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Perspective

Drugs for Vector-Borne Protozoal Diseases in a One Health Scenario. A European Perspective

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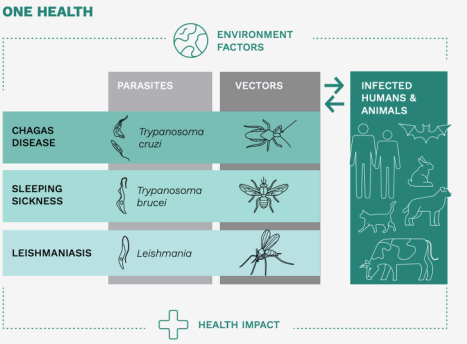
ABSTRACT: Vector-borne protozoal diseases (VBPD) represent an enormous health and economic burden, particularly in low- and middle-income countries. Their control requires integrated approaches that consider not only therapeutic interventions for affected human and animal populations but also preventive tools. Environmental contamination can lead to therapeutic ineffectiveness. Effective intervention must consider in-depth knowledge of the environmental factors that regulate the exposure, transmission and pathogenicity of VBPD within a One Health approach. In recent decades, the incidence and prevalence of VBPD have been substantially reduced in many regions of the world, although there are still hot spots and emerging epidemiological cycles. Except for a partially protective vaccine against malaria, vaccination is not available for any other human VBPD, and therefore epidemiological control and chemotherapy are the main control tools. Current therapeutics have several drawbacks, including reduced efficacy, toxicity and high price of safer formulations. In addition, the industrial pipeline is limited, and no therapeutic breakthroughs are expected. Integrated control of VBPD requires multitarget control systems adapted to the disease and region. In this scenario, harmonized surveillance systems, accurate reporting and increased public and private investment will ensure more rational use of the few available and new drugs.



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VECTOR BORNE PROTOZOAL DISEASES (VBPD). TRYPANOSOMATIDS INFECTIONS

Throughout evolution, parasitism has been a highly successful strategy, and some parasitic protozoa are among the most widespread organisms in the world (e.g., *Toxoplasma*, *Plasmodium*). Some parasitic protozoa require the involvement of a vector, often an arthropod, to complete their life cycle, and the diseases transmitted are known as vector-borne parasitic diseases (VBPD). Apart from malaria, which is not covered in our mini perspective, the most studied VBPD are caused by digenetic trypanosomatids (*Trypanosoma*, *Leishmania*), which infect a variety of vertebrates and cause a wide range of diseases. They represent an enormous health and economic burden, particularly in low- and middle-income countries. Due to their economic and public health impact, several VBPD have been studied since the 19th century, particularly those present in tropical and subtropical areas in humans and domestic animals. Chagas disease, leishmaniasis and Human African Trypanosomiasis (HAT) are estimated to affect about 18 million people worldwide, with more than one billion at risk of infection.[1] In addition to human infections, the impact of these VBPDs on animals, both domestic and wild, is of paramount importance. For example, African Animal trypanosomiasis (AAT) affects most domestic species in addition to cattle and is considered a devastating problem for livestock production in Africa. Other animal infections are of fundamental importance in the case of zoonotic diseases (e.g., leishmaniasis).

TRYPANOSOMIASIS AND LEISHMANIASIS: CURRENT STATUS

HAT or sleeping sickness, is endemic in sub-Saharan Africa and is caused by *Trypanosoma brucei gambiense* in West and Central Africa (92% of reported cases) and *T. b. rhodesiense* in East Africa (8% of cases).[2] The disease is closely associated with the rural environment. Human activities, including agriculture, human migration and animal movement, may alter their geographical distribution. Although as obligate

