic	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Ecuador	1104	1237	1632	1197	1479	1175	873	1512	1385	1629	1735	1479	1185	1536	1925	21,083
Egypt	1811	1161	566	643	2243	1444	464	1260	864	318	174	471	nd	nd	nd	11,419
El Salvador	230	50	44	13	20	29	16	21	17	4	0	31	36	46	24	581
Eritrea	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Ethiopia	1665	882	1011	425	534	342	85	95	225	nd	nd	nd	nd	nd	nd	5264
France	nd	5	4	3 3	5	8	5	5	6	8	2	4	3	3	0	58
Gambia	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Georgia	0	0	0	0	1	0	5	6	6	5	3	11	1	2	5	45
Ghana	nd	nd	nd	nd	nd	nd	nd	nd	129	nd	nd	0	17	0	14	160
Greece	nd	0	1	2	2	1	1	3	2	2	7	4	6	0	2	33
Guatemala	1167	1044	775	835	562	258	664	572	549	410	519	494	287	602	1243	9981
Guinea	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Guinea-Bissau	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Guyana	19	27	21	396	132	64	4	7	15	15	9	14	6	6	7	742
Honduras	1985	1636	1854	2671	2040	1936	2074	1927	1736	1362	1502	1759	855	1300	1574	26,211
India	nd	nd	nd	nd	nd	72	172	146	139	nd	187	172	156	114	152	1310
Iran	8161	15,485	12,208	14,536	18,607	16,024	16,054	20,947	19,426	22,921	24,586	26,824	26,493	24,517	21,419	288,208
Iraq	7056	11,426	18,854	17,566	17,525	2691	1648	2486	2978	3113	2086	1250	655	1339	2435	93,108
Israel	nd	276	218	240	226	342	321	353	310	230	133	884	904	575	686	5698
Italy	nd	70	nd	47	76	80	95	26	24	22	22	23	22	36	73	616

Jordan	69	150	155	126	70	182	146	103	136	155	148	244	354	181	162	2381
Kazakhstan	55	39	131	185	24	14	14	12	24	4	9	0	0	1	7	519
Kenya	47	44	25	29	160	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	305
Kuwait	nd	4	1	7	0	2	14	4	7	12	8	nd	nd	nd	nd	59
Kyrgyzstan	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Lebanon	2	0	0	0	3	2	0	2	5	6	1	0	0	0	1	22
Libya	6744	2977	2815	2662	1632	516	505	1500	1327	2273	1691	1800	3884	7180	3819	41,325
Malawi	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Mali	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	55	55	86	77	273
Malta	0	4	1	0	nd	nd	0	0	1	11	nd	16	13	3	4	53
Mauritania	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Mexico	1014	576	842	447	479	418	970	567	342	456	387	284	443	431	861	8517
Monaco	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Montenegro	nd	nd	0	0	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Morocco	5455	11,834	6802	4903	2809	2555	2592	2877	4319	8707	6013	5128	3290	3361	3039	73,684
Namibia	nd	nd	0	0	0	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Nepal	16	19	4	1	0	0	0	0	0	0	0	1	0	0	0	41
Nicaragua	3321	3722	4343	5423	1925	1649	3035	1884	3146	3497	4047	5826	3719	2125	3521	51,183
Niger	nd	521	600	107	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	1228
Nigeria	nd	nd	55	nd	0	5	0	0	95	nd	nd	7	6	4	8	180
Oman	0	1	nd	nd	0	0	nd	2	0	3	4	7	6	4	8	35
Pakistan	53,574	19,361	8024	27,151	16,647	14,634	3717	6598	12,938	1387	3731	3631	4390	4151	10,441	190,375
Panama	920	1143	1164	1198	930	1581	1762	1811	3221	3221	1866	2109	2199	3774	1649	28,548
Paraguay	52	84	92	135	122	124	162	177	184	262	251	92	535	457	591	3320

(continued)

Table 11.2 (continued)

