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Neglected tropical diseases: diagnosis, clinical management, treatment and control

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Summary

Branded in 2005, "neglected tropical diseases" have gained traction in terms of advocacy, interest for research, enhanced funding and political will for their control and eventual elimination. Starting with an initial set of 13 neglected tropical diseases – seven helminth, three bacterial and three protozoal infections – the list considerably expanded to more than 40 diseases that now also includes viral, fungal and ectoparasitic infections. In this review, we provide a comprehensive overview of the neglected tropical diseases, their causative agents and the current geographical distribution, including their importance for the general practitioners seeing returning travellers and migrants in Switzerland. We characterise the most important of the neglected tropical diseases in terms of at-risk population, estimated number of infections, annual mortality rates and global burden, including current knowledge gaps. With an emphasis on neglected tropical diseases due to helminths, protozoa and ectoparasites, we review common diagnostic methods and current recommendations for treatment at the population level and the individual patient, thereby juxtaposing the situation in highly endemic countries on one side, with Switzerland on the other. We highlight the clinical presentation and management of the neglected tropical diseases in general and then elaborate on two examples, strongyloidiasis and leptospirosis. Our review provides a global perspective of neglected tropical diseases and we hope that it will prove useful for the general practitioner and clinician in Switzerland and elsewhere to enhance their suspicion index, differential diagnosis, clinical management and treatment, including referral to specialised clinics and laboratories when need be.

Key words: *neglected tropical disease; diagnosis; clinical management; treatment; control; general practitioner; Switzerland*

Introduction

Diseases such as malaria, tuberculosis and HIV/AIDS are well known causes of major global mortality, morbidity and burden. Their negative impact on the social and economic development of the most severely affected countries has been emphasised [1–4]. Indeed, these "big three" are responsible for several million deaths every year and tens of millions of disability-adjusted life years (DALYs), which, in turn, exacerbates poverty [5–8]. Interestingly though, in two short assays pertaining to science, medicine and society, along with a comprehensive 25-year review of drug development efforts, published in leading journals a decade ago [9–11], malaria, tuberculosis and HIV/AIDS were still considered neglected diseases. In the meantime, funding for research and development of new tools has come to scale, and public-private partnerships and numerous initiatives have been put into place for the prevention, control and eventual elimination of the "big three". Clearly, the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria, in 2002, considerably altered the funding landscape, and large-scale implementation of control interventions has saved millions of lives [7, 12–14].

However, a host of viral, bacterial, ectoparasitic, fungal, helminth and protozoal diseases that occur mainly in the tropics and subtropics remain truly neglected, and hence the phrase "neglected tropical diseases" [15–18] is applied to characterise these diseases. Reasons for this neglect are many-fold. Among others, important issues are the intimate connection of these diseases with poverty, geographical isolation, stigmatisation, paucity of data regarding local and global burden estimates, insufficient political and financial resources for their control, lack of lobbies for the most vulnerable population groups who are most severely affected by these diseases, and fragmented funding mechanisms [16, 19–22].

In the present review, we provide an overview of the neglected tropical diseases from a global perspective. We first address the question why and when this "brand-name" was

coined, including implications for advocacy, policy, public health and research. Second, we put forth a comprehensive list of neglected tropical diseases, their causative agents and geographical distribution and highlight their importance for tourists, returning travellers, long-term expatriates and migrants in Switzerland. Given the large and growing size of the list, we then focus on the most important neglected tropical diseases, and characterise them in terms of the at-risk population, number of infections, mortality rates and global burden estimates. Knowledge gaps are identified and briefly discussed. The centre-piece of our review pertains to the diagnosis, clinical management and treatment of neglected tropical diseases. Emphasis is placed on helminth and protozoal infections and we focus on the situation in Switzerland within the global perspective. Hence, throughout our review, we highlight issues that are of particular relevance for the general practitioners, clinicians and reference laboratory personnel in Switzerland. We believe that issues discussed are central also for other countries in Europe, North America and elsewhere.

Neglected tropical diseases

Origin of a 'brand-name'

A search on PubMed, performed on 19 September 2012, using the term "neglected tropical diseases", revealed 730 hits. This search brought to bear that the first articles, editorials and personal viewpoints using the term "neglected diseases" in the title appeared in 2001/2002. For example, an interesting case study from India discussed the need for establishing local research and development capacity for neglected infectious and tropical diseases, emphasising medicines [23]. The lack of funds for research and development and the obviously limited interest of the industry to invest in diseases of poverty made this term necessary for researchers as well as public and private investors. In the same vein, a systematic review covering a 25-year period (1975–2000) revealed that virtually no new chemical entities were specifically developed for neglected diseases [10]. Hence, the need for efficacious, safe, easy-to-use and affordable drugs was discussed at a conference organised by Médecins Sans Frontières in early 2002 [9]. The pivotal role of public-private partnerships to stimulate discovery, development and deployment of new drugs for neglected diseases was stressed. This resulted, in 2003, in the creation of the Geneva-based Drugs for Neglected Diseases *initiative* (DND*i*; http://www.dndi.org) [10, 11, 24]. Of note, the paucity of accurate, robust and rapid diagnostics for one of the "big three" motivated the Bill & Melinda Gates Foundation (BMGF) to put forward a 5-year start-up grant, which helped to set up, also in 2003 and again based in Geneva, the Foundation for Innovative New Diagnostics (FIND; http://www.finddiagnostics.org/). FIND has gradually expanded its portfolio of activities with a growing emphasis on developing and validating novel diagnostics not only for tuberculosis, but also the other two of the "big three", as well as truly neglected diseases, such as human African trypanosomiasis, leishmaniasis and Chagas disease [25, 26].

The first published paper with the full term "neglected tropical diseases" in the title was a piece put forward by Molyneux, Hotez & Fenwick, in November 2005 in *PLoS Medicine* [15], closely followed by another landmark paper in the same journal written by Hotez and colleagues [16]. The authors discussed a strategy of regular, large-scale administration of drugs for morbidity control due to neglected tropical diseases, and outlined how this drug-based intervention could be integrated within the control of the "big three". An accompanying expert commentary critically examined the strengths and limitations of the proposed strategy [27]. A subsequent review by Hotez and colleagues entitled "Neglected tropical diseases", published in the *New England Journal of Medicine* clearly demonstrated that the term "neglected tropical diseases" had become mainstream [28].

Of note, in October 2007, the Public Library of Sciences published the inaugural issue of a new open-access journal, *PLoS Neglected Tropical Diseases* [29]. As of late September 2012, more than 1,600 original research papers, editorials, expert opinions, viewpoints and other magazine-type articles have been published. In *Swiss Medical Weekly*, thus far, only a single article has been published when entering the search term "neglected tropical diseases" [30].

What is meant by neglected tropical diseases?

Neglected tropical diseases refer to a group of mainly chronic, debilitating and often stigmatising diseases that primarily affect the poorest of the poor living in remote rural and deprived urban settings of tropical and subtropical countries [16, 18, 21, 31–33]. Typical features of the neglected tropical diseases are their intricate interrelationships with poverty and social-ecological systems [21, 34, 35]. These diseases are associated with negative effects on the course and outcome of pregnancy, delayed physical and intellectual development during childhood and reduced working productivity in older age [28, 36].

Evolving scope of the neglected tropical diseases

The two seminal papers published in 2005 and 2006 provided a list of 15 neglected tropical diseases, 13 of which were deemed of particular importance in terms of annual mortality rates and global burden [15, 16]. This list of 15 diseases formed the initial scope of *PLoS Neglected Tropical Diseases*. Included were nine helminth infections (cysticercosis/taeniasis, drancunculiasis [guinea worm], food-borne trematodiasis, lymphatic filariasis, onchocerciasis, schistosomiasis and the three main soil-transmitted helminthiases [ascariasis, hookworm infection and trichuriasis]), three protozoal infections (Chagas disease, human African trypanosomiasis and leishmaniasis) and three bacterial infections (Buruli ulcer, leprosy and trachoma).

Interestingly, at the time, the World Health Organization (WHO) featured some additional diseases on their list of neglected tropical diseases, namely cholera/epidemic diarrhoeal disease, dengue/dengue haemorrhagic fever and endemic treponematoses (e.g., yaws, pinta and syphilis) [18, 37]. Meanwhile, the list of neglected tropical diseases has been further expanded and currently comprises over 40 diseases, which is reflected in the escalating scope of *PLoS Neglected Tropical Diseases* [38]. Table 1 provides a com-

prehensive overview of these 40+ neglected tropical diseases, stratified into helminth, protozoal, bacterial, fungal, viral and ectoparasitic infections. For each disease, the causative agent(s) and the current endemic areas are summarised. Moreover, the presence, management and relative importance of these diseases for tourists, long-term travellers and migrants in Switzerland is given, based on a combination of national statistics, case reports, the authors' collective expertise and experience and useful input from two anonymous referees.

Global burden of neglected tropical diseases

Table 2 summarises the main parasitic neglected tropical diseases (helminth and protozoal infections) in terms of the at-risk population, number of infections, annual mortality rates and global burden of disease estimates. For comparison, the "big three" are also listed in table 2. Some authors have argued that the collective global burden due to the 13 most important neglected tropical diseases exceeds that of malaria and tuberculosis and is close to that of HIV/AIDS [16], which spurred advocacy for the integrated control of neglected tropical diseases [17, 39, 40]. Indeed, according to data presented by Hotez and colleagues, which is largely derived from technical reports of WHO and the annex table 3 of the world health report 2004, the collective global burden of the initial set of 13 neglected tropical diseases amounts to 56.6 million DALYs, which is higher than that due to malaria (46.5 million DALYs) and tuberculosis (34.7 million DALYs). However, it must be noted that there are considerable uncertainties regarding global burden estimates, and the neglected tropical diseases proved particularly challenging for estimating global burden estimates [18, 41–43]. For example, two different WHO sources reveal a more than 300-fold difference regarding the estimated global burden due to hookworm infection. While the lower estimate is as little as 59,000 DALYs [44], the upper estimate is 22.1 million DALYs [45] with the difference mainly explained by whether or not anaemia is partially accounted for by hookworm infections. It is hoped that current efforts to re-estimate the global burden of more than 175 diseases, injuries and risk factors will fill current gaps and resolve discrepancies [46].