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parasites of two completely different types of hosts (mammals and insect vectors), trypanosomes are mainly transmitted by the bite of tsetse flies (*Glossina* sp). All species in the genus are capable of transmitting human infectious trypanosomes, but the riverine group (*G. palpalis* and *G. fuscipes*) are the main species involved in HAT transmission.[3] WHO estimates the population at risk to be around 60 million, with only 3 million at medium-high risk (2016−2020).[1] AAT, also transmitted by tsetse flies (*Glossina* sp), live in the blood, lymph and other tissues of domestic (cattle, sheep and goats) and wild vertebrates and are mainly caused by *T. congolense*, *T. vivax* and *T. b. brucei*. Mixed infections with more than one trypanosome species are common. They are not usually zoonotic, although they share with HAT animal reservoirs (over 30 mammalian species) and vectors (mainly *G. morsitans*, *G.palpalis* and *G. fusca*) and are the most economically important livestock disease in Africa, especially in cattle (nagana).[4] Estimating the economic impact is difficult, although losses to livestock production are estimated at US $1.0−1.2 billion per year.[5] An indirect estimate is that the use of a repellent to avoid flies (5−50% of the livestock population) would save US$78−869 million per year in 18 African countries.[6] *T. vivax*, although mainly transmitted by tsetse flies in its original distribution, can be transmitted mechanically by the bite of hematophagous insects and has crossed the tsetse belt, expanding into non-*Glossina* areas and now including South America. *T. evansi*, possibly derived from cyclic trypanosomes and affecting a wide range of domestic animals, has expanded its distribution and is present in northern Africa, Asia and Central and South America, mainly affecting horses and camels.[7,8]

An estimated 6−7 million people worldwide, mostly in South America, are infected with *T. cruzi*, the parasite that causes Chagas disease. It is naturally transmitted (vector-borne) through the faeces of triatomine bugs (*Rhodnius* sp, *Triatoma* sp),[9] but this parasite species has extraordinary biological plasticity and can be transmitted orally, during pregnancy or childbirth (congenitally), through blood/blood products, solid organ transplants and laboratory accidents. As a result of these multiple modes of transmission and human migration, Chagas disease has spread beyond its original distribution. Most infected people now live in urban areas, and infection has been reported in 44 countries (including Canada, the United States of America, and many European and some Western Pacific, African and Eastern Mediterranean countries).[10,11]

Leishmaniasis is caused by more than 20 *Leishmania* sp, flagellated protozoa transmitted by the bite of female phlebotomine sandflies (over 90 species). Only a fraction of infected humans (and animals) develops overt clinical signs, as the outcome of the disease is highly dependent on the host's immune imbalance and parasite multiplication. It can be considered an immunopathology, which in turn depends on the weakness of the human immune system due to malnutrition, inadequate housing and few resources. There are three main clinical forms of leishmaniasis in humans: visceral, cutaneous and mucocutaneous. These diseases, together with the rare postkala-azar dermal leishmaniasis, account for an annual incidence of between 700,000 and 1 million people, according to WHO estimates.[12] Cutaneous leishmaniasis (CL), the most common clinical presentation, is characterized by skin lesions, mainly ulcers, which are sometimes long-lasting and cause social stigma, especially in women. Between 600,000 and 1 million cases are thought to occur in the Americas, the Mediterranean, the Middle East and Central Asia, although reporting is much lower (around 200,000 cases). Mucocutaneous leishmaniasis (MCL) causes destruction of the nose, throat and mouth and most cases are reported in South America.[1] Visceral leishmaniasis (VL), which occurs in Eurasia, Africa and the Americas, is the most severe form of the disease and has an almost 100% mortality rate without treatment, making it the second most deadly parasitic disease after malaria. Over the past 30 years, VL infection in adults has been increasingly associated with coinfection with HIV.[12] Approximately 90% of the global burden of VL occurs in just 7 countries, 4 of which are in East Africa (Sudan, South Sudan, Ethiopia and Kenya), 2 in Southeast Asia (India, Bangladesh) and Brazil, which accounts for almost all cases in South America.[13] Although the incidence of clinical cases in Europe is relatively low and deaths are rare, there is potential for an expanded geographical range due to climate change.[14,15] In addition, several *Leishmania sp* also infect animals, and in the Mediterranean region, dogs are considered the main reservoir for *L. infantum*, and several alternative wild and peri-urban hosts have been identified.[16,17] Canine leishmaniasis (CanL), in addition to its role in the transmission of zoonotic leishmaniasis, has a high impact on the health of domestic animals and is a major veterinary pathology in endemic areas. Although not discussed in this article, tick-borne pathogens affect 80% of the world's cattle population and are widespread throughout the world, particularly in the tropics and subtropics.

