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Review

Electrochemical biosensors for neglected tropical diseases: A review

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ABSTRACT

A group of infectious and parasitic diseases with prevalence in tropical and subtropical regions of the planet, especially in places with difficult access, internal conflicts, poverty, and low visibility from the government and health agencies are classified as neglected tropical diseases. While some well-intentioned isolated groups are making the difference on a global scale, the number of new cases and deaths is still alarming. The development and employment of low-cost, miniaturized, and easy-to-use devices as biosensors could be the key to fast diagnosis in such areas leading to a better treatment to further eradication of such diseases. Therefore, this review contains useful information regarding the development of such devices in the past ten years (2010–2020). Guided by the updated list from the World Health Organization, the work evaluated the new trends in the biosensor field applied to the early detection of neglected tropical diseases, the efficiencies of the devices compared to the traditional techniques, and the applicability on-site for local distribution. So, we focus on Malaria, Chagas, Leishmaniasis, Dengue, Zika, Chikungunya, Schistosomiasis, Leprosy, Human African trypanosomiasis (sleeping sickness), Lymphatic filariasis, and Rabies. Few papers were found concerning such diseases and there is no available commercial device in the market. The works contain information regarding the development of point-of-care devices, but there are only at proof of concepts stage so far. Details of electrode modification and construction of electrochemical biosensors were summarized in Tables. The demand for the eradication of neglected tropical diseases is increasing. The use of biosensors is pivotal for the cause, but appliable devices are scarce. The information present in this review can be useful for further development of biosensors in the hope of helping the world combat these deadly diseases.

1. Introduction

The neglected tropical diseases (NTDs) are important subjects of matter worldwide. The definition is not a consensus among the most important entities in the world devoted to NTDs studies, such as the World Health Organization (WHO), *Médecins sans Frontières*, the Centers for Disease Control and Prevention (CDC), and PLOS Neglected Tropical Diseases Journal, a peer-reviewed open journal devoted to the study of neglected tropical diseases. Independently, all agreed that NTDs consist of several infectious and parasitic diseases with prevalence in tropical or subtropical regions, usually found in populations in poor living conditions. They are called neglected because of the less attention they receive from drug manufacturers and public policymakers despite the high death rates [1,2].

According to WHO, NTDs affect 149 countries and more than 1 billion people [3]. To date, this represents more than 12% of the entire population in the world. The tropical and subtropical climates favor the emergence of disease agents and vectors because of the warm and wet environmental conditions [4]. This fact associated with the precarious conditions of basic sanitation, potable water, and efficient health

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policies in these countries is the main reason for the high number of cases and deaths. Most of the NTDs cause noticeable physical damage, with aggravating socioeconomic consequences because of discrimination and incapacity to work, which contributes to a poverty cycle where it is difficult to assert if the poverty is the consequence of the disease or the opposite [5].

Although these diseases are currently concentrated in Africa, Asia, and Latin America [6], they can also be found in developed countries such as Europe, North America, South-East Asia, and Australasia because of local poverty, immigration and other factors [7]. Furthermore, it was reported by Booth (2018) that even countries with almost zero cases of NTDs, might experience an increase in its numbers because of climate change on the planet [8].

The list of countries and diseases is also not consensual because it is constantly changing upon the eradication, emergence, reemergence of the diseases, and the interpretation of the responsible entities and internal government. The controversies are increased by viewpoints such as from Molloy et al. (2017) [9] claiming that cryptococcal meningitis should be (and it is not until this date) present in the WHO and PLOS lists. To pinpoint these divergences, the updated lists from WHO [10] and PLOS NTDs [11] were summarized in Table 1, where it is perceptible the longer worldwide list of PLOS than WHO.

Table 1
Neglected tropical diseases list by the entity.

NTDs	WHO	PLOS NTDs[a]
Amebiasis including *Naegleria*	–	X
Arboviral infections (Chikungunya, Zika, Japanese encephalitis, Jungle yellow fever, and others)	–	X
Babesiosis	–	X
Balantidiasis	–	X
Bartonella	–	X
Bovine Tuberculosis in Humans	–	X
Buruli ulcer	X	X
Chagas disease	X	X
Cholera	–	X
Dengue (Arboviral infection)	X	X
Dracunculiasis (Guinea-worm disease)	X	X
Echinococcosis	X	X
Enteric pathogens (Shigella, Salmonella, *E. coli*)	–	X
Enterovirus 71 and related viruses	–	X
Foodborne trematode infections	X	X
Giardiasis	–	X
HTLV-1, HTLV-2, and other non-HIV retrovirus infections	–	X
Human African trypanosomiasis (sleeping sickness)	X	X
Leishmaniasis	X	X
Leprosy (Hansen's disease)	X	X
Leptospirosis	–	X
Loiasis	–	X
Lymphatic filariasis (Elephantiasis)	X	X
Mycetoma, chromoblastomycosis, and other deep mycoses	X	X
Melioidosis	–	X
Noma (Orofacial Gangrene)	–	X
Onchocerciasis (river blindness)	X	X
Other food-borne helminthiases (Trichinosis, Anisakiasis, Gnathostomiasis)	–	X
Paracoccidiomycosis	–	X
Plasmodium vivax and other non-P. *falciparum* malaria	–	X
Podoconiosis	–	X
Q fever	–	X
Rabies	X	X
Relapsing Fever	–	X
Rift Valley fever	–	X
Scabies and other ectoparasites	X	X
Schistosomiasis	X	X
Snakebite envenoming	X	X
Soil-transmitted helminthiasis	X	X
Taeniasis and cysticercosis	X	X
Toxocariasis and other larva migrans (Baylisascaris)	–	X
Trachoma	X	X
Viral hemorrhagic fevers	–	X
Yaws (Endemic treponematoses)	X	X

[a] The list does not consider cusp diseases.

Initiatives all around the world have been pivotal in the fight against NTDs. The Drugs for Neglected Diseases initiative (DNDi), a non-profit research organization seeking the development of new treatments for neglected patients was created in 2003 by the initiative of the *Médecins Sans Frontières* after the donation of a portion of the Nobel prize award to help the cause [12]. The increasing pressure and conscientization alongside solidarity boosted the effective actions of pharmaceutical and related companies. In 2012, the London Declaration on NTD was signed. Constituted by several partners in a global effort, it is helping the neglected population. More than 1 billion people received treatment for at least one NTD in 2016 [13].

In the year 2020, it was established the first-ever World NTD Day (on January 30th) [14] to celebrate the recent progress in the fight against the diseases, to mobilize companies and countries for actions, investments, and as a reminder of the challenges yet to come. Over 350 partners signed up, and the funding to launch this endeavor was generously provided by the Crown Prince Court of Abu Dhabi. It is expected an eradication of most of NTDs by the year 2030, according to The Agenda 2030 [15].

Despite the joint efforts to develop effective and safe drugs, to treat patients, and to eliminate vectors, the correct and fast diagnosis is the first step necessary to hasten the treatment. Some diseases are easily diagnosed through pattern recognition or clinical evaluation of the physical symptoms, but the identification in the early stages and asymptomatic diseases is often difficult. A molecular and serological diagnosis such as reverse transcription-polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assay (ELISA) is usually the main choices of action making the use of the knowledge of the pathogen genome and the immunologic response in the host [16]. However, these and other tests demand high quality personal, expensive equipment and chemicals, and are time-consuming, drawbacks exponentiated by the NTDs major regions consisting of poor infrastructure and resources. Moreover, these tests still suffer from cross-reactivity, e.g., the arbovirus Dengue and Zika [17], and from false-positive and false-negative results, which can lead to a disastrous scenario as it is happening during the SARS-CoV-2 pandemic [18,19].

It becomes of the utmost importance the development of diagnostic platforms to detect the diseases at the earliest stages with high sensitivity, specificity, robustness, low-cost, allied to an easy-to-use device. Biosensors present these advantages besides the possibility of the development of miniaturized systems for in loco determination, which fits the requirements for low-income countries, and hard-to-reach regions, such as war zones or indigenous tribes.