Country	Year															Total all years
	2019	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	
Peru	5349	6062	6631	7271	5459	6231	6948	6969	11,204	7612	6513	7650	10,183	8248	8067	110,397
Portugal	nd	nd	nd	0	0	0	1	1	2	nd	nd	nd	nd	nd	nd	4
North Macedonia	nd	0	0	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Saudi Arabia	1096	921	1007	1337	1490	2190	1988	1464	1951	4129	2549	2321	3286	3602	3883	33,214
Senegal	39	6	17	44	32	35	nd	nd	nd	nd	nd	9	10	8	5	205
Slovenia	nd	0	0	0	0	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0
Spain	nd	nd	165	167	40	100	nd	18	10	10	10	16	6	6	16	564
Sri Lanka	nd	2189	980	883	1283	1367	nd	nd	nd	148	326	399	384	291	234	8484
The Sudan	nd	3299	4107	3011	3503	1053	336	206	111	752	nd	nd	nd	nd	nd	16,378
Suriname	130	118	132	255	241	390	382	594	nd	291	138	159	161	116	231	3338
Syrian Arab Republic	71,704	80,215	53,232	47,377	50,972	53,876	71,996	55,894	58,156	42,172	46,348	29,140	17,709	18,732	21,951	719,474
Tajikistan	55	40	28	60	83	128	86	26	13	3	22	38	13	nd	nd	595
Thailand	0	1	1	0	1	1	nd	nd	nd	nd	nd	nd	nd	nd	nd	4
Tunisia	7058	7467	4902	6065	6611	3368	4113	5376	5114	3811	1737	2750	2742	9030	15,373	85,517
Turkey	nd	1554	nd	1474	1986	1678	2268	1898	1803	2237	1696	1161	1499	1892	1926	23,072
Turkmenistan	105	212	182	52	49	55	59	158	81	nd	nd	89	101	69	73	1285
Ukraine	0	nd	0	0	0	0	0	2	2	0	nd	3	1	2	4	14
United States of America	nd	nd	nd	nd	nd	nd	nd	nd	nd	0	2	0	3	6	2	13
Uzbekistan	638	643	749	766	508	311	505	204	253	605	362	155	61	110	150	6020
Venezuela	2041	2612	2326	2057	2013	1661	1638	2104	1551	1952	2248	2392	2464	2553	2550	32,162
Yemen	4440	4763	4525	9120	4063	5000	3823	3629	2124	3234	1801	1090	1116	1975	2023	52,726
Total per year	277,058	261,285	217,288	234,857	214,927	184,811	192,216	202,621	213,966	199,317	197,594	165,432	166,598	177,311	203,406	3,108,687

nd no data

2006 to 2012 in the city of Ouagadougou, Burkina Faso. A recent evaluation of the disease in Ouagadougou from 2012 to 2016 by Sawadogo et al. [40] reported a total of 96 active cases across the years. Cases of TL have been reported in all regions of Colombia where a total of 102,010 cases occurred between 2007 and 2016. The Amazon region in the country recorded the highest incidence of TL cases, while the Andean region recorded the highest number of TL cases reported within this period [41].