CONTROL OF VBPD (TRYPANOSOMIASIS AND LEISHMANIASIS). INTEGRATED CONTROL AND ONE HEALTH

Humans, animals (both domestic and wild) and parasites are part of the same ecosystem. The transmission of protozoal diseases, whether anthroponotic (human-to-human) or zoonotic (animal-to-human), particularly in the case of VBPD, requires the establishment of a balance between hosts, parasites and vectors. Unravelling the intricacies of this delicate equilibrium has been the task of medical, veterinary and epidemiological scientists, who were able very early to recognize the impact of environmental factors on the life cycles of parasites and, ultimately, on the incidence of disease in humans and domestic animals (Figure 1). This knowledge has led to several preventive measures to reduce the parasitic burden, including water purification and chemical and nonchemical approaches to vector populations. The close interaction between all actors, including the role of environmental characteristics, was recognized more than 20 years ago and was coined as One Health. Thus, One Health is an integrated, unifying approach to balance and optimize the health of people, animals and the environment.[18] This concept goes beyond human health to include animal health and the sustainability of the environment (ecosystems). By considering humans, animals and the environment as closely linked and interdependent in our context, it is expected to include prevention, detection, preparedness, response and management. Integrated control of VBPD has been addressed by identifying the bottlenecks of parasite transmission at a very early stage, sometimes long before the actual pathogen involved was known. Historical examples range from successive attempts to drain swampy areas to limit malaria transmission (e.g., ancient Rome) to modern-day mosquito nets in endemic

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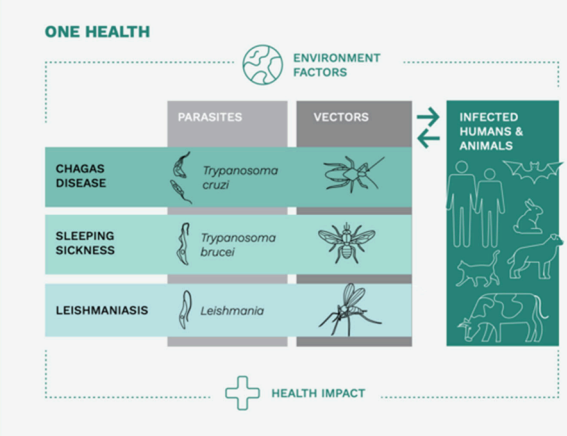

Figure 1. One Health in Vector Borne Protozoal Diseases: Integrating human, animal, and environmental health for a sustainable future. Parasites induce different diseases: *Trypanosoma cruzi* responsible for Chagas disease, *Trypanosoma brucei* for Sleeping sickness and *Leishmania* for Leishmaniasis in humans and animals. Transmission requires adequate insect vectors and suitable environmental conditions.

areas or insect repellents, spot-on or collar, applied to livestock and pets. The adoption of these practices and their eventual efficacy illustrate the close relationship between VBPD and environmental characteristics, including vector populations.[15,19] The ecological approach to the control of these diseases must consider every event and factor from the effects of the parasites on their hosts to the impact of environmental factors on the transmission and pathogenicity of VBPD. This is a formidable task in the case of VBPD due to the fragmentary knowledge of many critical aspects of parasite transmission, the vectorial capacity of the insects involved in the life cycles, the immune response and its modulation, the effect of physical and chemical interventions on the environment to limit the spread and severity of VBPD, and the economic and social issues involved. For example, to control HAT, it is important to consider that the animal reservoir is critical for *T. b. rhodesiense* and less so for *T. b. gambiense*, although it may explain the long term endemicity in some foci despite control interventions. Knowing this, transmission can be interrupted by depleting the parasite reservoir through detection and treatment of infected people and/or domestic animals, and by reducing the tsetse fly population and human-tsetse contact. In controlling human cases of leishmaniasis, it should be remembered that some 70 species of animals, including humans in the case of anthroponotic VL, can be sources (reservoirs) of *Leishmania* parasites or water contaminants can facilitate the development of drug resistance.[20,21] Key strategies to prevent Chagas disease include vector control in Latin America; blood screening before transfusion and transplantation; testing and treatment of women of reproductive age, newborns and siblings of infected mothers; and information, education and communication to communities and health professionals.[22]