Therefore, the objective of this work is to present the results from a survey in the past ten years (2010–2020) regarding the recent developments of electrochemical biosensors for some NTDs reported in the WHO list (Table 1), particularly with the focus on Malaria, Chagas, Leishmaniasis, Dengue, Zika, Chikungunya, Schistosomiasis, Leprosy, Human African trypanosomiasis (sleeping sickness), Lymphatic filariasis and Rabies. Each disease is discussed individually, with a critical analysis of the proposed devices regarding new trends, efficiency, challenges, and cost. Researchers eager to join the fight against NTDs through the development of biosensors will find useful information about proof of concepts for point of care (POC) devices, commercial systems already in use, and perspectives to further developments.

2. Electrochemical biosensors

Biosensors are a billion-dollar global market invested in the improvement in health, environment, agribusiness, food, and several industrial segments. They reached scientific and commercial notoriety due to their many advantages such as sensitivity, selectivity, steady-state and transient response times, sample throughput, reproducibility, stability, and lifetime [20].

The system operates using bioreceptors (enzymes, genetic material,

antibodies, antigens, cells, or tissue) immobilized directly or indirectly over a transducer surface so the biologic material may recognize the specific analyte under evaluation. The transducer is responsible for the conversion of the response from the biological event into a quantifiable and measurable signal.

Among the many transduction options, the electrochemical stands out as one of the most used in biosensor development because of its particularities such as low-cost equipment, the possibility of simultaneous determination of different analytes, and analysis in complex samples. Moreover, there is the availability of a roster of techniques based on the specificity of each system. The application, alteration, and measurement of different units such as potential, current, charge, and resistance are used in potentiometric, amperometric, coulometric, and impedimetric systems, respectively. Such biosensors possess similar or even superior features when compared to conventional techniques [20, 21]. Fig. 1 shows a general scheme of a biosensor with electrochemical transduction.

The growing interest in biosensor development and their application is based on the availability of several biologic materials, the diversity of electrodes as transducers, and the enormous possibility to modify the electrodes to properly fit the bioreceptor, such as magnetic compounds, conductive, functionalized, or molecularly imprinted polymers, self-assembled monolayers, nanosized structures, and dendrimers.

The genosensors operate with fragments of DNA or RNA as probes, immobilized over the transducers as well as targets. The high specificity and strong interaction between the strands through hybridization avail direct detections through the oxidation/reduction of the nitrogenated bases, mass increase, or impedance change. Also, indirect detection can be applied through the electrochemical signal of mediators or intercalators [22].

The immunosensors are based mainly on the specific interactions between an antigen and an antibody, but they can also include other components of the immune system. Both molecules can be immobilized over the surface of the transducer, with the purpose to detect pathologic changes in the biologic system as cancer [23] and tropical diseases [24].

Enzymatic biosensors work based on the catalytic properties of the enzymes, quantifying the increase in the product concentration, the decrease in the substrate concentration, or no alteration in these profiles because of the action of enzymatic inhibitors, such as pesticides. The specific configuration of the enzymes ensures the development of a biosensor with high specificity [25].

Despite enzymes, antibodies, antigens, and DNA derivatives are the main choices for biosensor development, other molecules can be used to develop important biosensors, such as glycans and lectins [26], and bacteriophage [27]. Moreover, innovative systems based on the traditional biomolecules are gaining attention as molecularly imprinted polymers, responsible to mimic the active site of a biomolecule [28], and aptamers for the development of aptasensors [29].

In the last few years, the excellent results and perspectives have motivated the use of biosensors as an emergent alternative in comparison with clinical analysis, for the detection of such diseases, especially with the premise of low-cost point of care devices. In this sense, for disease diagnosis, electrochemical biosensors make use mainly of enzymes, genetic material, and antigens or antibodies as bioreceptors, based on their applicability in a determined field of interest.

3. Recent developments in electrochemical biosensors for NTDs

NTDs are a worldwide public health problem that affects the poorest regions of the planet that suffers from government negligence, disinterest from pharmaceutical companies, and low investments in research for fast and early diagnosis.

For most of the diseases reported here, robust, costly, and time-consuming diagnostic methods are used as a standard, which limits the carrying out of field tests. Some examples of methodologies are immunochromatographic tests, molecular methods such as polymerase chain reaction (PCR), or using proteomic studies [30–32].

Biosensors for NTDs diagnosis are prominent. Although a survey points several prototypes, no device was approved by legislation, and it is ready to use so far. This fact stresses the importance of investments once the aggregated advantages of these systems would reduce the expenses with unnecessary or mistaken medication and treatment.

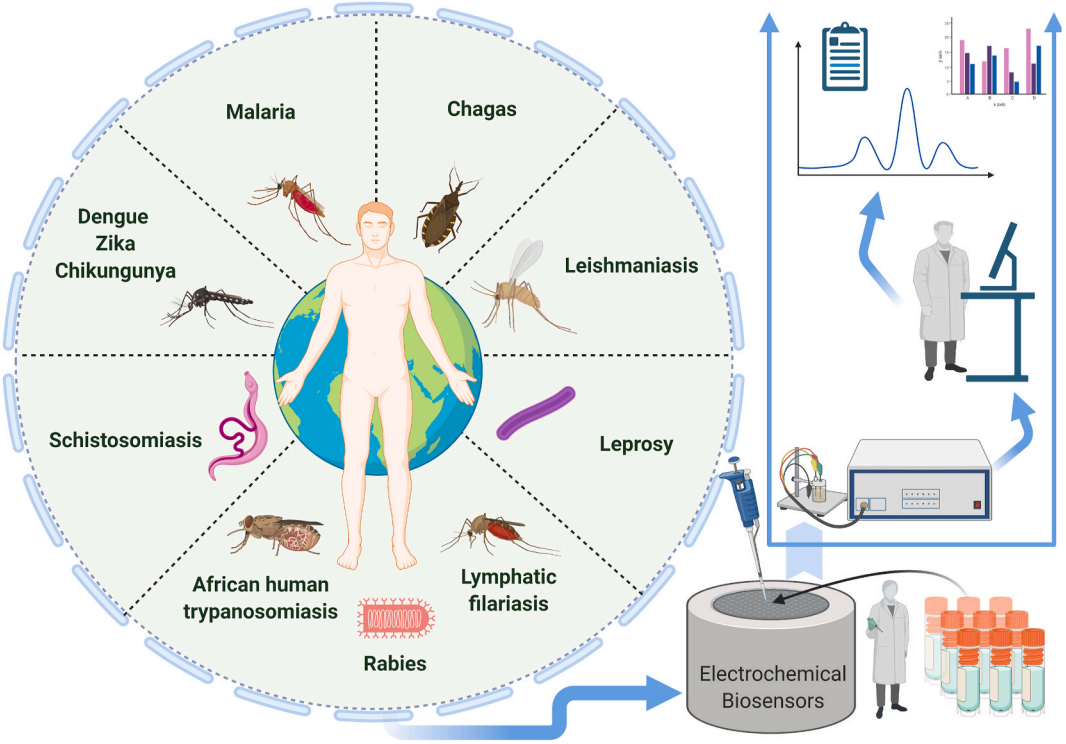

Fig. 1. General scheme of the biosensor with electrochemical transduction. Created with BioRender.com.

Therefore, this work brought together the electrochemical biosensors developed for the main NTDs, as shown in Fig. 2, found in articles published in the past ten years (2010–2020).

Whereas to early detect the diseases, to solve specificity issues like cross-reactivity usually obtained using traditional methods, or to present an innovative, improved, and low-cost system, it is clear the reasons for the growing attention at the profitable and practical biosensors field. Despite the many efforts and innovative studies such as the use of a paper-based biosensor [33], and wearable perspectives [34], few systems are available in the market, which demands an urgent upgrade from proof of concepts to operated and commercial devices.