Diagnosis

While the primary indices of an infection are mostly the presentation of clinical signs and symptoms, outcomes due to an infection with neglected tropical diseases are often unspecific, if signs and symptoms are present at all. Yet, an accurate and early diagnosis is important for adequate patient management and treatment [47–49]. The lack of rapid, accurate, simple-to-use, point-of-care tests for many of the neglected tropical diseases is an important feature for their general neglect and the under-appreciation of their disease burden [50, 51].

The diagnosis of neglected tropical diseases, and particularly the detection of the endoparasitic infections emphasised here, is primarily based on well established and widely used laboratory techniques, such as the examination of blood, stool and urine samples under a microscope. As shown in table 3, the mainstay to detect intestinal helminths and protozoan infections is the visualisation of helminth eggs or larvae and protozoan cysts or trophozoites, respectively, in stool smears [50, 52–54]. Lymphatic filariasis, acute or congenital Chagas disease and human African trypanosomiasis are diagnosed through the microscopic identification of microfilariae or trypomastigotes in blood and other body fluids [55–60]. Leishmaniasis is confirmed by the isolation and visualisation of the amastigote parasite stage from tissue [61–63]. Noteworthy, the reliable identification of parasitic infections requires in-depth training for specimen preparation, and expertise and experience for subsequent microscopic examination. While microscopy of parasites is considered as highly specific, its sensitivity depends on the intensity of infection, which is a function of the number of parasitic elements in a sample [49, 64, 65].

For the diagnosis of chronic Chagas disease, echinococcosis, toxocariasis and trichinellosis, the direct documentation of the infecting parasite is difficult and immuno-assays as well as physical imaging techniques or trichinelloscopy, respectively, are applied [54, 60, 66–68].

Immunodiagnosis is applicable for most of the neglected tropical diseases, but may lack sensitivity and/or specificity. While some serological tests show excellent performance (i.e., for the diagnosis of Chagas disease and visceral leishmaniasis), or are particularly useful when parasite loads are low or for patients from non-endemic countries (i.e., for the diagnosis of schistosomiasis and strongyloidiasis), others are highly error-prone. For example, antibodies produced against one helminth species are known to cross-react with antigens from other helminths [66, 69]. Moreover, antibodies produced against infectious agents do not give any indication of the severity of infection [70], and are often detectable for several months or years after an infection has cleared, and hence do not allow to distinguish between current and past infections [71–74]. In European clinics specialised for returning travellers and migrants, immunodiagnosis applied in combination with physical imaging or microscopy, and particularly in consideration of disease history and clinical outcome, is a valuable tool for the assessment of neglected tropical diseases. The commercial availability of standardised test kits is still the exception rather than the norm. Indeed, often high-valuable in-house antigen preparations and tests are in use, but efforts are underway to develop rapid diagnostic tests that can be used at the point-of-care in developing countries [51].

The development and use of molecular tools such as polymerase chain reaction (PCR) tests for the diagnosis of neglected tropical diseases is the focus of multiple research groups, but the commercial availability of DNA amplification kits is rare. Moreover, the isolation of parasite DNA from stool or tissue is challenging, cumbersome and quite often not fruitful at all [72]. Nevertheless, progress has been made with molecular high-throughput multiplexing. For example, multiplex real-time PCR assays have been developed and are increasingly being utilised in a specialised laboratory in Leiden, the Netherlands for differential diagnosis of helminths and intestinal protozoan infections [75–77]. Hence, according to some authors, multi-parasitic screenings based on molecular assays might one day replace microscopy and immunodiagnosis, at least in spe-

Table 1: Neglected tropical diseases, stratified by helminthic, protozoal, bacterial, fungal, viral and ectoparasitic infections, including causative agents, current endemic areas and their relative importance for tourists, long-term travellers and migrants in Switzerland.

Neglected tropical disease	Causative agent(s)	Endemic areas	Transmission in Switzerland[a]	Management[b]	Tourists[c]	Long-term travellers[c]	Migrants[c]	Reference(s)
Helminth infections								
Cysticercosis/ taeniasis	*Taenia solium*	Worldwide (pig breeding), mostly South and Central America, sub-Saharan Africa, Asia		°	((+))	(+)	+	[115, 116]
	Taenia saginata	Worldwide (cattle breeding), mostly sub-Saharan Africa, Middle East, South and Central America	✓		((+))	(+)	+	[117]
	Diphyllobothrium latum	Worldwide, mostly Northern Hemisphere (America, Asia, Europe)	✓		((+))	(+)	+	[118]
Dracunculiasis	*Dracunculus medinensis*	Ethiopia, Mali, South Sudan (Chad)			(+)	(+)	((+))	[119, 120]
Echinococcosis	*Echinococcus granulosus*	Global distribution (pastoral communities), particularly South America, Mediterranean, Eastern Europe, Near and Middle East, East Africa, Central Asia, China, Russia	✓	°	(+)	(+)	+	[116, 121, 122]
	Echinococcus multilocularis	Central and Eastern Europe, Near East, Russia, China, Northern Japan	✓	°°	((+))	((+))	((+))	[116, 121, 122]
Enterobiasis	*Enterobius vermicularis*	Global distribution (highest rates in developing countries)	✓		+	+	+	[123]
Food-borne trematodiasis								
- Clonorchiasis	*Clonorchis sinensis*	China, Republic of Korea, Taiwan		°	((+))	(+)	+	[124, 125]
- Fascioliasis	*Fasciola gigantica*, *F. hepatica*	Bolivia, Chile, Cuba, Ecuador, Egypt, France, Islamic Republic of Iran, Peru, Portugal, Spain	✓ (*F. hepatica*)	°°	((+))	(+)	+	[124, 125]
- Intestinal fluke infections	*Echinostoma* spp., *Fasciolopsis buski*, *Metagonimus* spp., *Heterophyidae*	Bangladesh, Cambodia, China, India, Indonesia, Lao PDR, Malaysia, Philippines, Taiwan, Thailand, Vietnam		°°	((+))	(+)	+	[124]
- Opisthorchiasis	*Opisthorchis felineus*	Kazakhstan, Russian Federation, Siberia, Ukraine		°°	((+))	(+)	+	[124, 125]
	Opisthorchis viverrini	Lao PDR, Thailand, Vietnam, (Cambodia)		°°	((+))	(+)	+	[124, 125]
- Paragonimiasis	*Paragonimus* spp.	Cameroon, China, Costa Rica, Ecuador, Equatorial Guinea, Gabon, Guatemala, India, Japan, Lao PDR, Liberia, Malaysia, Mexico, Nepal, Nigeria, Pakistan, Panama, Peru, Philippines, Republic of Korea, Siberia, Sri Lanka, Taiwan, Thailand, Vietnam		°°	((+))	(+)	+	[124, 125]
Loiasis	*Loa loa*	Central and West Africa (rainforest and some savannah areas)		°°°	((+))	(+)	+	[126]
Lymphatic filariasis	*Wuchereria bancrofti*, *Brugia malayi*, *B. timori*	Africa, Asia, Central and Southern America		°°	((+))	(+)	+	[127]
Mansonellosis	*Mansonella perstans*, *M. streptocerca*, *M. ozzardi*	Central and South America, Caribbean, sub-Saharan Africa		°°	((+))	(+)	(+)	[59]
Onchocerciasis	*Onchocerca volvulus*	Africa, small foci in Southern and Central America		°°	((+))	(+)	+	[127]
Schistosomiasis	*Schistosoma haematobium*	Sub-Saharan Africa, Middle East, some islands in the Indian Ocean		°	(+)	+	++	[128, 129]
	S. guineensis, *S. intercalatum*	Parts of Central and West Africa		°	(+)	((+))	(+)	[128, 129]
	S. japonicum	China, Indonesia, Philippines		°	((+))	(+)	+	[128, 129]
	S. mansoni	Sub-Saharan Africa, parts of South America (e.g., Brazil), some Caribbean islands		°	(+)	+	++	[128, 129]
	S. mekongi	Cambodia, Lao PDR		°	((+))	(+)	+	[128, 129]
Soil-transmitted helminthiasis								
- Ascariasis	*Ascaris lumbricoides*	Global distribution	✓		(+)	+	++	[83, 130]
- Hookworm infection	*Ancylostoma duodenale*, *Necator americanus*	Global distribution	✓		(+)	+	++	[83, 130]
- Strongyloidiasis	*Strongyloides stercoralis*	Global distribution	✓	°°	(+)	+	++	[54, 83]
- Trichuriasis	*Trichuris trichiura*	Global distribution	✓		(+)	+	++	[83, 130]
Toxocariasis	*Toxocara canis, T. cati*	Global distribution	✓	°	((+))	(+)	+	[54, 131]