CHEMOTHERAPEUTIC CONTROL: SUCCESSES AND HURDLES

HAT caused by *T. b. gambiense* and *T. b. rhodesiense* caused devastating epidemics in the 20th century. Effective control programmes implemented since 1990 have reduced the number of human cases, and over the past two decades the number of reported cases in endemic countries has fallen to historically low levels.[23] In 1995, there were about 25,000 detected cases, an estimated 300,000 undetected cases and an estimated 60 million people at risk of HAT infection. In 2001, WHO launched an initiative to strengthen control and surveillance, and HAT declined significantly in the following years. Since 2019, fewer than 1000 cases are reported annually. It is possible that HAT transmission has apparently stopped in some countries (e.g., Benin, Botswana, Gambia), although this has not yet been fully assessed. This reported reduction appears to be real, as active and passive screening has generally been maintained at similar levels (about 2.5 million people screened per year).[2] Fifteen years ago, triatomine transmission of Chagas disease was significantly reduced or even stopped in some countries in South America.[24] However, the disease still has a severe social, economic and public health impact in most South American countries.[25,26] In the case of leishmaniasis, a significant reduction in VL cases and an increase in CL have been reported in the eastern Mediterranean region.[22]

There is currently no human vaccine against trypanosomes, and this goal seems elusive due to host immunosuppression induced by infection and the antigenic variability of HAT and AAT. Promising results against an animal trypanosome (*T. vivax*) with an invariant flagellar antigen (IFX) in laboratory models[27] may pave the way for the development of effective vaccines against AAT and, hopefully, HAT and Chagas disease. While the development of vaccines against human leishmaniasis has been unsuccessful, several vaccines against canine leishmaniasis have been developed using different approaches. Two of these have been withdrawn (Leishmune, 2014; Canileish, 2022), but LeishTec (A2 antigen+ saponins) is marketed in Brazil[28] and LetiFend (Protein Q)[29] and the more recently launched DNA vaccine Neoleish (pPAL-LACK)[30] are marketed in Europe. Protection provided is not complete, some require annual revaccination and long-term longitudinal studies are ongoing. Despite the differences between the canine and human immune systems and the course of the disease in both species, the development of protein, DNA or RNA-based vaccines for VL seems feasible in the near future.

VBPD cannot be eradicated if animal reservoirs, especially wildlife, play a significant epidemiological role.[26] Long-term control is therefore only possible through an integrated approach that includes reduction of vector populations, reduction of transmission, vaccination and effective treatment of infected individuals. Therapeutics, while far from being the only measure, has proven to be a cost-effective and fast-acting tool to control these diseases. Reductions in human cases have been achieved largely through chemotherapy. However, the therapeutic options for VBPD are very limited and often restricted to old drugs with high toxicity. Treatment of HAT varies depending on the causative agent, *T. b. rhodesiense* (suramin, melarsoprol) or the most common *T. b. gambiense* (pentamidine, eflornithine, nifurtimox, fexinidazole), and the stage of infection.[2] Drugs are available to treat AAT (isometamidium chloride, homidium bromide and homidium chloride), but their efficacy is limited. Currently available drugs for Chagas disease (nifurtimox and benznidazole) are generally considered to be effective in treating acute and early chronic infection in children under 15 years of age, but their efficacy and availability are inconsistent and their value in chronic infection remains controversial.[31] The four main treatment options for VL are pentavalent antimonials (Sb^V), amphotericin B (AmB), miltefosine and paromomycin, and two of these

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are also used to treat canine leishmaniasis (CanL). Treatment of CanL is essential because infected animals are the main risk factor for zoonotic VL in endemic regions, and therefore chemotherapy of dogs with AmB is not recommended to avoid potential cross-resistance.