3.1. Malaria

Malaria is one of many illnesses listed in Table 1, that occurs around the world for a long time, but lacking good control, making this a risk for society [35]. It is more intense in developing countries, which normally present poverty and worst health conditions. Generally, the climate of these places is tropical or subtropical, which can be favorable to find the major vector of the disease [36,37]. Despite the development of technology, science, and medicine, the Malaria world mortality is more than 100 million people per year [38]. There was an increase of two million new notifications of Malaria around the world according to WHO just between 2016 and 2017 [37].

The manifestation of Malaria occurs due to protozoan microorganisms. The most common species to cause Malaria in humans are the following plasmodium*: falciparum, vivax, malariae, knowlesi,* and *ovale,* of which the *P. falciparum* and *P. vivax* are responsible for the worrying cases [38,39]. The main way of Malaria transmission is per sting of *Anopheles* mosquito infected with the *Plasmodium*. The other two possibilities of infection can be through blood transfusion (having contact with the contaminated blood), and during pregnancy, with an infected mother passing the disease to the fetus [40,41].

During the plasmodium incubation stage, the host is asymptomatic. When the cycle of plasmodium starts in the human body, any symptoms are common, which can variate according to the type of plasmodium or the disease level. High fever, myalgia, abdominal pain, fatigue, and arthralgia are examples of the symptoms associated with Malaria infection. The usual symptoms are nausea, vomit, jaundice, and pallor, and it depends on patient conditions, like age, health, or pregnancy [42,43]. In this sense, the early diagnostic of malaria is crucial to control the disease and to have good results in the treatments with medication.

There are a variety of papers addressing the use of electrochemistry to develop biosensors for Malaria detection [44,45]. Soraya et al. (2019) [46] for example, developed a biosensor to identify *Plasmodium falciparum* Histidine-Protein II (P*f*HRP2) in saliva samples. In this work, it was used interdigitated electrodes associated with impedimetric measurements. Moreover, the authors investigated the sensor behavior in buffer solution and saliva samples, with considerable limits of detection (2.5 pg mL^{-1} in buffer solution and 25 pg mL^{-1} in saliva samples), with lower values than the obtained through the rapid tests (4.0 ng mL^{-1}). It is important to emphasize that the use of saliva as a sample is an advantage in terms of a new method with simplicity, no invasive tests, and less cost.

Ruiz-Vega et al. (2020) [44] developed an amperometric magnetic immunosensor using a compact cell and portable electrode as can be seen in the representation of the assay presented in Fig. 3. The microfluidic paper double-sided screen-printed carbon electrode (MP-sdSPCE) associated with magnetic beads was developed for this work. The linear range obtain was between 6.25 and 100 ng mL^{-1} and the limit of detection found was 8.5 ng mL^{-1} in blood samples. The authors also presented detection studies with *Plasmodium* in vitro, with responses around 300 parasites μL^{-1} (200 parasites μL^{-1} is the limit recommended by WHO). The developed sensor was quite satisfactory and therefore proved its efficiency in real applications.

Table 2 presents more examples of biosensors towards the detection of Malaria. There are different ways of assembling these sensors and different techniques used, which further increases the variety of methods to assist in disease control.

It is worth noting that the major analyte used for Malaria detection is the biomarker *Plasmodium falciparum* (glutamate dehydrogenase, lactate dehydrogenase, or histidine-rich protein 2) through immunoassays using antibodies or through selected aptamers. Usually, antibody-

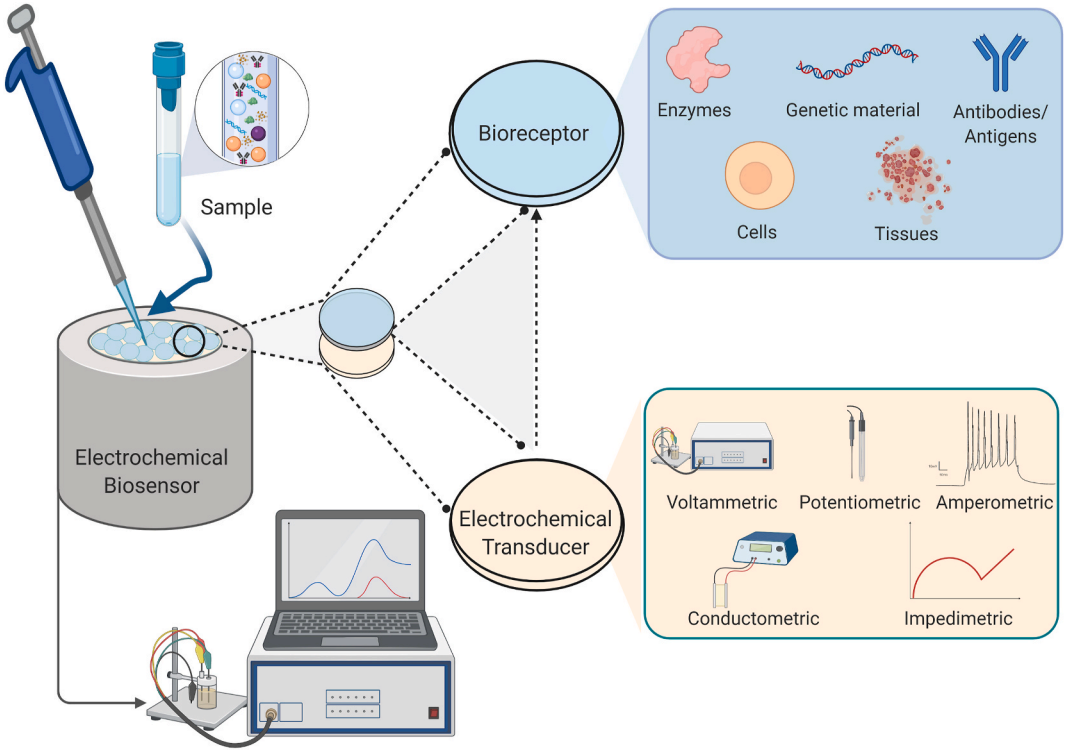

Fig. 2. Main neglected tropical diseases that were investigated in this work using electrochemical biosensors for their detection. Created with BioRender.com.

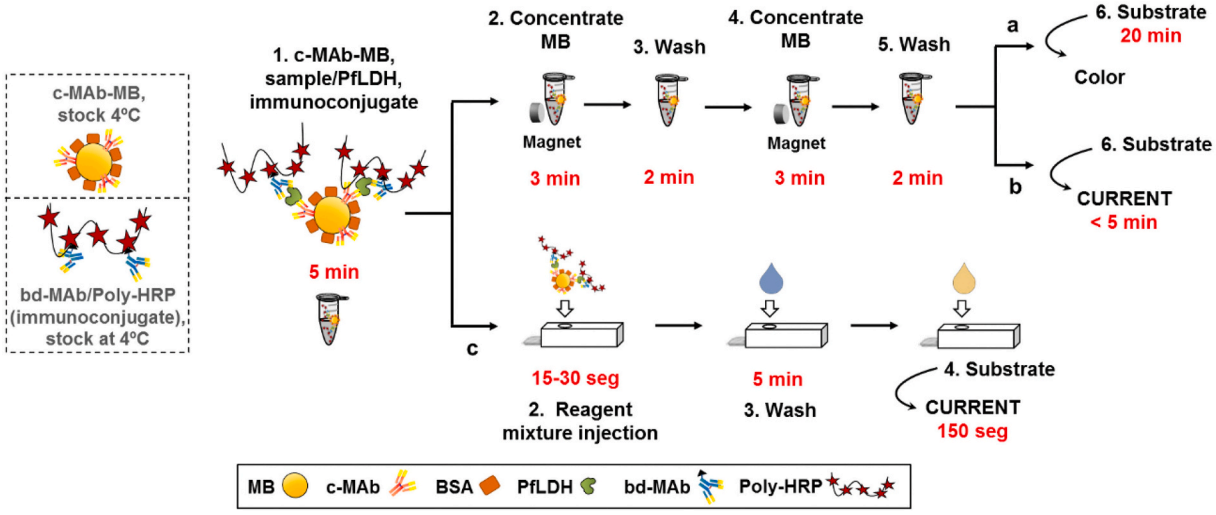

Fig. 3. Different formats of the single-step magneto-immunoassay. a) Spectrophotometric detection. b) Electrochemical detection using SPCE. c) Electrochemical detection at a MP-dsSPCE, with washes and detection performed on-chip. Republished from Ref. [44]; permission conveyed through Copyright Clearance Center, Inc, License Number 5083630133668.