11.4 Current Treatment Regimens for VL and TL

In treating VL, considerations are on the following: the use of specific antileishmanial drugs and vigorous management of accompanying or secondary parasitic or bacterial infections, malnourishment, anemia, and reduced blood volume [3]. Treatment options available are insufficient and of unacceptable standards, owing to issues associated with efficacy, adverse effects, proliferating drug resistance, expense, and required hospitalization for treatment to be completed [58–60]. The display of drugs for treating VL is limited to antimonials and meglumine antimonite, paromomycin, oral miltefosine, and amphotericin B, the latter having two formulations in the form of free deoxycholate and lipid. Liposomal amphotericin B is the latest formulation of this drug [3, 24, 58, 61]. Efficacy rates reported for these drugs were above 90% with 93–95%, 85%, and 90% recorded in India, East Africa, and Ethiopia, respectively [24]. Pentavalent antimonials (Sb^v) were the first-line drug for the treatment of the disease [62]. In the mid-1990s, retrogression in efficacy of the drug was reported in Bihar where 39–69% of cases treated were only successful at doses of 20 mg/kg/day given for 30 days [63]. However, the drug remained effective in other endemic countries such as Bangladesh [64] and the Sudan [65]. In the Sudan, 95% or higher cure rate was achieved with Sb^v given as 30 days regimen [65]. Pentamidine became the second-line treatment for cases of VL, especially to prevent the problem posed by resistance to Sb^v in Bihar [66]. Its efficacy has also declined over the years, with 70% efficacy reported [66, 67]. In Bihar, patients who showed resistance to Sb^v demonstrated 83% possible cure and 73% absolute cure at posttreatment of 6 months [68]; while in the Sudan, a limited number of patients resistant to Sb^v showed resistance to pentamidine [69]. Its treatment toxicity, resistance, declining efficacy, and high cost led to its abandonment in India as well as being categorized as an unsuitable alternative to pentavalent antimonials [70].

Amphotericin B (AmB) was reintroduced in India for treating resistant VL [67], and it recorded high efficacy rate of >95% when used at a regimen of 0.75–1 mg/kg, given as 15–20 intravenous injections [67, 71]. AmB recorded similar efficacy in Uganda, and it is currently adopted as a second-line drug in East Africa [72]. However, a limitation of the drug is that it is unsuitable for use in interior remote areas, lacking or with inadequate, hospital facilities [62]. Overcoming the disadvantages of AmB led to lipid formulations of AmB [67] that include AmB colloidal dispersion [ABCD (Amphocil)], liposomal AmB (AmBisome), AmB lipid complex

[ABLC (Abelcet)] [73], and Fungisome [74]. All these formulae have been tested successfully in countries such as Kenya, Brazil, and India and from continental Europe. AmBisome has been used in Ethiopia [75] and the Sudan [67, 76] under basic field conditions: it also showed 89–100% efficacy in Bihar and 96% cure rate in northeastern India [77]. AmBisome monotherapy has shown treatment failures in the Sudan [78] and in Ethiopia where lack of efficacy was reported for patients co-infected with HIV [75]. Treatment regimen with AmBisome differs from one region to another: for example, in Southern Asia, 10 or 15 mg/kg AmBisome regimens can be used, and elsewhere it is 20 mg/kg [79]. Abelcet, another lipid formulation that has been used in India, has a cure rate was 90–100% [67]. However, it showed an efficacy of 33–42% when tried on HIV-co-infected patients in Europe [80, 81]. First usage of Amphocil was in Brazil where it was reported to have an efficacy rate of 90% and 100% at 10 and 14 mg/kg doses, respectively [82]. Different regimens of Amphocil used in clinical studies at doses of 7.5, 10, and 15 mg/kg produced 96–97% cure rates in India at posttreatment of 6 months [83]. A new AmB formulation, Amphomul, was safe and greatly effective on VL patients in a small study in India involving three varying short-course dosing plans [84]. Additionally, Fungisome at 14–21 mg/kg produced a cure rate of between 90.9 and 100% in India [85], while at 10 mg/kg, a 90% cure rate was recorded in patients with the disease [86].

The alkylphospholipid derivative, miltefosine, tested on patients aged 12 years in India showed 94% cure rate after 28 days [87]. In Northern Ethiopia, only one study on the drug was conducted, with a reported cure rate of 94% initially in HIV-negative patients and 78% initially in HIV-co-infected patients [88]. Limitations of this drug include its long half-life, which encourages resistance [89], VL relapse after treatment as reported in Nepalese patients [90], and post-kala-azar dermal leishmaniasis (PKDL) development in two patients in India reported after successful treatment of the disease with the drug [68]. Others limitations include reactions such as vomiting, anorexia, nausea, and diarrhea, all of which are usually brief and resolved as treatment continues [87], and teratogenic actions in animals that make it unsuitable for pregnant women [91].