Trichinellosis	*Trichinella spiralis* and other *Trichinella* spp.	Global distribution	✓	°	((+))	(+)	(+)	[54, 67]
Protozoal infections								
Chagas disease	*Trypanosoma cruzi*	Latin America		°°	((+))	(+)	+-++	[56, 60]
Human African trypanosomiasis	*Trypanosoma brucei gambiense*, *T. brucei rhodesiense*	Africa		°°°	((+))	((+))	((+))	[58, 109, 133]
Intestinal protozoan infections								
- Amoebiasis	*Entamoeba histolytica*	Global distribution (highest rates in developing countries)	✓	°	(+)	+	++	[134]
- Balantidiasis	*Balantidium coli*	South America, Middle East, Philippines, Papua New Guinea		°	((+))	(+)	+	[132]
- Giardiasis	*Giardia intestinalis* (syn.: *G. duodenalis, G. lamblia)*	Global distribution (highest rates in developing countries)	✓	°, in case of treatment failure	+	++	++	[135]
Leishmaniasis	Visceral leishmaniasis: *Leishmania donovani*, *L. chagasi*, *L. infantum* (Muco-)cutaneous leishmaniasis: *L. major*, *L. tropica*, *L. braziliensis*, *L. mexicana* and other *Leishmania* spp.	Indian subcontinent, Asia, Africa, Mediterranean basin, South America	✓ (Ticino)	°°°	(+)	+	+	[61-63]
Bacterial infections								
Bartonellosis	*Bartonella henselae* and other *Bartonella* spp.	Global distribution		°	((+))	(+)	(+)	[136]
Bovine tuberculosis in humans	*Mycobacterium bovis*	Global distribution (highest rates in developing countries)		°°	((+))	((+))	(+)	[137]
Buruli ulcer	*Mycobacterium ulcerans*	Australia, Guyana, Malaysia, Mexico, Papua New Guinea, Peru, Sri Lanka, West and Central Africa		°°	((+))	((+))	(+)	[138, 139]
Enteric bacterial infections								
- Cholera	*Vibrio cholerae*	Recent outbreaks in Southern and Central Africa (Angola, Democratic Republic of the Congo, Guinea-Bissau, Republic of the Congo, Tanzania, Zimbabwe), Central America (Dominican Republic, Haiti), Asia (Cambodia, Indian subcontinent, Malaysia, Papua New Guinea, Thailand)		°	(+)	(+)	(+)-+	[140]
- ETEC infection	Enterotoxigenic *Escherichia coli* (ETEC)	Global distribution (highest rates in developing countries)	✓		++	++	++	[141]
- Salmonellosis	Non-typhoidal salmonellosis: *Salmonella enterica* serovars *S.* Enteridis, *S.*Typhimurium and other serovars Enteric fever: *S.enterica* serovars *S.* Typhi, *S.* Paratyphi	Global distribution (highest rates in developing countries)	✓		+	+	++	[142]
- Shigellosis	*Shigella dysenteriae*, *S. boydii*, *S. flexneri*, *S. sonnei*	Global distribution (highest rates in developing countries)	✓		+	+	+	[143]
Leprosy	*Mycobacterium leprae*	Brazil, China, Guinea, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Philippines, Sudan, Vietnam, other tropical and sub-tropical regions		°°°	((+))	(+)	(+)	[144]
Leptospirosis	*Leptospira interrogans* group	Global distribution (highest rates in developing countries)			(+)	(+)	(+)	[98]
Relapsing fever	*Borrelia recurrentis, B. duttoni* and other *Borrelia* spp.	Africa (highest rates), parts of the Americas, Asia, Europe			(+)	(+)	(+)	[145]
Trachoma	*Chlamydia trachomatis*	Africa, Middle East, Mexico, large parts of Asia and South America, Australia			((+))	((+))	((+))	[146]
Treponematoses (bejel, pinta, syphilis, yaws)	*Treponema pallidum*	Global distribution (highest rates in tropical regions)	✓ (syphilis)	°	(+)	(+)	+	[147]
Fungal infections								
Mycetoma (“Madura foot”)	Various fungi (eumycetoma) and bacteria (actinomycetoma, pseudomycetoma)	“Mycetoma belt” between latitudes of 15° South and 30° North (Africa, India, Yemen, Central and South America)		°	((+))	((+))	(+)	[148, 149]
Paracoccidiomycosis	*Paracoccidioides brasiliensis*	Brazil (80%), Venezuela, Colombia, Ecuador, Argentina, Mexico, parts of Central America		°°	((+))	((+))	((+))	[150]
Viral infections								

Dengue	Dengue fever virus (genus: *Flavivirus*)	South-East Asia, Central and South America, Pacific Islands, Indian subcontinent, occasionally in parts of Africa and Northern Australia			++	++	++	[151]
Japanese encephalitis	Japanese encephalitis virus (genus: *Flavivirus*)	South-East Asia (rice agriculture, pig farming), Indian subcontinent, sporadically in Northern Australia and the Western Pacific		°°	((+))	((+))	(+)	[152, 153]
Yellow fever	Yellow fever virus (genus: *Flavivirus*)	West and Central Africa, South America, occasionally in East Africa and Central America		°°	((+))	((+))	(+)	[151, 154]
Rabies[d]	Rabies virus (genus: *Lyssavirus*)	Global distribution (highest incidence in Africa, Asia, South and Central America, Eastern Europe)	✓ (European bat-rabies)	°°	(+)	++	++	[155]
Rift Valley fever	Rift Valley fever virus (genus: *Phlebovirus*)	Arabian Peninsula and whole Africa (especially North-East, West and South-Central Africa, including Madagascar)		°°	((+))	((+))	((+))	[156]
Viral haemorrhagic fevers	Important *Arenaviridae*: Lassa virus, Chapare virus, Guanarito virus, Junín virus, Machupo virus, Sabiá virus *Bunyaviridae*: Crimean-Congo haemorrhagic fever virus (HFV), Hanta viruses including Puumala virus *Filoviridae*: Ebola virus, Marburg virus *Flaviviridae*: Omsk HFV, Kyasanur forest disease virus	South America (Argentina, Bolivia, Brazil, Venezuela) Lassa virus: West Africa (Guinea, Liberia, Nigeria, Sierra Leone) Crimean-Congo HFV: South-Eastern Europe (especially Bulgaria), Turkey, South-West Russia, Arabian Peninsula, Central Asia, Africa Hanta virus: Global distribution *Filoviridae*: Angola, Democratic Republic of the Congo, Gabon, Kenya, Republic of the Congo, Sudan, Uganda Omsk HFV: West Siberia Kyasanur forest disease: India	✓ (Hantavirus: Nephropathia epidemica)	°°°	((+))	((+))	((+))	[157] [158] [159] [160] [161] [162] [162]
Ectoparasitic infections								
Myiasis	Parasitic fly larvae (*Calliphoridae, Oestridae, Sarcophagidae* and others)	Global distribution (highest incidence in tropical and subtropical countries)			(+)	+	+	[163]
Scabies	*Sarcoptes scabiei*	Global distribution (highest incidence in tropical and subtropical countries)	✓		+	+	+	[164]

[a] Consultation with specialist in tropical medicine: ° = helpful; °° = important; °°° = necessary.
[b] ✓ (CH): can be transmitted autochthonously in Switzerland and/or neighbouring European countries.
[c] +-+++ = existing to heavy risk; (+) = low risk; ((+)) = very low risk; – = no risk.
[d] Grading refers to dog or other animal bites.

cialised laboratories in the industrialised world [78]. An advantage of microscopy though, is that it is an untargeted approach, and hence well trained laboratory technicians might detect an infection that would have been missed by a more targeted molecular approach [50].

As discussed in the next section under the example of clinical management of strongyloidiasis, to avoid false negative results due to the lack of sensitivity of any single diagnostic technique, examination of multiple specimens obtained over consecutive days and the combination of different methods is recommended [74, 79, 80]. The development of advanced and standardised sensitive diagnostic approaches that are practicable and affordable not only in well equipped laboratories of the North, but also in developing country settings is of prime importance to identify and tackle neglected tropical diseases [81].

Clinical management

General considerations

The signs and symptoms of the various neglected tropical diseases are perhaps as diverse as the different infectious agents involved in their pathogenesis. The spectrum of possible clinical presentations ranges from asymptomatic infection to fulminant life-threatening or to chronic debilitating conditions. As virtually all organs can be affected, a high suspicion index and knowledge about the different groups of tropical pathogens can assist clinicians for an early recognition and timely diagnosis of these infections in returning travellers, long-term expatriates, migrants and patients from endemic areas, based on knowledge of the respective geographical epidemiology. Clinical signs and patient complaints are often indistinctive, thus seldom allowing a specific diagnosis based on history and clinical examination alone without knowledge of epidemiology and further diagnostic work-up.

Table 4 comprises common clinical presentations of selected parasitic neglected tropical diseases. Despite many similarities, some infections exhibit unique features clinicians should know about, as they may be encountered in the tropics as well as in temperate regions (e.g., in Switzerland and elsewhere in Europe). Due to space restrictions in this review, only two neglected tropical diseases are presented in greater detail: (i) strongyloidiasis (a helminth infection that might be fatal in immunocompromised patients) and (ii) leptospirosis (a bacterial infection that might cause outbreaks and is emerging in Europe). For a third example – Chagas disease (caused by a protozoon infection that is emerging in Switzerland due to the growing number of Lat-

in American migrants) – the reader is referred to a recent excellent review by Jackson and Chappuis [82].

Strongyloidiasis

While the three main soil-transmitted helminth species (i.e., *Ascaris lumbricoides*, *Trichuris trichiura* and hookworm) are easily diagnosed and cause mainly chronic, often asymptomatic infections that usually respond well to empiric treatment with albendazole or mebendazole, particular attention has to be paid to the diagnosis and clinical management of *Strongyloides stercoralis* (threadworm). Figure 1 shows the life cycle of *S. stercoralis*. In contrast to the common soil-transmitted helminths [54, 83], *S. stercoralis* is able to replicate within the intestines of infected individuals for long time periods (autoinfection) [54, 84]. The larvae hatch in the gut and are able to penetrate the intestinal mucosa, from where they may spread to all organs [85]. As these tissue-invasive larvae carry bacteria on the surface, their migration can lead to systemic infections with septicaemia, leading to a high fatality rate (hyperinfection syndrome). Such dissemination may occur even decades after the first contact, so that the absence of recent travel to endemic areas is never sufficient to exclude strongyloidiasis as a potential differential diagnosis in symptomatic patients. Asymptomatic strongyloidiasis must be ruled out in patients requiring immunosuppressive treatment who may have experienced exposure, as this parasite may flare up as a life-threatening infection. Symptoms may be absent or unspecific in healthy individuals, but can rapidly evolve in immunosuppressed hosts [86].