antigen interactions or aptamer-antigen interactions do not provide direct electrochemical detection, such as redox sites or potential change. Therefore, it is usual to use biomolecules labeled with the enzyme horseradish peroxidase (HRP) [47,57] for the indirect detection of the electroactive products of catalyzes and the use of redox indicators, such as methylene blue [55,56]. However, the majority of the papers dedicated their efforts in the direct electrochemical detection through EIS based on the electrode surface changes upon the presence of the analyte. The efficiency of such systems can be verified by the work of Singh [52], with the lowest LOD found for Malaria detection on the scale of attomolar. Thus, through impedimetric technique, the number of modification steps is diminished, so the cost, but with very effective devices.

Based on the amount of information obtained through Table 2 and the diversity of biosensors, it is interesting to note that this health problem is still recurring. The different possibilities reported here can be further explored to improve not only the identification of the disease but also to give a fast prognosis to Malaria. This would probably facilitate the earlier treatment and likely cure Malaria resulting in a decrease in mortality.

3.2. Chagas disease

Although the parasite has existed for centuries, it was only in 1909 that the symptoms were associated with Chagas disease (CD) due to the studies of Carlos Chagas. Without such pretensions, Carlos Chagas started a new study on blood-feeding insects living in the precarious area. Then, after dissecting the insects, he could identify the protozoan *Trypanosoma* [67]. Today, it is well-known that the disease is caused by the protozoan parasite *Trypanosoma cruzi*.

The most common vector is the *Triatomine* bugs (*Triatomite infestans, Triatomite dimiata, or Triatomite barberi*), a species that may variate according to the region or country. These insects also determine the biology behavior. In Brazil, they are knowing as "*Barbeiro*" and have two dissemination characteristics: the nocturnal and hematophagy habits. Moreover, these bugs live typically into the wall or roof cracks, normally in peri-domiciliary structures, found recurrently in rural and poor properties [68,69].

The vector generally excretes the protozoan with its feces and *T. cruzi* enters the host through the bite wounds. Also, the bitten person may scratch the region taking the excretion to the eyes or mouth. Alternatively, the transmission of Chagas can be from contact with contaminated food, blood transfusion, mother-to-child transmission during pregnancy, during organ transplant, or due to laboratory accidents [70–72].

The symptoms depend on the disease stage. In the first phase, with a big quantity of *T. cruzi* in the blood, the recurrent symptoms are mild and unspecific. The infected present fever, headache, muscle pain, pallor, difficulty in breathing, enlarged lymph glands, and abdominal or chest pain. In the worst phase, the parasites dwell mainly in the heart or digestive muscle, and the patient is susceptible to cardiac disorders, digestive, and neurological alterations. Without treatment, the problems can evolute to cardiac arrhythmias or progressive heart failure, which can lead to death [67,70,73].

The CD is also known as American trypanosomiasis because of the high number of infected people on this continent. The estimate is that around 6 and 8 million people get infected and 50,000 die a year because of disease [71,74]. Therefore, the necessity of early identification, good treatment, and control of Chagas is clear. An alternative to circumvent some of the diagnostic problems was reported by Regiart et al. (2016) [75] through an amperometric immunosensor to identify *T. cruzi* in human serum. *T. cruzi* shed-acute-phase-antigen (SAPA) was immobilized over a screen-printed carbon electrode (SPCE) modified with gold nanoparticles (MPA-AuNP). The immunosensor (SAPA–MPA–AuNP/SPCE) showed a limit of detection of 3.03 ng mL^{-1}, good stability, and reproducibility. Moreover, the method presented a faster test (26 min) when compared with the usual ELISA (90 min). Associated with the simplicity of this sensor in terms of modification and immobilization methodology, it is a good option to use to diagnose CD.

Alternatively, Cortina et al. (2016) [76] developed a portable and inexpensive methodology of point-of-care serodiagnoses to some disease depending on the microorganism immobilized. Fig. 4 shows a schematic representation of the electrochemical enzyme-linked magnetic beads immunoassay (EMBIA) and detection principle using a screen-printed carbon electrode. The immunosensor was validated with four diseases, amongst them the Chagas Disease. In this case, comparative tests with ELISA and immunomagnetic assay using the same combination antigen showed excellent results of EMBIA.

Table 3 presents information regarding electrochemical biosensors development for Chagas Disease determination. It is interesting to note the evolution of biosensor development over the years within the same research group. Ferreita et al. (2010) [77] developed a study using a screen-printed electrode modified with the Chagas' protein Tc85. The work focused only on electrode modification without analyte detection. One year later, the same research group developed a completed

Table 2
Electrochemical biosensors to Malaria.

Technique[a]	Electrode[b]	Modification[c]	Analyte	Sensor	Sample	Limit of detection	Reference
AP	m-GEC	MNP or MB/anti-HRP2 IgM MAb/*Pf*HRP2/anti-HRP2-HRP IgG MAb	*Pf*HRP2	Immunosensor	Spiked human serum	3.6×10^{-10} g/mL	[47]
QCM	GQC	TA/DDT/EDC/NHS/anti-*Pf*HRP-2 antibody	*Pf*HRP2	Immunosensor	Human serum	1.2×10^{-8} g/mL	[48]
EIS	Au	Thiol-modified *Pf*LDH and *Pv*LDH aptamer	*Pv*LDH *Pf*LDF	Aptasensor	Human blood	1.085×10^{-13} M (*Pv*LDH) 1.201×10^{-13} M (*Pf*LDF)	[49]
QCM	SQC	MPA/EDC/NHS/avidin/ biotinylated probe from *P. falciparum* and *P. vivax*	target DNA amplified from blood infected with either *P. falciparum* and *P. vivax*	Genosensor	Human blood	nd	[50]
QCM	SQC	MPA/EDC/NHS/avidin/ biotinylated probe from *P. falciparum* and *P. vivax*	target DNA amplified from blood infected with either *P. falciparum* and *P. vivax*	Genosensor	Human blood	nd	[51]
EIS	GCE	fCZnONF/MPA/EDC/NHS/ Anti-P*f*HRP2	*Pf*HRP2	Immunosensor	Commercial	6.8×10^{-18} g/mL	[52]
DPV **EIS**	GCE	GO/P38	*Pf*LDH	Aptasensor	Human blood	5×10^{-16} M	[53]
EIS	SPGE	AuNP/MabD2	*P. falciparum* infected red blood cells	Immunosensor	Red blood cells	nd	[54]
CV **EIS** **SWV**	SPCE	Carboxylated CNTs/EDC/NHS/ EA CSP210-270	Anti-CSP 210 or Anti-CSP 247 antibodies	Immunosensor	Serum	5×10^{-14} g/mL	[45]
CV **CC**	ITO	APTES/GA/anti-*Pf*HRP2 IgM	*Pf*HRP2	Immunosensor	Human saliva	2.2×10^{-12} g/mL	[55]
CV **CC**	ITO	APTES/GA/anti-*Pf*HRP2 IgM	*Pf*HRP2	Immunosensor	Human plasma and whole blood	1×10^{-14} g/mL (plasma) 1.8×10^{-14} g/mL (blood)	[56]
CA	SPGE	anti-PfHRP 2/HRP/AuNP	*Pf*HRP2	Immunosensor	PBS and human serum	3.6×10^{-11} g/mL (PBS) 4×10^{-11} g/mL (serum)	[57]
CA	SPGE	anti-PfHRP 2/HRP	*Pf*HRP2	Immunosensor	PBS and human serum	2.14×10^{-9} g/mL (PBS) 2.95×10^{-9} g/mL (serum)	[57]
CR	Au	MWCNT-ZnO NF/EDC/NHS/ anti-HRP2 antibody	*Pf*HRP2	Immunosensor	Synthetic	9.7×10^{-16} g/mL	[58]
EIS	Au	DSP/B4	*Pf*HRP2	Aptasensor	Human serum	3.15×10^{-12} M	[59]
CC	Au	CM-Ru$(NH_3)_6^{3+}$/CM-anti*Pf*HRP2-MeBl/VPS-AO/ PET	*Pf*HRP2	Immunosensor	Human blood	nd	[60]
EIS	Au	2008s aptamer/MCH	*Pf*LDH	Aptasensor	Buffer and human serum	8.4×10^{-13} M (buffer) 1.3×10^{-12} M (serum)	[61]
CA	SPGE	pLDH antibody/AuNP	*Pf*LDH	Immunosensor	Buffer and serum	1.9×10^{-11} g/mL (buffer) 2.3×10^{-11} g/mL (serum)	[62]
EIS	Au	MCH/NG3	*Pf*GDH	Aptasensor	Serum	7.7×10^{-13} M	[63]
PO	ISFET	LAMP and pH-LAMP	gene Kelch 13 of *P. falciparum* (LAMP-PfK13)	Genosensor	Synthetic	1 copy per reaction for LAMP and 10 copies per reaction for pH-LAMP	[64]
PO	IDμE	*Pf*DGH aptamer/MCH	*Pf*GDH	Aptasensor	Spiked buffer and serum	1.67×10^{-11} M (buffer) 4.86×10^{-11} M (serum)	[65]
EIS	IDE	APTES/GA/Anti-*Pf*HRP2 IgG MAb	*Pf*HRP2	Immunosensor	Spiked saliva	2.5×10^{-11} g/mL	[46]
EIS	Au	Malaria 2008s Aptamer/PEG	*Pf*LDH	Aptasensor	Diluted and whole human serum	7.7×10^{-13} M (diluted) 1.49×10^{-12} M (serum)	[66]
AP	MP-dsSPCE	MB/c-MAb/PfLDH/bd-MAb/ Poly-HRP	*Pf*LDH	Immunosensor	Human blood	2.51×10^{-9} g/mL	[44]