In Kenya, first successful use of paromomycin (an aminoglycoside broad-spectrum antibiotic) in treating VL was carried out in the 1980s [92]. Cure rates of 94.6% were achieved in patients with the disease in India between 2003 and 2004, using a regimen of 15 mg/kg of paromomycin administered 21 days intramuscularly [93]. Short-course treatment with the drug produced cure rates of 84.3% and 92.8% in patients with VL in India, with doses of 11 mg/kg/day for 14 and 21 days, respectively [94]. Nonetheless, usage of paromomycin as a single treatment drug can pose problems such as relapse, treatment failure, and resistance development [66]. Sitamaquine, a primaquine analogue characterized by its significant antileishmanial activity and administered orally, was developed by the Walter Reed Army Institute in collaboration with GlaxoSmithKline as WR6026 [62]. Phase II trial of WR6026 on 120 VL patients in India at doses of 1.75–2 mg/kg/day for 28 days achieved a cure rate of 89–100% [66, 95]. In Kenya, a dose of 1 mg/kg/day for 28 days achieved a 50% cure rate [95]. In Brazil, a dose of 1 mg/kg/day did not

achieve any cure, whereas 4 days at a dose of 2 mg/kg/day resulted in an efficacy rate of 67%, but an increased dose of 2.5 mg/kg/day decreased efficacy [96]. Side effects of Sitamaquine include nephritis, headache, and abdominal pains, which occur mostly in patients that received higher doses [62]. Although the last 10 years have seen improvements in new drug development for VL, there still exists the need for more novel cures that are safe, effective, and easily transported to remote places across the globe [61].

The clinical manifestations of TL and the diameter and position of the sores/lesions are factors to be considered in treatment [42]. To prevent the disease from evolving to the severe and destructive mucosal form, it is important to treat the disease adequately and timely [43]. Drugs used for treating TL include sodium stibogluconate, systemic or intralesional pentavalent antimonials, meglumine antimonials (Glucantime®) [42], N-methylglucamine antimoniate (NMG) [44], and pentamidine [45]. First-choice drugs used in treating TL are the pentavalent antimonials (Sb^v), but failures are reported in various regions of the globe. Sb^v has two formulations, namely, sodium stibogluconate and meglumine antimoniate [10]. Sb^v prevents fatty acid oxidative and glycolytic pathways in amastigotes, although the mechanism of this action remains unknown [46]. Treatment of patients with a dose of 20 mg/kg/day for 20 and 30 days achieved a cure rate of 94.2% and 7% failure in Bolivia [47]. In Brazil, a dose of 5 mg/kg/day for 30 days had a cure rate of 86% in patients, with a reported failure at 16% [48]. Patients treated in Colombia with a dose of 20 mg Sb/kg/day for 10 and 20 days showed cure rates of 61% and 67%, respectively, with drug failure reported to be 39% [49]. Significant aftereffects of the drug include arthritis, muscle pain, cardiotoxicity, and nephrosis, with the latter two occurring primarily in older patients [10]. Pentamidine has been used to treat patients with *L. (V.) guyanensis* infection in French Guyana and Marseille, France, at a dose of 4 mg/kg on days 1 and 3, with treatment failures of 5% and 25% reported, respectively. Treatment failure corresponded to the commencement of treatment, 5% failure was observed when treatment was given within 1 month of infection, and 25% failure was observed when treated was commenced later [50]. In a treatment trial in Peru for *L. (V.) braziliensis* infection, 2 mg/kg every other day for seven injections recorded a 35% cure rate and a 58% failure in patients [51]. Clinical trials that involved local treatment with various formulations of paromomycin showed cure rates of 64% in Colombia [52] and 88.6% in Guatemala, although variation in the cure rates was likely attributed to the species of *Leishmania* predominant in a particular area [53]. TL was initially treated in 2005 with miltefosine in Colombia [54]. Treatment of *L. (V.) braziliensis* TL with oral miltefosine at a dose of 2.5 mg/kg/28 days and intravenous/hypodermal antimonial at a dose of 20 mg/kg/20 days was compared in Bolivia, with cure rates reported to be 88% and 94%, respectively [55]. Treatment trial with oral miltefosine in Colombia, where *L. (V.) panamensis* is the prevalent species, showed a cure rate of 91%, which was similarly reported for antimonials [56]. An efficacy rate of 53%, which is notably lower than antimonials, was reported in Guatemala where *L. (V.) braziliensis* and *L. (L.) mexicana* [56] predominate. In Brazil, miltefosine recorded a cure rate of 71.4% for *L. (V.) guyanensis* infection treatment [57].