Both hosts and parasites evolve, and the much higher reproductive potential of protozoa favors the emergence of resistant strains to available drugs. Thus, resistance phenomena to available drugs against VBPDs are widespread, sometimes even to first-line treatments. This has been reported for HAT, AAT, Chagas disease and leishmaniasis, especially when the therapeutic pressure is higher. Cross-resistance between animal and human strains is not limited to "classical" zoonotic infections (e.g., leishmaniasis) but can also be a challenge in HAT (*T. b. rhodesiense* and to a lesser extent *T. b. gambiense*), where domestic animals can act as reservoirs.[1] The poor efficacy, toxicity and resistance of available drugs means that alternative drugs with different mechanisms of action are urgently needed. However, drug discovery efforts for VBPD by the pharmaceutical sector and the number of products in the drug development pipeline are not proportional to the disease burden.[32]

IMPLEMENTING ONE HEALTH: ROLE OF REGULATORY AGENCIES

Recognizing the close interrelationship between human, animal and environmental health, several international agencies, including WHO and its veterinary counterpart, the World Organisation for Animal Health (formerly OIE), and the Food and Agriculture Organization (FAO), have made efforts to establish coordinated actions to achieve the goals of One Health in a sustainable world. Progress has been uneven, with environmental safety still lagging behind. The European Union (EU) has been at the forefront of these tasks (e.g., Agenda 2030) and in the context of the control of VBPD, the recommendations for the use of veterinary medicinal products for the treatment of infectious diseases in the EU area are outlined in the new Veterinary Medicinal Products Regulation (EU) 2019/6, which was implemented in January 2022. Thus, these guidelines describe the criteria and the reserved list of antimicrobial substances intended exclusively for the treatment of specific human infections[33] with the aim of promoting a rational and responsible use of medicines to minimize the development of antimicrobial resistance. The EU's efforts were primarily aimed at regulating the use of antibiotics in livestock to prevent the transmission of antimicrobial resistance or coresistance to humans via the food chain. As such, this initiative, based on increasing reports of therapeutic failures with antibiotics, was expected and requires compliance within the European area and hopefully beyond. The current therapeutic options for Chagas disease, HAT, AAT and leishmaniasis are not suitable for inclusion in the European Medicines Agency (EMA) Reserved List, as their characteristics do not meet the first two criteria for inclusion, but only the last one: nonessentiality of the antimicrobial for animal health and nonsignificant impact on animal health, animal welfare or public health. Moreover, this regulation is limited to the European Union, where the extent of human infections by these VBPD is limited, despite the nonvectorial transmission of *T. cruzi*, and where neither AAT nor HAT are present for biogeographical reasons, and the main target of this therapeutic restriction would be zoonotic leishmaniasis in pets (dogs, cats).

Parasitic diseases in general, and VBPD in particular, tend to be endemic, as opposed to epidemics caused by viruses or bacteria. This is due to the close interaction between host, parasite and vector within an ecosystem. This interdependence, in turn, is responsible for the current distribution of VBPD in the world. Changes in environmental conditions, whether natural (e.g., rainfall, humidity, vegetation) or anthropogenic (e.g., deforestation, construction), can have a huge impact on host and vector populations, transmission rates and even the pathogenicity of infections and the immune response elicited. There are examples of this effect (e.g., expansion of the tsetse fly range by road construction) and therefore, although the One Health goal is global, intervention tools need to be local, considering disease foci, people involved and their activities - pastoral, agricultural, urban, rural - animal reservoirs, vector species and their availability and habits. Regional initiatives such as the EMA's should therefore be the rule, avoiding 'one-size-fits-all' solutions and developing tailor-made local responses that balance the need to improve environmental conditions with the sustainability of animal and human populations and welfare.