[a] **AP:** Amperometry; **QCM:** Quartz crystal microbalance; **EIS:** Electrochemical impedance spectroscopy; **DPV:** Differential pulse voltammetric; **CV:** Cyclic voltammetry; **SWV**: Square wave voltammetry; **CC:** Chronocoulometry; **CA:** Chronoamperometry; **CR:** Chemiresistive; **PO:** Potentiometric.

[b] **m-GEC:** Graphite-epoxy composite paste with a small neodymium magnet placed into the center of the electrode; **GQC:** Gold quartz crystal; **SQC:** Silver quartz crystal; **GCE:** Glassy carbon electrode; **SPGE:** Screen-printed gold electrode; **SPCE:** Screen-printed carbon electrode; **ITO:** Indium tin-oxide coated glass slide; **ISFET:** Ion-sensitive field-effect transistor; **IDμE:** Inter-digitated gold microelectrodes; **IDE:** Interdigitated electrode; **MP-dsSPCE:** Microfluidic paper, double-sided, screen-printed carbon electrode.

[c] **MNP**: magnetic nanoparticles; **MB**: magnetic beads; **P*f*HRP2**: *Plasmodium falciparum* histidine-rich proteins 2; **IgG**: immunoglobulin G; **MAb**: monoclonal antibodies; **TA**: DL-thioctic acid; **DDT**: 1-dodecanethiol; **EDC**: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; **NHS**: N-hydroxysuccinimide; ***Pv*LDH:** *Plasmodium vivax* L-Lactate Dehydrogenase; *Pf*GDH**:** *Plasmodium falciparum* Glutamate Dehydrogenase; **MPA**: mercaptopropionic acid**; fCZnONF**: functionalized Cu-doped ZnO nanofibers; **GO**: graphite oxide; **P38-GO**: *Plasmodium falciparum* lactate dehydrogenase specific aptamer immobilized in carbon oxide matrix; **AuNP**: gold nanoparticles; **MabD2**: Monoclonal antibody raised against the malaria infected cells and antibody control); **CNT**: carbon nanotube; **EA**: ethylenediamine; **CSP**: Circumsporozoite protein containing the antigen region; **APTES**: (3-Aminopropyl)triethoxysilane; **GA**: glutaraldehyde; **IgM:** Immunoglobulin M; **MWCNT:** multi walled carbon nanotube; **DSP**: Dithiobis (Succinimidyl Propionate); **B4**: Amine functionalized aptamer; **CM**: cellulose membrane; **MeBl**: methylene blue; **VPS**: Vivid plasma separation membrane; **AO**: ascorbic oxidase; **PET**: polyethylene terephthalate film with inlet; **MCH**: 6-mercapto-1-hexanol; **NG3**: Thiolated *Plasmodium falciparum* glutamate dehydrogenase aptamer; **LAMP**: loop-mediated isothermal amplification; **PEG**: Monofunctional methoxy-polyethylene glycol thiol **c-MAb**: capture monoclonal antibodies; **bdMAb**: detection monoclonal antibodies; **Poly-HRP**: poly-horseradish peroxidase streptavidin conjugate.