Liposomal amphotericin B was evaluated in Brazil in an open clinical trial with doses ranging from 17 to 37 mg/kg, administered in 7–14 days. This regimen registered a cure rate of 70% after 3 months although a drop to 65% was recorded after 4 months of treatment owing to the one reported relapse. However, doses above 30 mg/kg achieved a final cure rate of 75% [58]. Concerning azoles, a 28-day administration of oral ketoconazole at 600 mg was assessed in 120 and 8 patients in Guatemala and Belize, respectively, and recorded 30% and 25% cure rate in patients having *L. (V.) braziliensis* infection and 89% and 100% cure rates in patients with *L. (L.) mexicana* infection. Patients with *L. (V.) panamensis* infection showed similar responses to ketoconazole and antimonials [59].

A more recent study in Brazil by Carvalho and colleagues [3] described the efficacy of systemic meglumine antimoniate against TL and proposed it as a future therapeutic drug for the disease. However, they suggested that improvements in drug delivery were necessary, to improve adherence to treatment, reduce side effects, and optimize cost-efficiency.

11.5 An Introduction to Vaccine Development for VL and TL

Considering the issues associated with drugs for treating VL, scientists continue to examine preventive vaccines for the disease [97, 98]. The possibility of developing a potent vaccine is helped by the knowledge that individuals who heal and recover from active infection are protected from reinfection [3]. Developing an efficient vaccine against VL depends on producing strong T-cell immunity [99]. Current research on preventing VL infection is directed at identifying novel preventive antigens that are capable of conferring immunity to uninfected persons [100]. Possible prophylactic vaccines to be considered should contain antigens that have the potential to activate cells in healthy persons not exposed to the parasites [101, 102]. Different experimental vaccines have been tested, especially in rodent and/or dog models [100].

In the first generation of vaccines, dead parasites were inoculated [103–105] in a process called leishmanization [105]. The killed parasites were either tested alone or combined with various adjuvants [100, 105]. Alum-precipitated, autoclaved *L. major* (ALM) administered together with Bacillus Calmette-Guerin (BCG) adjuvant showed promise as VL and post kala-azar dermal (PKDL) leishmaniasis vaccines [106]. When patients with persistent PFDL were given antimonial therapy combined with alum-precipitated autoclaved *L. major* (ALM)-BCG adjuvant, there was an improvement in cure rates, and the degree of relapse was lowered compared to treatment with antimonial alone [107]. Initial studies with this vaccine received recommendations for further evaluation for their prophylactic and therapeutic actions on VL and PKDL [108].

Second-generation vaccines include genetically modified parasites or recombinant proteins that were encoded by viruses expressing leishmanial genes, while third-generation vaccines include plasmid DNA-based vaccines encoding genes

containing eukaryotic promoter vectors [103, 104]. Recently, a third-generation vaccine that used simian adenovirus (ChAd63) was shown to efficiently evoke a broad range of CD8+ T-cell specific for *Leishmania* antigens. It contains two genes of *Leishmania donovani* encoding the KMP-11 and HASPB proteins [109]. Osman et al. [109] showed that intramuscular doses of 1×10^{10} and 7.5×10^{10} ChAd63-KH into mice effectively produced IFN-γ and activated dendritic cells and were safe. However, all of these experimental vaccines have not yet progressed to human trials [100].