The diagnosis of *S. stercoralis* is challenging, as microscopy of stool samples usually fails to detect the larvae (table 3). Hence, more laborious techniques have to be employed (e.g., agar plate culture and Baermann funnel technique), but the sensitivity of these methods is usually limited [80]. Multiple examinations and the combination of techniques enhance the diagnostic sensitivity [79, 80, 87, 88]. The direct demonstration of larvae in bronchoalveolar lavages, bronchial or duodenal aspirates or faecal specimens proves *S. stercoralis* infection, but lacks sensitivity in

Table 2: Current estimates for the global burden due to the most important neglected tropical diseases caused by helminthic and protozoal infections. For comparison, the "big three" are also shown.

Disease	At-risk population (millions)	No. of people infected (millions)	No. of people with morbidity (millions)	Death (thousands)	Global burden (thousand DALYs)	Reference(s)
Neglected tropical disease						
Helminth infections						
- Soil-transmitted helminthiasis						
Ascariasis	5,416	807–1,221	350	3–60	1,817–10,500	[17, 83, 130]
Hookworm infection	5,346	576–740	150	3–65	59–22,100	[17, 83, 130]
Trichuriasis	5,307	604–795	220	3–10	1,006–6,400	[17, 83, 130]
Strongyloidiasis	n.d.	30–100	n.d.	n.d.	n.d.	[83]
- Lymphatic filariasis	>1,000	120	43	0	5,777	[17, 127]
- Schistosomiasis	779	207	120	15-280	1,702–4,500	[17, 165]
- Food-borne trematodiasis						
Clonorchiasis	601	15.3	1.1	5.6	275	[43, 124]
Paragonimiasis	292	23.2	5.3	0.2	197	[43, 124]
Fascioliasis	91	2.6	0.3	0	35	[43, 124]
Opisthorchiasis	80	8.4	0.3	1.3	74	[43, 124]
Intestinal fluke infections	n.d.	6.7	0.9	0	84	[43, 124]
- Onchocerciasis	120	37	n.d.	0.05[a]	484	[127, 166]
- Cysticercosis/taeniasis	n.d.	n.d.	n.d.	n.d.	>2,000	[117]
- Echinococcosis	n.d.	n.d.	n.d.	n.d.	>285	[122]
- Mansonellosis	581 (Africa)	>114 (Africa)	n.d.	n.d.	n.d.	[59]
- Dracunculiasis	n.d.	0.001	0.001	n.d.	<100	[119]
- Enterobiasis	n.d.	n.d.	n.d.	n.d.	n.d.	[123]
- Loiasis	>29.6	>9.2	n.d.	0	n.d.	[167]
- Toxocariasis	n.d.	n.d.	n.d.	n.d.	n.d.	[131]
- Trichinellosis	n.d.	n.d.	n.d.	n.d.	n.d.	[67]
Protozoal infections						
- Leishmaniasis	350	12	n.d.	70	2,090–2,400	[44, 61, 168]
- Chagas disease	120	8	n.d.	14	667	[56]
- Human African trypanosomiasis	>60	>0.03	n.d.	<10	n.d.	[169]
- Intestinal protozoan infections						
Amoebiasis	n.d.	n.d.	n.d.	40–100	n.d.	[53, 134]
Giardiasis	n.d.	n.d.	200	n.d.	n.d.	[135]
Balantidiasis	n.d.	n.d.	n.d.	n.d.	n.d.	[132]
The "big three"						
Malaria	2,211	n.d.	515	889–1,272	34,000–46,490	[8, 44, 170, 171]
HIV/AIDS	n.d.	33.3	n.d.	1,800–2,777	58,500–84,500	[44, 171, 172]
Tuberculosis	n.d.	n.d.	>8.8	1,464–1,566	34,200–34,700	[44, 171, 173]

[a] In the 'Onchocerciasis Control Programme' (OCP) area [174]. n.d. = not determined.

Table 3: Clinical hints and methods for the diagnosis of parasitic neglected tropical diseases (due to helminth, protozoal and ectoparasitic infections)[a].

Neglected tropical disease	Diagnosis in travel clinics	Reference(s)
Helminth infections		
Cysticercosis/taeniasis	Suspicion upon neurological symptoms plus cystical central nervous system (CNS) lesions. Combination of questioning, parasitological examination, immunodiagnosis, molecular methods or imaging. • Stool microscopy • Perianal egg detection (Graham's test applying adhesive tape) • Morphological examination of tapeworms from purges • Coproantigen detection by enzyme-linked immunosorbent assay (ELISA) • Serology: detection of species-specific circulating antibodies against *T. solium* • Molecular methods/copro-DNA assays (i.e. polymerase chain reaction [PCR])	[74]
Dracunculiasis	Visual detection of a blister and the emerging female worm	[175]
Echinococcosis	Suspected in patients with abdominal fullness and/or dyspnoea leading to detection of cystic lesions. Immunodiagnostic methods (for primary serological screenings, to confirm clinical findings and for follow-up of patients after surgical or pharmacological treatment) in combination with physical imaging techniques (for definitive diagnosis). Detection of serum antibodies and parasite antigen with: • Indirect haemagglutionation tests (IHAT) • ELISA • Immuno-blotting Physical imaging methods: • Radiology • Ultrasonography • Computed axial tomography (CT scanning) • Nuclear magnetic resonance (NMR) imaging to detect cysts PCR tests can help to identify *Echinococcus*-specific DNA in biological specimens resected or biopsied from patients.	[66]
Enterobiasis	Perianal itching (irritability of small children), leading to detection of eggs and adult worms. • Adhesive tape technique	[176, 177]
Food-borne trematodiasis	Various abdominal symptoms leading to detection of eggs, adult worms, and parts of worms under a microscope, immunological and molecular methods. • Faecal examination to detect eggs (sedimentation, Kato-Katz, ether-concentration, McMaster, FLOTAC techniques) • Immunodiagnosis to detect worm-specific antibodies or antigens in serum or stool (counter-immunoelectrophoresis, ELISA) • Molecular methods to amplify DNA from eggs or other biological components or products of the worms (PCR) Non-invasive imaging techniques to examine organ damage: • Ultrasonography • Magnetic resonance imaging • Computerised tomography • X-ray	[69, 74, 125]
- Clonorchiasis	Detection of eggs in faeces or bile aspirates. Imaging techniques to identify adult worms and lesions in the hepatic ducts.	[74]
- Fascioliasis	Abdominal discomfort and fever. • Detection of eggs in faeces or bile aspirates • Imaging techniques to identify hepatic lesions and "tunnel-like" migration paths	[74]
- Intestinal fluke infections	Faecal examination to detect parasite eggs (note that the parasite eggs of *Fasciola*, *Fasciolopsis* and *Echinostoma* and of *Opisthorchis*, *Clonorchis* and *Heterophyidae* are difficult to differentiate): • Stoll's dilution • Formalin-ether concentration • Direct faecal smear • Kato-Katz technique Recovery of adult worms from purges after treatment.	[178]
- Opisthorchiasis	• Detection of eggs in faeces or bile aspirates • Imaging techniques to identify adult worms and lesions in the hepatic ducts • Detection of eggs in faeces or bile aspirates • Imaging techniques to identify adult worms and lesions in the hepatic ducts	[74] [74]
- Paragonimiasis	• Detection of eggs in sputum • Chest X-ray to identify nodules and opacities in the lung parenchyma or signs of pleuritis and pneumothorax	[74]