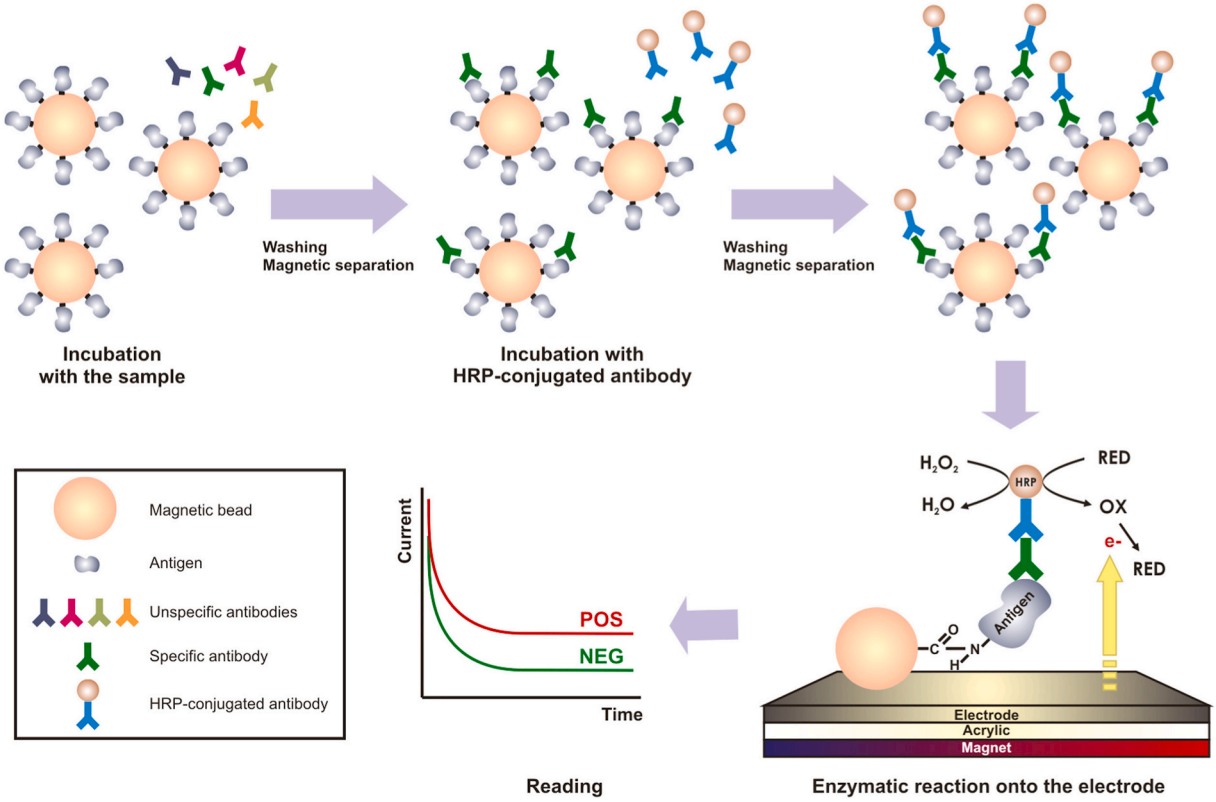

Fig. 4. Schematic representation of the electrochemical enzyme-linked magnetic beads immunoassay and detection principle. Antigen-coated magnetic particles are incubated with the serum samples, washed and then incubated with HRP-conjugated secondary antibodies. After washing, the particles are magnetically collected and placed onto the surface of the electrode. Peroxidase activity is amperometrically recorded using an 8-channel portable potentiostat after adding H2O2 and hydroquinone as the substrate and redox mediator, respectively. All incubation and washing steps are performed in 8-tube strips using a magnetic rack without the need of centrifugation. Republished from Ref. [76]; permission conveyed through Copyright Clearance Center, Inc, License Number 5083630841813.

Table 3
Electrochemical biosensors for Chagas disease.

Technique[a]	Electrode[b]	Modification[c]	Analyte	Sensor	Sample	Limit of detection	Reference
EIS	SPGE	GA/*T. cruzi* antigen	nd	Immunosensor	Synthetic	nd	[77]
AP	Au	MPSA/DPC/TRX-pL-Q1	anti-*T. cruzi* IgG	Chimeric biosensor	Human Serum	6.2×10^{-8} g/mL	[80]
AP	SPCE	AuNP/MPA/EDC/NHS/*T. cruzi* antigen	anti-*T. cruzi* IgG	Immunosensor	Human serum	3.065×10^{-9} g/mL	[79]
LSV	CD-trode	SBZA/*T.cruzi antigen*	anti-*T. cruzi*	Immunosensor	Human serum	nd	[78]
CV							
CA							
EIS	ITO	PVS/AgNP/SiPy^{+}Cl^{-}/Chagas antigen	anti-*T.cruzi*	Immunosensor	Extract from ELISA test kit	nd	[81]
AP	SPCE	SCMB/NHS/EDC/*T.cruzi* antigens	anti-*T.cruzi*	Immunosensor	Human serum	nd	[76]
AP	SPCE	AuNP/MPA/EDC/NHS/SAPA/	anti-*T. cruzi* IgM	Immunosensor	Human serum	3.03×10^{-9} g/mL	[75]
PO	FET	InP NW/PEG-NHS/EDC/anti-IBMP8.1	IBMP8.1	Immunosensor	Synthetic protein	6.0×10^{-15} M	[82]
EIS	dSPCE	poly(4-HPA)/IBMP8.1	anti-*T. cruzi*	Immunosensor	Human and dog sera	1:10,240 dilution	[83]

[a] **EIS:** Electrochemical impedance spectroscopy; **AP:** Amperometry; **LSV:** Linear sweep voltammetry; **CV:** Cyclic voltammetry; **CA:** Chronoamperometry; **PO:** Potentiometric.

[b] **SPGE:** Screen-printed gold electrode; **SPCE:** Screen-printed carbon electrode; **CD-trode:** Gold film electrode obtained from a recordable compact disk; **ITO:** Indium tin-oxide coated glass slide; **FET:** Field-effect transistor; **dSPCE:** Dual screen-printed carbon electrode.

[c] **GA:** Glutaraldehyde; **MPSA:** 3-Mercapto-1-propanesulfonic acid; **DPC:** 1,3-diisopropylcarbodiimide; **AuNP:** Gold nanoparticles; **MPA:** Mercaptopropionic acid; **SBZA:** 4- (methylmercapto)benzaldehyde; **PVS:** Polyvinyl sulfonate; **AgNP:** Silver nanoparticles; **SiPy^{+} Cl^{-}:** 3-n-propylpyridinium chloride; **SCMB:** Super-paramagnetic COOH-modified microbeads; **NHS:** N-hydroxysuccinimide; **EDC:** 1-ethyl-3-(3-di-methyl-aminopropyl) carbodiimide hydrochloride; **InP NW:** Indoum phosphite nanowires; **PEG:** Polyethylene glycol; **AuNP:** Gold nanoparticles; **SAPA:** Recombinant *T. cruzi* shed-acute-phase-antigen; **poly(4-HPA):** poly(4-hydroxyphenylacetic acid); **TRX-pL-Q1**: chimeric protein bearing Thioredoxin Residue - (Lys)3 – Recombinant peptide 1 and Recombinant peptide 2; IBMP8.1: recombinant antigen from Instituto de Biologia Molecular do Paraná – Brazil.

cost-effective, gold CDtrode-based biosensor using the same protein to detect anti-*T. cruzi* with excellent responses with real samples from positive patients for Chagas' disease [78]. Pereira et al. (2011) [79] developed a microfluidic device based on the purification of antigens from epimastigote of *T.cruzi* to detect anti-*T. cruzi* IgG. In 2016 the same research group improved specificity using a recombinant antigen *T.cruzi* [75]. Both devices share the same biosensor assembly and virtually similar figures of merit (linear range, LOD, intraday, and interday precision), with the difference of the microfluidic system and type of immunoglobulin used (IgM and IgG). However, the latter presents simplicity and the possibility of miniaturization for a point-of-care device.

One advantage of developing an immunosensor is the possibility of immobilizing either the antibody or the antigen over the electrode. Janissen et al. (2017) [82] and Cordeiro et al. (2020) [83] developed Chagas' biosensor based on the recombinant protein IBMP8.1. While Janissen immobilized the antibody to detect the antigen, Cordeiro immobilized the antigen to detect the antibody. Both systems, despite the difference in the methodology, reached excellent electrochemical results. However, apart from this exception, it seems a consensus that almost every work performed to diagnose Chagas uses the immobilization of the antigen for antibody detection. One reason is the possibility to perform a sandwich ELISA-like assay with HRP-labeled secondary antibodies bound to the analyte. Therefore, an electrochemical signal can arise from the detection of a redox enzymatic product, such as 4-tert-butylcatechol [75,79], hydroquinone [76], ferrocenemethanol [80], and iodide [78], mediated by the reaction of the enzyme and hydrogen peroxide.

The number of recent works about biosensors to diagnose Chagas disease is smaller than the presented to Malaria. According to our survey, several scientific developments using other robust methodologies, such as the chromatographic or molecular methodologies have been more common [84,85]. CD is an important disease with high death rates and biosensor research can help to improve the diagnosis. The few papers published in the last ten years are worrisome since it is a matter of public health and the results obtained from the data in Table 3 seem promising.

3.3. Leishmaniasis

Leishmaniasis is a worrisome tropical disease that can affect animal and human species with occurrence all over the world and with around 40,000 deaths and one million new infected people annually [86,87].

Leishmaniasis is caused by a vast group of *Leishmania* protozoan species. The disease manifestation change according to these species and region [88]. In general, the most important are Visceral leishmaniasis (VL) and Cutaneous leishmaniasis (CL). VL is commonly harmful to the internal organs (spleen, liver, ganglia, or bone marrow) and the CL usually causes ulcerations and skin wounds. Both cause symptoms like fever, slimming, anemia, and bleeding, which can lead to death if untreated [89,90].

For other neglected diseases, leishmaniasis is common in developing countries and precarious sanitation resources. Moreover, a high number of infected people come from places near forestation areas, without control of the parasite and the disease vector, the Sandfly insect [91–93].