Other vaccines developed using molecular approaches include polyprotein and heterologous prime boost vaccines. Q protein, Leish-111f, Leish-110f, and KSAC are multiphase or polyprotein compounds/products that have shown improved defense against experimental VL [98]. Q protein contains five genetically fused antigenic determinants (Lip2a, Lip2b, H2A, and P0 proteins) and was evaluated alongside BCG or CpG-ODN in mice and dogs [110, 111]. In dogs, 90% protection was recorded with Q protein + BCG along with a potent DTH reaction, while in cats, Q protein + CpG-ODN motifs induced permanent or lasting IgG production [110, 111]. Heterologous DNA-prime protein boost has also been used successfully against VL with antigens such as ORFF, cysteine proteinases, and GP63, although they remain untested in clinical trials [98]. Against *Leishmania infantum*, 60% immunity was obtained for dogs immunized with DNA-LACK primer/VV-LACK boost [112]. Similar levels of immunity were also reported in studies by Tewary et al. and Donji et al. [113, 114] with the murine intracutaneous model for VL.

The failure to develop TL vaccines stems from the lack of knowledge of memory responses and healing mechanisms produced following infections with *Leishmania* and how to evaluate these responses [115]. The availability of genome sequences has transformed vaccine development by enabling in silico identification of $CD4^+$ and/or $CD8^+$ T-cell epitopes [116, 117]. For example, Silva et al. identified $CD4^+$ and $CD8^+$ T-cell epitopes within the proteome of *L. (Viannia) braziliensis* using an in silico approach [118]. The first generation of TL vaccines were based on live attenuated or killed parasites [119]. TL patients in Venezuela who received immunotherapy together with monthly intradermal injections of a combination vaccine that contained autoclaved promastigotes form of *L. mexicana amazonensis* [MHOM/VE/84/MEL and active BCG] recorded varying cure rates from 91.2 to 98.7%, averaging at 95.7% [120]. First-generation TL vaccines are useful for developing countries because of their low cost of production [121], although maintaining consistent quality control could be a barrier [119]. Difficulties could be experienced when conditions for culture are standardized to produce the immunogen, with parasite subculturing leading to decreases in infectivity [122, 123].

Second-generation TL vaccines consist mainly of defined products to produce immune responses [119]. Crude or purified *Leishmania* have been used to generate immune responses. Currently explored *Leishmania* vaccines include antigenic parasite proteins produced in recombinant form [124]. A plethora of *Leishmania* proteins have been purified or expressed as recombinant proteins for evaluation as potential vaccines [119]. For example, receptors for C kinase (LACK) induced

resistance to *L. major* in immunized mice [125, 126]. Immunity against *L. major* infections has been achieved using the N-terminal region of H2B histone protein and the complete protein [127]. Vaccination of monkeys with Histone HI and Montanide ISA 720 adjuvant resulted in the reduction of lesions caused by *L. major* infection with increased self-healing [128]. GP63, a *Leishmania* parasite cell surface metalloprotease and a purified protein conferred strong immunity in mice against both *L. mexicana* and *L. major* infection, but immunity in monkeys was limited [129, 130].

Third-generation TL vaccines mainly consist of genetic immunization, and their stability offers practical advantages in tropical regions [119]. The gene encoding for GP63 protein was the first reported TL DNA vaccine, and it induced robust immunity in mice against *L. major* infection [131, 132]. Immunization of BALB/c mice with the iron superoxide dismutase protein of *L. donovani* reduced *L. amazonensis* parasite burden through induction of IFN-γ [133]. *L. infantum* H2A, H2B, H3, and H4 histone gene products and the A2, KMP11, and HSP70 proteins [134] were able to control *L. major* and *L. braziliensis* infections in BALB/c mice [135, 136]. Recently, Domínguez-Bernal et al. [137] reported that a HisAK70 DNA vaccine offered cross-immunity against *L. amazonensis* infection in BALB/c mice.

11.6 Conclusions

VL and TL remain major neglected tropical diseases reported globally. Their incidence is likely to increase with climate change and vector spread and population migration. Both diseases urgently need research into new safe and affordable drugs and effective prophylactic vaccines.

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