Filariasis	The suspicion is based on cutaneous and lymphatic signs and symptoms, whereas the diagnosis of filariae relies on the detection of microfilariae in blood or skin snip samples taken at a specific time at the day or night. New molecular techniques (PCR) for the detection of filaria DNA are becoming more common but are not yet commercially available or routinely applied.	[59]
- Loiasis	Identification of clinical characteristics such as Calabar swelling or worm crossing the subconjunctival eye. Detection and quantification of sheathed microfilariae in blood taken around noon. • Thin and thick blood film stained with haematoxylin • Concentration techniques, including sedimentation or filtration of blood may be required, if the microfilariaemia is low Ultrasonography to visualise the movements of living adult filarial worms. Immunodiagnostic methods often lack sensitivity and they might cross-react with other filarial species. PCR to amplify species-specific DNA is accurately detecting microfilariaemia and occult loiasis.	[179, 180]
- Lymphatic filariasis	Microscopic examination of blood (taken at night) for sheathed microfilariae using low power: • Counting chamber technique • Thin and thick blood film stained with Giemsa • Knott concentration technique • Membrane (Nucleopore) filtration technique Immunochromatographic tests (ICT) as card or ELISA are sensitive and specific for the detection of *W. bancrofti* microfilariae carriers. Molecular diagnostic techniques include PCR to detect filarial DNA in human blood samples (taken at night) and molecular xenomonitoring (MX) to detect parasite DNA in pooled mosquitoes or human blood by PCR.	[181, 182]
- Onchocerciasis	Diagnosis relies on the detection of unsheathed microfilariae under the skin: • Detection of unsheathed microfilariae in skin snips under the microscope • Diethylcarbamazine (DEC)-based patch test, which provokes an itchy papular rash when read 24-48 hours after application Newer techniques have been developed: • Dipstick test to detect *O. volvulus*-specific antigen • Three recombinant antigens cocktail • PCR	[127, 183]
- Mansonellosis	Microscopic examination of blood (taken anytime at day or night) for unsheathed microfilariae from *M. perstans* and *M. ozzardi.* • Counting chamber technique • Thin and thick blood film stained with Giemsa or haematoxylin • Knott concentration technique • Membrane filtration Microscopic identification of unsheathed microfilariae from *M. streptocerca* in skin snips stained with haematoxylin or Giemsa.	[59]
Schistosomiasis	Often asymptomatic, occasionally acute generalised disease with (Katayama) fever. Microscopic detection of schistosome eggs in faeces or urine is the current mainstay of diagnosis in endemic settings. The miracidium-hatching test can also be used to test infections. Imaging techniques are used to identify schistosomiasis characteristic periportal and bladder fibrosis. • Ultrasonography • Computed tomography • Magnetic resonance imaging Most commercially available immunodiagnostic kits are not very sensitive or specific and cannot distinguish between past and present infection. A commercially available point-of-care cassette test to detect circulating cathodic antigen (POC-CCA) in urine is a sensitive tool for *S. mansoni* diagnosis. PCR-based assays that are specific and highly sensitive have been developed for the detection of schistosome DNA in human excreta or sera and plasma, but need further validation and standardisation. In patients with clinical signs but negative stool or urine examinations a biopsy of bladder or rectal mucosa must be used for diagnosis.	[71, 184, 185]
	For *S. haematobium*: filtration (Nucleopore) of 10 ml of urine or sedimentation (after centrifugation) of urine sample to detect eggs under a microscope	[186]
	For *S. mansoni*, *S. japonicum*. *S. mekongi*, *S. guineensis* and *S. intercalatum*: detection of species specific eggs in stool using • Kato-Katz technique • Formalin-ether concentration • Sedimentation technique • FLOTAC (first experiences for *S. mansoni*)	[187-189]
Soil-transmitted helminthiasis	Often clinically asymptomatic. Eggs or larvae of soil-transmitted species are routinely detected by microscopic examination of stool samples. Immunological or molecular approaches are not widely applied due to cross-reactions and technical constraints to isolate DNA from stool samples, respectively.	[49, 54]

- Ascariasis	Eggs can be detected by the application of the following methods: • Kato-Katz technique • Formalin-ether concentration • Sedimentation technique • McMaster technique • FLOTAC	[65, 187, 188, 190, 191]
- Hookworm disease	Signs and symptoms of anaemia. Eggs can be detected by the application of the following methods: • Kato-Katz technique • Formalin-ether concentration • Sedimentation technique • McMaster technique • FLOTAC	[65, 187, 188, 190, 191]
- Strongyloidiasis	Gastrointestinal, cutaneous and respiratory signs and symptoms. Larvae can be detected by the application of the following methods: • Baermann method • Koga agar plate method Serology is considered a valuable tool for screening and evaluation of therapies in non-endemic target groups: • ELISA • IFAT • Western blot	[85, 192, 193]
- Trichuriasis	Eggs can be detected by the application of the following methods: • Kato-Katz technique • Formalin-ether concentration • Sedimentation technique • McMaster technique • FLOTAC	[65, 187, 188, 190, 191]
Toxocariasis	Cutaneous, respiratory or CNS (eye) symptoms. Since the human is not the definitive host, no worm eggs can be identified in stool samples. The diagnosis relies on immunodiagnosis, imaging techniques and biopsies of tissues and organs: • Immunoassay (EIA) using standardised *T. canis* excretory-secretory (TES) antigens from infective-stage larvae to diagnose visceral and ocular larva migrans • Western blot to confirm positive results • High resolution ultrasonography to reveal hypoechoic areas in the liver	[68, 194, 195]
Trichinellosis	Muscle pain and fever. Besides the interpretation of the clinical picture, diagnosis relies on the detection of non-specific parameters (eosinophilia, elevated level of muscle enzymes). Immunodiagnostic methods and trichinelloscopy of a small muscle tissue sample: • ELISA • Western blot • Counterimmunoelectrophoresis • Latex agglutination	[67, 196, 197]
Protozoal infections		

Chagas disease	Gastrointestinal and cardiac signs and symptoms. Trypanosomes can be detected in the peripheral blood during the acute phase of infection by microscopy. Trypomastigotes can be identified in: • Thick blood films • Buffy coat preparation (microhaematocrit technique) • Serum precipitate (Strout's technique) • Centrifugation of blood after lysis of red cells with 0.87% ammonium chloride To diagnose congenital infections, the following methods are applicable: • Microhaematocrit • PCR Diagnosis in newborns relies on: • Microscopic examination of cord blood or peripheral blood • Test for anti-*T. cruzi* IgG antibodies In the chronic phase of infection, the following techniques may be applied: • Xenodiagnosis • Blood culture • ELISA • Indirect immunofluorescencent antibody test (IFAT) • Indirect haemagglutination	[56, 198]
Human African trypanosomiasis	Cutaneous chancre and fever. Diagnosis relies on visualisation of parasites in blood, lymph or cerebrospinal fluid (CSF). Of note, it is not possible to discriminate *T. brucei gambiense* and *T. brucei rhodesiense* by microscopy. Clinical signs and serological or molecular methods can provide only indirect evidence of an infection and the presence of parasites must be confirmed before administering toxic treatment: • Examination of finger-prick blood • Thick blood film • Haematocrit centrifugation • Quantitative buffy coat technique combines haematocrit centrifugation with fluorescent detection (acridine orange) of trypanosomes • Mini anion exchange centrifugation technique (mAECT) to separate trypanosomes from red cells before centrifugation • Card agglutination trypanosomiasis test (CATT) for *T. brucei gambiense* • LATEX/*T. brucei gambiense* test • Immunofluorescence • ELISA • IHAT • PCR	[57, 109, 199]
Intestinal protozoan infections		
- Amoebiasis	History of diarrhoea, abdominal discomfort and fever. Cysts can be detected by the application of the following methods: • Fresh stool preparation • Formalin-ether concentration • Sedimentation technique Serological and molecular methods	[50, 53, 72]
- Balantidiasis	Large motile trophic ciliates can be detected in fresh diarrhoeic faeces and bronchoalveolar wash fluid. Cyst stages are more commonly found in formed stool. • Wet mount slide preparations • Concentration techniques (sedimentation or flotation) Trophozoites can also be obtained from biopsies of the margins of ulcers identified with proctosigmoidoscopy.	[50, 132]
- Giardiasis	Foul-smelling diarrhoea, bloating. Irritability (children). Cysts can be detected by the application of the following methods: • Fresh stool preparation • Formalin-ether concentration • Sedimentation technique Serological and molecular methods	[50, 52]

Leishmaniasis	The parasite species can be identified using culture and DNA identification. Cutaneous leishmaniasis: • Microscopy to identify amastigotes in biopsies, scrapings, or impression smears, staining with the panoptic May Grünwald-Giemsa stain or mouse anti-*Leishmania* immune serum and peroxidase coniugate • Growth of promastigotes in Novy-MacNeal-Nicolle culture • Serology has a limited application in the diagnosis of current cutaneous leishmaniasis and is not routinely used in clinical practice • PCR to detect parasite DNA in infected skin lesions Visceral leishmaniasis: • Microscopy to identify amastigotes in aspirates from lymph nodes, bone marrow or spleen • Culture from aspirates of spleen, bone marrow, lymph node, or liver • ELISA, IFA, Western blot, direct agglutination test (DAT), immunochromatographic test (ICT) • PCR to detect parasites in blood or organs	[61, 200-202]
Ectoparasitic infections		
Myiasis	Diagnosis of furuncular myiasis solely based on clinical grounds. Imaging techniques can support the identification of maggots within furuncles: • Dermoscopy • Ultrasonography • Colour Doppler sonography	[163]
Scabies	Clinical diagnosis by detection of severely itching burrows, lesions, papules, vesicles and pustules at typical predictor sites. Microscopic detection of the mite, ova, or faecal pellets is specific, but not very sensitive.	[203–205]

[a] It is important to note that any parasitological diagnosis should always consider the clinical history of the patient.

patients with low worm loads. Recent advantages in serology, the development of a faecal antigen-capture enzyme-linked immunosorbent assay (ELISA) for *S. stercoralis* and the ongoing validation of a PCR approach will help to further improve the diagnosis of strongyloidiasis [84, 88, 89]. Frequently affected organs are the gastrointestinal tract, the skin and the lungs, whereas the central nervous system (e.g., meningitis) is rarely affected (table 4). Possible symptoms and clinical observations are diarrhoea, abdominal bloating and tenderness, a skin rash, pruritus ani, wheezing on pulmonary auscultation and chronic cough. A distinctive, fast-moving cutaneous itchy eruption called "larva currens" is sometimes observed by the patient and peripheral blood eosinophilia is suggestive of parasitic infection, but not always present.

Disseminated infection should always be excluded in patients on immunosuppressive long-term treatment, especially organ transplant recipients (e.g., following renal transplantation), and in symptomatic individuals from endemic areas with a history of chronic alcohol abuse [90] or HTLV-1 co-infection, which is common in Japan, Jamaica, South America, sub-Saharan Africa and parts of Asia [91]. Corticosteroids appear to activate hormone receptors of *S. stercoralis* larvae and might mediate the development of a hyperinfection syndrome [92]. Hence, patients from endemic areas should be screened for asymptomatic strongyloidiasis before starting immunosuppressive medication. Due to the broad range of possible clinical presentations, the decision to treat a patient suspected of carrying *S. stercoralis* remains challenging. An indication for treatment is usually given if at least two of the following observational criteria are met: (i) pulmonary, abdominal and/or skin symptoms, (ii) elevated peripheral eosinophil count and (iii) positive serology [93]. However, all patients with a positive *S. stercoralis* serology prior to organ transplantation should be treated to avoid the development of a life-threatening hyperinfection syndrome. Recommended treatment options include albendazole and ivermectin, whereas the latter has become the drug of choice to treat strongyloidiasis [36, 92].