Characterized by the yellow color, these invertebrate species present variations of names according to the region. They are of the same group of bugs in general and the most common transmission happens because of the bite of the insect. When it occurs, the vertebrated animal will become the host of the *Leishmania*. It is important to state that the host can be humans or wild mammals, like the skunk and laziness, or domestics animals as dogs [94,95].

The extensive use of printed sensors shows the ease of many diagnostic methodologies. Cordeiro et al. (2020) [83] proposed a dual detection system based on an impedimetric immunosensor for the simultaneous detection of anti-*T. cruzi* and anti-*L. infantum* antibodies in human and dog serum samples using a dual screen-printed carbon electrode modified with poly(4-hydroxyphenylacetic acid), where IBMP 8.1 and rLci1A/rLci2B recombinant antigens were immobilized

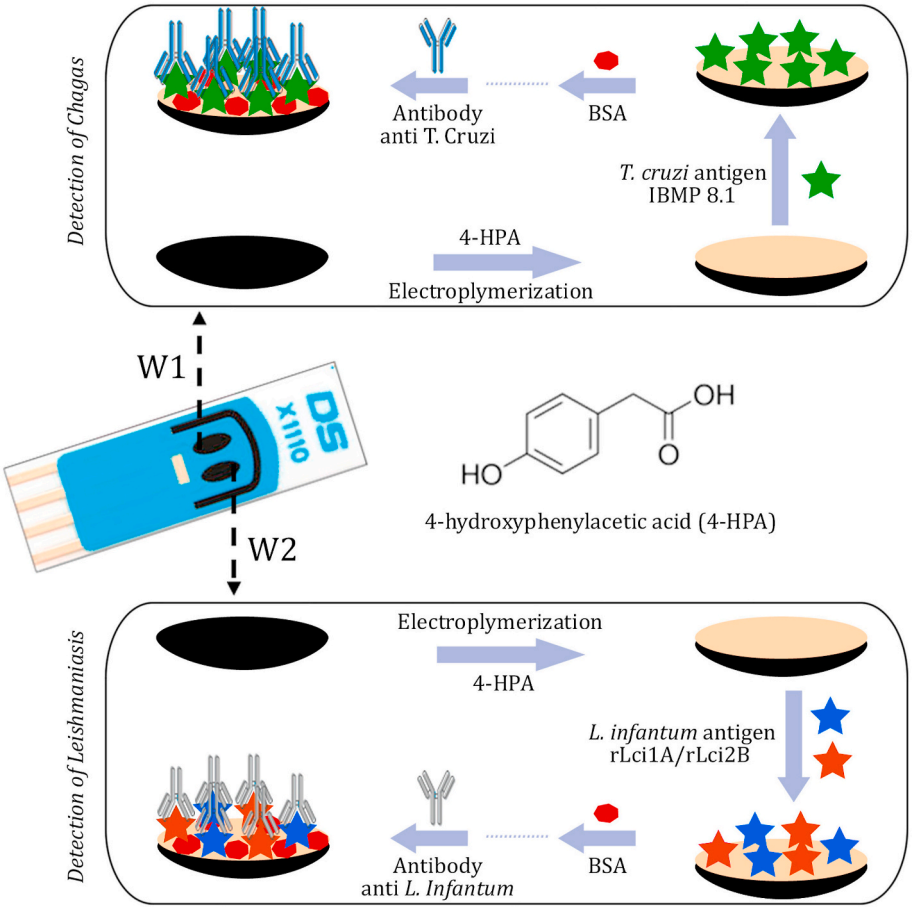

Fig. 5. Representation of dual screen-printed carbon electrode (dSPCE) and sequence of surface modification in the preparation of the immunosensor platform. Republished from Ref. [83]; permission conveyed through Copyright Clearance Center, Inc, License Number 5083631055897.

separately in each electrode as shown in Fig. 5. The immunosensor recognized specific interactions for anti-T. cruzi antibodies up to a dilution of 1:10,240 and for anti-L. infantum up to 1:5120 in canine serum samples. The results using the recombinant proteins revealed that all antigens discriminated between negative and positive samples ($p < 0.0001$) in both dog and human groups, as well as no cross-reactivity could be detected among sera with other infections. The immunosensor-based diagnostic tests achieved 100% accuracy.

De La Escosura-Muñiz et al. (2016) [96] studied the development of a genosensor with magnetic beads/gold nanoparticles immobilized over the SPCE surface. This sensor allowed the fast detection of Leishmania parasites in dog serum. Moreover, less than one parasite per microlite of blood could be detected. The methodology, compared with PCR showed more sensitivity, cost effective and user-friendly. Although having a more elaborate modification using conjugated DNA, this work presents a simple method compared to the tests available for the disease.

In this sense, Table 4 summarizes examples of studies with electrochemical biosensors to diagnose leishmaniasis using different methodologies. The biosensors developed for Leishmania presented innovative systems when compared to the devices for other NTDs. Several papers used well-known electrochemical techniques to optimize and validate their sensors. However, Perinoto et al. (2010) [92] applied chemometrics through principal component analysis (PCA) to determine anti-*L. amazonensis* IgGs. The results showed specific clusters differentiating positive and negative samples, including anti-*T.cruzi* antibodies. De La Escosura-Muñiz et al. (2016) [96] modified primers before the

Table 4
Electrochemical biosensors for Leishmaniasis.

Technique[a]	Electrode[b]	Modification[c]	Analyte	Sensor	Sample	Limit of detection	Reference
CM	Au-IDE	PAMAM/proteoliposomes	anti-*L. amazonensis*	Immunosensor	Mice blood	1×10^{-8} g/mL	[92]
DPV	ITO	NiO/probe oligonucleotide	DNA extracted from *L.dovani* cultured isolates	Genosensor	Cultures isolates	2×10^{-8} g/mL	[98]
QCM	QCE	SAM/rLci3B	anti-*L. chagasi*	Immunosensor	Canine serum	1:3200 dilution	[99]
EIS	SPCE	IrO_2-NPs/oligonucleotide probe	PCR amplified DNA of dog with *L. infantum*	Genosensor	PCR amplified	nd	[100]
CA	SPCE	AuNPs and MBs-labeled primers	DNA extracted from dog blood with *L. infantum* infection	Genosensor	Dog blood	0.8 parasites/mL	[96]
DPV	Au	Au nanoleaves/ oligonucleotide probe	Synthetic oligonucleotide and PCR amplified DNA of human samples with *L. major* infection	Genosensor	Specimens human	2.98×10^{-21} M (synthetic) 1.1×10^{-7} g/mL (genomic DNA)	[101]
DPV	Au	Au nanoleaves/ oligonucleotide probe	Synthetic oligonucleotide and PCR amplified DNA of human samples with *L. major* infection	Genosensor	Human specimens	1.8×10^{-20} M (synthetic) 7×10^{-8} g/mL (genomic)	[102]
CV **DPV**	CPE	$Co_{0.5}Zn_{0.5}Fe_2O_4$/ oligonucleotide probe	Synthetic oligonucleotide and PCR amplified DNA of human samples with *L. major* infection	Genosensor	Specimens and blood human	2×10^{-19} M (synthetic) 1.8×10^{-20} g/mL (genomic)	[103]
EIS **CV**	Au	PANIAuNp/*L. infantum* primer	PCR amplified DNA of dog serum with *L. major* infection	Genosensor	Canine serum	1×10^{-14} g/mL	[104]
QCM	QCE	AuNP-Nafion/rLci2B	anti-*L. infantum*	Immunosensor	Canine serum	3.0×10^{-6} g/mL	[105]
EIS	ITO	ThNT/aminated oligonucleotide	*L. infantum* DNA extracted from infected blood	Genosensor	Canine genomic	1×10^{-13} g/mL	[106]
DPV	Au	ns-AuNPs/thiolated oligonucleotide probe	Synthetic oligonucleotide and DNA extracted from *L. infantum*	Genosensor	Clinical	2×10^{-19} M (synthetic) 2.9×10^{-5} g/mL (genomic)	[107]
EIE	SPGE	MPA/SAM/rLCi1A/rLci2B	anti-*L.infantum*	Immunosensor	Canine and human sera	1:1280 dilution	[108]
EIS	Au	PA6/chitosan/PSA38S	anti- PSA38S *L. braziliensis*	Peptide biosensor	Human serum	1.6×10^{-12} g/mL	[97]
CA	Paper	Ag NPr-GQDs nano-ink/CysA-AuNPs/oligonucleotide probe	Complementary oligonucleotide	Genosensor	Human plasma	1×10^{-21} M	[109]
CV	SPE	AuNPs/*L. infantum* antigens	anti-*L.infantum*	Immunosensor	Human serum	2×10^{-7} g/mL	[110]
SWV	Au	AuNPs/oligonucleotide probe	Complementary oligonucleotide	Genosensor	Human plasma	1×10^{-21} M	[111]
EIE	dSPCE	poly(4-HPA)/rLCi1A/rLci2B	anti-*L.infantum*	Immunosensor	Human and dog sera	1:5120 dilution	[83]
EIS	Pt	CSN/probe oligonucleotide	Synthetic oligonucleotide and DNA extracted from *L. infantum*	Genosensor	Human and dog specimens	8.1×10^{-19} M (synthetic) 1.2×10^{-6} g/mL (genomic)	[112]