CHALLENGES TO CONTROL OF VBPD IN A CHANGING WORLD: EUROPEAN PERSPECTIVE

In a One Health framework the control of VBPD, especially zoonotic infections, must be integrated, including all actors involved: parasites, hosts populations and environmental conditions regulating the dynamics of infection transmission. Moreover, the impact of the control measures on the environment must be assessed. With the currently available tools and the effort of international agencies, charities and governments we are in the path to effectively reduce the extension and severity of most VBPD in most affected regions of the world (Africa, Asia, Central and South America). Despite this success, a continuing and coordinated effort is needed given the fragility of the host-parasite-environment equilibrium. Most of the human VBPD are not of great concern in northern hemisphere on biogeographical and socioeconomic grounds. However, not foreseen events such as the economic crisis in 2008 clearly showed that in some European regions, reducing public health awareness and surveillance lead to the occasional re-emergence of previously controlled VBPD. Vectorial transmission of Chagas disease, HAT or AAT currently is not expected in Europe where only CL and VL have available insect vectors and the number of infected humans is generally low. However, climate change has resulted in a wider distribution of vectors and consequently diseases as has been widely reported in the case of leishmaniasis[1,14,15] along other VBPD not considered in this perspective.

Of particular interest is the new scenario created by human (and parasites) migrations and the newly recognized epidemiological patterns. Nonvectorial transmission of *T. cruzi* (e.g., pregnancy or childbirth; blood or blood product transfusion; solid organs (heart, kidney) transplantation) has resulted in Chagas disease reaching a global expansion including Europe.[10,11,34] Relevance of progressive aging population in affluent societies such as Western Europe must be examined since the clinical presentation and severity of some VBPD is strongly linked to the functionality of the host' immune system. There is a need for evidence-based common practices or guidelines that can be applied to the definition of risk, and for the preparedness and readiness concepts. Of

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paramount importance is the knowledge of the actual prevalence and incidence of VBPD. Despite the efforts developed to encourage infection notifications, there are several items that are still lacking concerning VBPD, including the actual human cases. Leishmaniasis, the most common VBPD in Europe, is not a notifiable disease[35] and the notification to national health authorities varies among countries. It is compulsory in Greece, Italy, Portugal, and parts of Spain but not in France. Harmonization of notification models among European countries would provide a faithful image and the model, in a One Health framework, should include both medical and veterinary records. Although a challenging process, the information would give an accurate picture of the VBPD status in Europe. Epidemiological surveillance and risk evaluation is critical and information on human and animal cases would yield first-hand knowledge on comorbidities (e.g., HIV + leishmaniasis) and differential susceptibility and resilience to the infection (immunogenetics) thus identifying patients' subpopulations.

The therapeutic arsenal against VBPD is reduced and the possible extension of the reserved list (EMA) to include protozoa, without additional measures, could have a scarce impact, even limiting its application to the EU. In addition, sustainable control of VBPD requires careful evaluation of interventions, considering regional and local specificities. Although this aspect is more relevant in HAT and AAT endemic regions, the need to use locally adapted methods to increase their effectiveness (e.g., rural vs urban areas; pastoral vs industrial occupation) should be emphasized. Despite the attractiveness of global solutions, the endemicity and focal presentation of VBPD highlight the relevance of local human, animal and environmental characteristics and the need for case-by-case analysis. In addition, the socio-economic characteristics of the target foci must be considered, with the aim of reconciling the need to control and eventually reduce the use of antiparasitic drugs with the reasonable maintenance of agricultural and livestock practices. This aspect is currently less relevant in the case of Europe, given the current distribution of VBPD, but is critical in the regions with the highest burden of AAT, HAT and Chagas disease.

With the current lack/stagnation of new drug launches by the pharmaceutical industry, the increasing reports of resistance and therapeutic failure in VBPD point to the need for refinement of treatments. This includes improving the currently available drugs through a deeper knowledge of their pharmacological properties, presentations and treatment regimens, as well as clinical outcomes in treated patients. This requires accurate identification of resistant parasite strains circulating in humans and/or animals and their drug sensitivities. In addition, nonresponse or innate drug resistance leading to therapeutic failure may have a characteristic genetic profile (pharmacogenetic profile) and the immune events associated with the success or failure of the treatment administered. The discovery of biomarkers to understand disease susceptibility and outcome, in addition to data knowledge and epidemiology in different countries, would require sustained public and private investment to ensure more rational use of the few available drugs.

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Notes

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