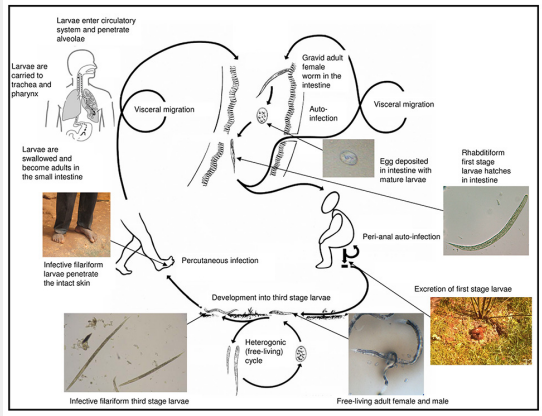

Figure 1

Life cycle of *Strongyloides stercoralis*. (Adapted from Olsen A, van Lieshout L, Marti H, Polderman T, Polman K, Steinmann P, et al. Strongyloidiasis – the most neglected of the neglected tropical diseases? Trans R Soc Trop Med Hyg. 2009;103:967–72 [85]. © Elsevier, 2009. Printed with permission).

Leptospirosis

Leptospirosis is probably the most common zoonosis affecting humans worldwide, with the highest disease burden encountered in tropical and subtropical countries [94, 95]. Figure 2 depicts its life cycle. In brief, bacteria of the genus *Leptospira* are spirochetes, able to survive in the environment for long time periods of time, especially in warm and humid areas [95]. Pathogenic *Leptospira* spp. infect many different kinds of mammals (e.g., rodents, pigs and dogs), which excrete the bacteria in their urine. Human infection occurs either by direct contact with infected animals or indirectly through contact with urine-contaminated water or soil. As the spirochetes easily penetrate human skin, farmers using traditional methods of irrigating their fields are at an elevated risk of infection [96]. While recre-

Table 4: Organ-specific clinical manifestations of selected neglected tropical diseases (helminth and protozoal infections).

Disease	Affected organ system						
	Central nervous system	**Cardio-vascular**	**Pneumo-logical**	**Gastro-intestinal**	**Hepato-biliary**	**Genito-urinary**	**Cutaneous**
Soil-transmitted helminthiasis							
Ascariasis	–	–	Cough, chest pain, wheezing (*Loeffler's syndrome* = pulmonary migration of maturating parasite)	Abdominal pain; in severe infection: nutritional deficiency, mechanical bowel obstruction (in children)	Rare: obstruction of the bile or pancreatic duct due to aberrant parasite migration	–	–
Hookworm infection	–	Light to moderate iron-deficiency anaemia; rare: cardiac failure due to severe anaemia in heavy infection	Cough, chest pain, wheezing fever (*Loeffler's syndrome* = pulmonary migration of maturating parasite)	Abdominal pain, indigestion, nausea, vomiting, diarrhoea constipation; in severe cases ascites due to protein deficiency	–	–	(*Cutaneous larva migrans*: animal hookworms)
Strongyloidiasis	–	–	Cough, chest pain, wheezing (*Loeffler's syndrome* = pulmonary migration of maturating parasite)	Diarrhoea, bloating, tenderness, blood in the stool	–	–	Skin rash, *larva currens*
Trichuriasis	–	–	–	Abdominal pain, bloody diarrhoea (leading to anaemia); in severe infection: rectal prolapse	–	–	–
Schistosomiasis							
Intestinal schistosomiasis	Rare: neuro-schistosomiasis due to aberrant oviposition	Pulmonary hypertension	Cough, chest pain, wheezing, fever (acute schistosomiasis = allergic reaction to maturating parasite)	Chronic or intermittent (bloody) diarrhoea, abdominal pain	Hepatic fibrosis, leading to portal hypertension, hepato-splenomegaly, gastrointestinal bleeding from varices	–	Initially: localised skin rash (penetration site of parasite at infection) Later: urticarial skin rash (allergic reaction to maturating parasite)
Urinary schistosomiasis	Rare: neuro-schistosomiasis due to aberrant oviposition	–	Cough, chest pain, wheezing, fever (acute schistosomiasis = allergic reaction to maturating parasite)	–	– (Hepatic fibrosis)	Painless haematuria, suprapubic discomfort, burning micturation, hydronephrosis risk for bladder cancer in chronic cases	Initially: localised skin rash (penetration site of parasite at infection) Later: urticarial skin rash (allergic reaction to maturating parasite)
Filariasis							
Dracunculiasis	–	–	–	–	–	–	Skin lesions, bacterial superinfection
Lymphatic filariasis	–	–	Cough, wheezing, fever *(tropical pulmonary eosinophilia (TPE)*)	–	–	Funiculitis, epididymitis, hydrocele	Lymphadenitis, lymphadenopathy, lymphangitis
Loiasis	Encephalopathy (treatment induced)	–	–	–	–	–	Angiooedema, ("Calabar" swellings), pruritus, subconjunctival migration of adult parasite

Mansonellosis	Visual impairment, loiasis-like eye lesions	–	Serositis	Abdominal pain	Hepatomegaly	–	Pruritus, papular eruptions, rash, reduced skin pigmentation, angiooedema, loiasis-like subcutaneous swellings (due to migration of adult worm)
Onchocerciasis	Eye lesions (keratitis, chorioretinitis, neuritis, blindness); encephalopathy (treatment induced)	–	–	–	–	–	Nodules, pruritus, rash, skin atrophy
Leishmaniasis							
Cutaneous/ mucocutaneous	–	–	–	–	–	–	Skin (or mucosal) lesions (ulcers)
Visceral (Kala azar)	–	–	–	Anorexia, weight loss	Fever, hepato-splenomegaly, pancytopenia, hepatitis		–
Human African trypanosomiasis	Meningo-encephalitis	Perimyocarditis	–	Diarrhoea	Fever, hepatomegaly, jaundice	–	Skin ulcer (“chancre”), rash, (“trypanid”), lymphadenopathy
Chagas disease	Meningo-encephalitis, space occupying lesions	Dilated cardiomyophathy, conduction abnormalities	–	Megacolon, megaoesophagus (Achalasia), resulting in weight loss, malnutrition	–	–	Romaña sign (periorbital swelling at conjunctival inoculation of the parasite)
Food-borne trematodiasis							
Paragonimiasis	Eosinophilic meningitis (ectopic parasite migration)	–	Chest pain, cough, haemoptysis, pleural effusion, infiltrations, pneumothorax	–	Hepatomegaly	–	Urticaria, aberrant subcutaneous migration of parasite
Clonorchiasis	–	–	–	Abdominal pain, diarrhoea	Fever, right upper quadrant pain, hepatomegaly, cholangitis, cholezystitis, chol-angiocarcinoma	–	Urticaria
Opisthorchiasis	–	–	–	Abdominal pain, diarrhoea	Fever, right upper quadrant pain, hepatomegaly, cholangitis / cholezystitis, chol-angiocarcinoma	–	Urticaria
Fascioliasis	–	–	Pulmonary infiltrations, cough	Abdominal pain, nausea, vomiting	Fever, right upper quadrant pain, hepatomegaly, subcapsular hepatic haemorrhage, cholangitis / cholezystitis, biliary cirrhosis		Urticaria, aberrant subcutaneous migration of parasite
Intestinal fluke infections	–	–	–	Diarrhoea, abdominal pain	–	–	–

ational sources (e.g., adventure travellers and water-based sports activities) account for most leptospirosis cases and outbreaks in industrialised countries, close contact with infected animals and a contaminated environment remain the major source of infection in most tropical countries, particularly in social-ecological contexts characterised by traditional agriculture and crowded urban settings, where inadequate sanitation and poverty prevail [96, 97].

Outbreaks accounting for thousands of deaths worldwide underline the importance of leptospirosis as a re-emerging, yet severely neglected infectious disease. It is widely under-recognised due to difficult, poorly standardised diagnosis and often mild and unspecific clinical presentations. It is estimated that more than 500,000 severe cases occur annually around the world [98] with a recent trend towards

a higher proportion of infections with severe pulmonary haemorrhages in endemic populations [99].

The typical combination of high fever, chills, calf myalgia, headache and an abrupt onset of disease in the early stage is seldom present, so that clinicians should include leptospirosis in their differential diagnosis in any unexplained febrile illness when risk factors for infection are present. In a second disease stage, multiple organ failure may occur. Hepatic dysfunction leading to jaundice and acute renal failure are relatively frequent, but as a result of haematogenous spread, every organ including the central nervous system (e.g., meningitis, meningoencephalitis) can be affected. Laboratory confirmation of leptospirosis, e.g. by microscopic agglutination test, is difficult and often time-consuming, expensive, relatively insensitive and not available in many diagnostic centres, especially in the developing world [100]. Rapid serological testing, e.g. by an ELISA detecting *Leptospira*-specific IgM antibodies, is easy to perform and recommended by the WHO in resource-constrained settings. The introduction of such assays represented a major step forward, as they are increasingly becoming available throughout the tropics and allow rapid confirmation of the diagnosis of suspected leptospirosis cases. The diagnostic accuracy of the IgM assay, however, has been reported to vary in different settings [101, 102]. If severe leptospirosis is suspected, patients should receive early antibiotic treatment with doxycycline, penicillin G or ampicillin, even if recent meta-analyses question the clinical benefit of such therapeutic regimens [103]. Supportive treatment in the case of organ failure (e.g., haemodialysis for acute renal failure) is essential, while uncertainty remains regarding the use of immunosuppressive medication [96].

Treatment

Table 5 summarises the most widely used drugs and treatment schemes for parasitic neglected tropical diseases. We distinguish between large-scale community-based drug interventions (an approach phrased "preventive chemotherapy" [36]) that have become the key strategy in resource-constrained settings of the developing world on one hand, and individual patient management as applied in Switzerland and other non-endemic settings on the other hand. For example, while in Switzerland mebendazole is used as 100 mg two times daily for three days in the treatment of common soil-transmitted helminthiases, a single dose of 500 mg is administered in preventive chemotherapy programmes in endemic settings. Given the ease of administration of the latter treatment scheme, as a result, non-medical personnel (e.g., school teachers) can deliver these drugs to large populations (e.g., all children in a school) as a public health measure [36]. A disadvantage, however, is that the efficacy of single doses is often lower than multiple dosing. For example, while overall cure rates of 63–89% have been reported for multiple doses of mebendazole against *T. trichiura* infection, the cure rate of single-dose mebendazole is considerably lower (36%) [104]. Nevertheless, in terms of parasite burden reduction (indirectly measured by egg reduction rates), single dosing usually results in high efficacy. Hence, preventive chemotherapy has been endorsed by WHO as the key strategy for morbidity control and tens of millions of people in developing countries are treated every year [28, 36, 105–108].

It is interesting to note that the neglected tropical diseases are often classified on the basis of available control tools, hence separating between "tool-deficient" (costly and difficult to manage) and "tool-ready diseases" (safe and highly efficacious drugs available for large-scale administration by personnel outside the health sector) [36]. While the helminth diseases summarised in tables 1 and 2 would fall into the category of "tool-ready diseases", for *T. brucei rhodesiense*, currently available drugs cause serious adverse events in a considerable proportion of all treated patients [58, 109].

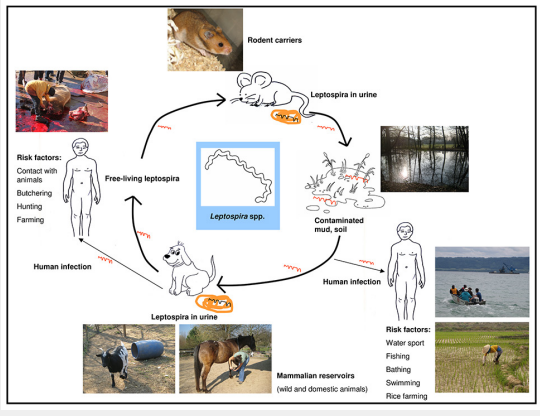

Figure 2

Life cycle of pathogenic *Leptospira* spp., the infectious agents of leptospirosis.

Prevention and integrated control

While the unit of intervention to address the neglected tropical diseases in the developing world is often at the population level (e.g., many of the helminth infections), some diseases require enhanced patient management (e.g., Buruli ulcer and human African trypanosomiasis). Clearly, the advent of safe, efficacious and cheap drugs that can be administered by non-health personnel spurred the way for preventive chemotherapy [36]. It should be noted, however, that this strategy has several shortcomings. For example, it is difficult to reach some of the most vulnerable population groups. Moreover, compliance is an issue, particularly when interventions must be repeated once or twice a year for an unknown period of time. Indeed, a growing number of people might feel healthy, and hence might not appreciate the need for repeated treatment. Growing drug pressure must be carefully monitored in terms of potential resistance development. Importantly, rapid reinfection occurs, as preventive chemotherapy does not address the root behavioural, ecological and socio-economic causes [18, 110]. These issues call for preventive measures, such as improved access to clean water, sanitation and hygiene have to been emphasised [18, 111, 112]. Whenever resources allow, integrated control approaches should be pursued (i.e., implementation of a set of interventions that are readily tailored to an endemic setting and adapted over time). This will re-

Table 5: Recommended treatment for selected neglected tropical diseases, juxtaposing the situation in Switzerland (typical non-endemic setting) with large-scale control emphasising preventive chemotherapy (in highly endemic settings).

Disease	Recommended treatment (individual patient treatment in non-endemic setting, e.g., Switzerland)	Control (preventive chemotherapy in endemic setting)
	Drug / dosage[a]	Drug / dosage
Hookworm infection	Albendazole 400 mg OD x 3 d Mebendazole 100 mg BID x 3 d	Albendazole 400 mg OD x 1 d Mebendazole 500 mg OD x 1 d (Pyrantel pamoate) (10 mg/kg OD x 1 d)* (Levamisole) (2.5 mg/kg OD x 1 d)*
Ascariasis	Albendazole 400 mg OD x 1 d Mebendazole 100 mg BID x 3 d	
Trichuriasis	Albendazole 400 mg OD x 3 d Mebendazole 100 mg BID x 3 d	
Strongyloidiasis	Ivermectin** 200 µg/kg OD x 2 d** Albendazole 400 mg BID x 7 d	Ivermectin** 200 µg/kg OD x 2 d Albendazole 400 mg OD x 1d or 400 mg BID x 3 d
Toxocariasis	Albendazole 400 mg BID x 5-10 d Mebendazole 100–200 mg BID x 5 d	Not available, however diethylcarbamazine (DEC) administered in the framework of the global programme to eliminate lymphatic filariasis (GPELF) might have an impact on toxocariasis
Trichinellosis	Steroids (e.g., prednisone) 30–60 mg OD x 10-15 d tapering plus albendazole 400 mg BID x 8-14 d	
Schistosomiasis	Praziquantel** 60 mg/kg OD on days 0 and 21–30 (*S. haematobium*, *S. mansoni*, *S. intercalatum*)[b]; 25 mg/kg TID (*S. mekongi*, *S. japonicum* on days 0 and 21–30)	Praziquantel 40 mg/kg single dose
Lymphatic filariasis	Doxycycline 100 mg BID x 4 weeks + ivermectin 200 µg/kg once ± albendazole 400 mg once alternative: single dose diethylcarbamazine (DEC) 6 mg/kg + albendazole 400 mg every 3–6 months	GPELF, launched by the Global Alliance to Eliminate Lymphatic Filariasis (GAELF; http://www.filariasis.org). Ivermectin and albendazole are used in Africa and diethylcarbamazine (DEC) and albendazole in areas outside Africa
Mansonellosis - *M. perstans* - *M. ozzardi* - *M. streptocerca*	Albendazole 400 mg BID x 10 d Mebendazole 100 mg BID x 30 d Doxycyline 200 mg OD x 6 w Ivermectin 200 µg/kg Diethylcarbamazine (DEC) 6 mg/kg OD x 12 d Ivermectin 200 µg/kg	Most individuals with *Mansonella* spp. infection are asymptomatic. Preventive chemotherapy control programmes against lymphatic filariasis and soil-transmitted helminthiasis are likely to have an impact on mansonellosis. Note that DEC should not be administered in areas where onchocerciasis is endemic, due to the provocation of serious adverse events, including exacerbation of ocular disease
Loiasis	>100 MF/ml: albendazole 200 mg BID x 3 weeks (± plasmapheresis) + when <100 MF/ml: diethylcarbamazine (DEC) x 3 weeks: day 1, 1 mg/kg; day 2, 3 mg/kg; day 3, 6 mg/kg; days 4–21, each day 9 mg/kg (MF = microfilaria)	Not available. Note that presence of loiasis interferes with mass drug treatment for onchocerciasis as albendazole and ivermectin may cause serious adverse events in loiasis patients
Onchocerciasis	Doxycycline 100 mg BID x 4 weeks + ivermectin* 200 µg/kg once + ivermectin* 200 µg/kg once after 4-6 months (*not in case of *Loa loa* co-infection)	Africa: ivermectin every year for at least 15–17 years South America: ivermectin twice every year until transmission has been interrupted
Leishmaniasis Visceral cutaneous Mucosal	Liposomal Amphotericin B 3 mg/kg i.v. days 1–5, 14 and 21 Various drugs and regimens and route of application, according to species and clinical manifestation [207]. *Topical*: 15% paromomycin / 12% methylbenzethonium-chloride ointment, local heat-/cryotherapy, pentavalent antimonials intralesional *Systemic*: pentavalent antimonials, Miltefosine, liposomal Amphotericin B, Ketoconazole	Active case detection, vector control and treatment are recommended in countries suffering the greatest burden.
Human African trypanosomiasis*** *T. brucei gambiense* First (hemolymph.) stage Second (meningoenceph.) stage *T. brucei rhodesiense* First (hemolymph.) stage Second (meningoenceph.) stage	Pentamidine 4 mg/kg i.m. or i.v. (max. 200 mg/d) x 7 d Nifurtimox-eflornithine combination treatment (NECT): nifurtimox (oral 15 mg/kg/day (in 3 doses) x 10 d + eflornithine i.v. 400 mg/kg/day (in 2 doses) x 7 d Suramin 20 mg/kg i.v. (max. 1 g/d) on days 1, 3, 7, 14 and 21 Melarsoprol 2.2 mg/kg i.v. x 10 d	National sleeping sickness control programmes including case detection and treatment

Chagas disease	Nifurtimox 8–10 mg/kg x 30-60-(90) d or Benznidazole 5–7.5 mg/kg x 30-60-(90) d	Surveillance and control programmes, with an emphasis on vector control ongoing
Paragonimiasis	Praziquantel** 25 mg/kg TID x 3 d Triclabendazole** 10 mg/kg OD x 1–2 d	Preventive chemotherapy strategy currently under development
Clonorchiasis	Praziquantel** 25 mg/kg TID x 1 d	
Opisthorchiasis	Praziquantel** 25 mg/kg TID x 1 d	
Fascioliasis	Triclabendazole** 10 mg/kg OD (x 2 d)	
Intestinal fluke infections	Praziquantel** 25 mg/kg OD x 1 d	
Dracunculiasis	No drug available	

Based on www.documed.ch: WHO report on neglected tropical diseases; WHO model formulary 2008; the Medical Letter Drugs for parasitic infections

[a] Dosages are oral if not specifically indicated.

[b] Recommended treatment regimen by the Swiss Tropical and Public Health Institute (Swiss TPH; Basel, Switzerland); others might still rely on a single 40 mg/kg oral dose.

* Pyrantel pamoate and levamisole do not have a prominent role in preventive chemotherapy programmes since dosages are weight-based.

** Ivermectin, praziquantel and triclabendazole tablets are not available in Switzerland and are therefore often imported (e.g., from France). Eflornithine, suramin and melarsoprol are not available in Switzerland; pentamidine is registered for *Pneumocystis jiroveci* pneumonia. Given the paucity of human African trypanosomiasis outside Africa, treatment recommendations are based on studies conducted in endemic regions and the limited availability of the drugs outside endemic regions often determine the choice of drug. Of note, drugs against human African trypanosomiasis can be obtained for free from WHO or from several medical centres in non-endemic countries [206].

OD: once a day, BID: twice a day, TID: three times a day

quire a deep understanding of the demographic, health and social-ecological systems contexts [18].

In Switzerland and other industrialised countries, the focus is on the individual patient, in line with a growing emphasis on personalised health care. However, preventive measures (e.g., raising awareness among travellers about common risk factors and mitigation strategies for neglected tropical diseases in endemic countries) [113, 114] are as important as adequate patient management of the returning traveller and migrants.

Conclusions

Starting with an initial set of 13–15 diseases, there are now over 40 helminth, protozoal, bacterial, viral, fungal and ectoparasitic infections covered under the brand-name of the neglected tropical diseases. Important gaps in our understanding of the epidemiology and control of many of the neglected tropical diseases remain, which calls for additional funding, so that innovative research will eventually lead to new validated tools and strategies that can be applied in the field. Although rarely seen in industrialised countries, specific signs and symptoms should prompt physicians to rule out neglected tropical diseases, particularly among travellers, expatriates and migrants with a history of geographical and behavioural exposure to disease-endemic areas. Importantly, many of those infections are easily and effectively treated with short oral drug regimens (e.g., soil-transmitted helminthiasis, including strongyloidiasis). Other neglected tropical disease may cause extensive and more costly investigations (e.g., leishmaniasis, leprosy). In many cases, additional advice from, or referral to specialists in tropical medicine is recommended for more detailed laboratory and clinical work up. Due to the growing importance of neglected tropical diseases in Switzerland and elsewhere in Europe, partially driven by enhanced international travel, trade and migration, efforts should be made by scientific societies and networks (e.g., Network for Education in International Health, tropEd in short) to train and inform general practitioners on the prevention, diagnosis, treatment and management of neglected tropical diseases, including proper referral when need be.

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Figures (large format)

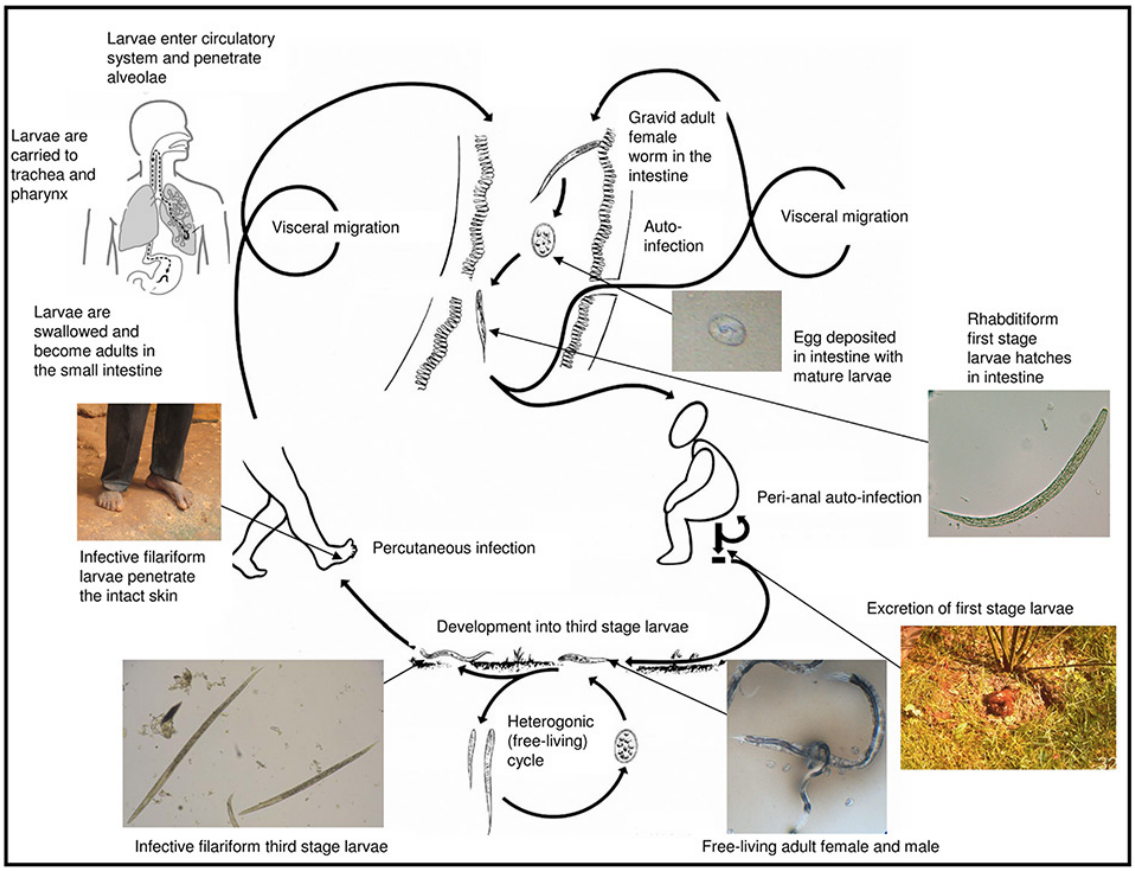

Figure 1

Life cycle of *Strongyloides stercoralis*. (Adapted from Olsen A, van Lieshout L, Marti H, Polderman T, Polman K, Steinmann P, et al. Strongyloidiasis – the most neglected of the neglected tropical diseases? Trans R Soc Trop Med Hyg. 2009;103:967–72 [85]. © Elsevier, 2009. Printed with permission).

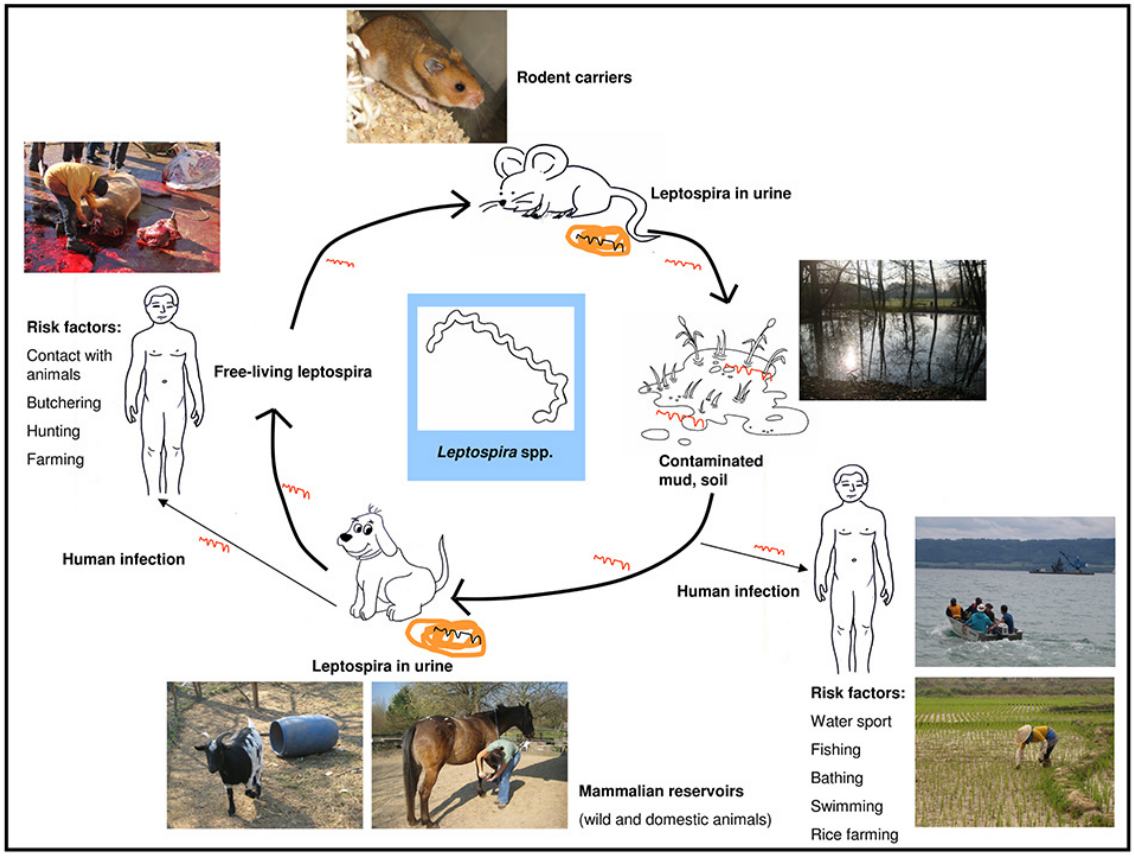

Figure 2

Life cycle of pathogenic *Leptospira* spp., the infectious agents of leptospirosis.