[a] **CM:** Capacitance measurements; **DPV:** Differential pulse voltammetric; QCM: Quartz crystal microbalance**; EIS:** Electrochemical impedance spectroscopy; **CA:** Chronoamperometry; **CV:** Cyclic voltammetry; **SWV**: Square wave voltammetry.

[b] **Au-IDE:** Gold interdigitated electrodes; **ITO:** Indium tin-oxide coated glass slide; **QCE:** Quartz crystal electrode; **SPCE:** Screen-printed carbon electrode; **CPE:** Carbon paste electrode; **SPGE:** Screen-printed gold electrodes; **dSPCE:** Dual screen-printed carbon electrode.

[c] **PAMAM/proteoliposomes:** Polyamidoamine generation 4 dendrimer/proteoliposomes layers; **NiO:** Sol-gel synthesized nickel oxide; **SAM:** Self-assembled monolayer; **IrO_2-NPs:** Thionine layer and iridium oxide nanoparticles; **AuNPs/MBs:** Primers labeled with gold nanoparticles and magnetic beads; **$Co_{0.5}Zn_{0.5}Fe_2O_4$:** Quantum dots of magnetic cobalt-zinc ferrite; **PANIAuNp:** Polyaniline matrix containing gold nanoparticles; **AuNP-Nafion:** Cysteamine modified with gold nanoparticles and Nafion film; **ThNT:** Thiolated carbon nanotube; **ns-AuNPs:** Non-spherical gold nanoparticles; **MPA/SAM:** 3-Mercaptopropionic acid/Self-assembled monolayer; **PA6/chitosan:** Polyamide-6/chitosan nanofibers; **Ag NPr-GQDs nano-ink/CysA-AuNPs:** Gold nanoparticles functionalized with cysteamine electrodeposited on the surfaces of Ag NPr/GQDs nano ink/paper-based electrodes; **AuNPs:** Gold nanoparticles; **poly(4-HPA):** poly(4-hydroxyphenylacetic acid); **CSN:** Cadmium sulfide nanosheets; rLCi1A, rLci2B, rLci3B: *L. infantum* recombinant proteins expressed from antigens; PSA38S: peptide-based probe of the Promastigote Surface Antigen.

DNA amplification through recombinase polymerase amplification. This methodology is an alternative for the expensive and time-consuming gold standard PCR. One primer was modified with gold nanoparticles and the other with magnetic beads. Positive samples were labeled with both nanoparticles. The magnetic beads proved efficiency in the immobilization over the SPCE through magnet attraction, while the gold nanoparticles proved efficient in the electrochemical signal through hydrogen evolution reaction. The usual choices observed are the development of an immunosensor or a genosensor, probably because of the accessibility of the biological material. However, Liberato et al. (2019) [97] developed a peptide-based sensor for *L. amazonensis* determination. The biomarker, named PSA-38, has a leucine-rich repeat as the main signature, presented in many Leishmania species. This peptide was immobilized over a polyamide/chitosan-modified gold--sputtered cellulose acetate electrode and used to detect anti-PSA38 antibodies with efficiency in buffer and human serum samples. As the work of Perinoto et al. (2010) [92], they have also used PCA to present part of the data.

Leishmaniasis is the second most investigated NTD (alongside Malaria) in the number of publications regarding biosensor development, only behind Dengue, Zika, and Chikungunya. Interestingly, the papers present the lowest limit of detection of all NTD biosensors reported in this review, even in the yocta range [103], and the majority of devices are based on DNA. The genetic material can be detected on the first day of the infection, while the host needs more time to develop the specific antibodies to fight the disease. This fact allows the genosensor to be the best candidates for early detection. One research group [101–103,107] has been working with Leishmania genosensors, and they have been improving their systems regarding simplicity, specificity, and sensitivity. The probes, complementary targets, and non-complementary targets were all obtained from Iranian suppliers, also used by Farshchi et al. (2020) [109] to develop innovative, cutting-edge technology, flexible paper-based biosensor for *L.infantum* detection. The cost-effective genosensor proved the high efficiency and specificity by the discrimination of a single nucleotide mismatch target sequence (the same specificity resulted in the work from Nazari-Vanani et al. (2018) [107]) and a low limit of detection in the zepto range.

3.4. Dengue, Zika and Chikungunya

Mosquito-transmitted infections constitute a considerable percentage of life-threatening infectious diseases [113]. Dengue, Zika virus, and Chikungunya are arboviral diseases, causing a major public health crisis, especially in tropical countries. Since both the pathogens are transmitted by the same vector named *Aedes aegypti*, the epidemiology and clinical signs and symptoms of these infections are similar.

Dengue is a non-contagious infectious disease caused by a *Flavivirus* transmitted to people by a bite of infected *Aedes* mosquitoes. Annually, 3.6 billion people are at risk of infection [114]. The evolution is fast, the diagnosis is imprecise, clinical diagnostic and delayed and expensive laboratory diagnostic. This disease does not have an effective vaccine and the treatment is palliative, treating the symptoms and not the infection. Zika virus (ZIKV) is a flavivirus of the *Flaviviridae* family of the same genus as the viruses that cause dengue and yellow fever that was first identified in 1947 [115]. Initially, the virus was of little concern for health authorities given there were very few casualties among those suffering an infection. However, the Zika virus recently emerged as an epidemic and a public health emergency of global concern because it induces microencephaly and serious neurological disorders in infants born to infected mothers [116,117]. Chikungunya virus (CHIKV) is a disease that causes acute fever, acute and chronic musculoskeletal pain and is transmitted to humans by Aedes mosquitoes. The virus was first described in 1952 during a febrile illness outbreak in Makonde, a province in southern Tanzania [118,119]. Since its description, in 1952, CHIKV has caused millions of human infections in Africa, the Indian Ocean islands, Asia, Europe, and the Americas. CHIKV disease can be highly debilitating, and large epidemics have severe economic consequences. Due to genetic similarity, the cross-reactivity of antibodies, and nonspecific symptoms became difficult to assess clinically the infections of the Zika and Dengue virus in the Americas. Moreover, as both viruses are transmitted by the same mosquito species, their distributions largely overlap and the reliable serological distinction between the viruses is essential. Although there are tests to identify both infections at the same time, current diagnostic methods are slow, nonspecific, and costly [120].

The early diagnosis of these infections is critical for clinical management and patient survival. Therefore, the development of simple, precise, cost effective, and portable devices that can be easily handled by end-users diagnostic tools is necessary to allow a fast diagnostic to treat the symptoms, identify focuses of infection, and thus prevent the spreading of the diseases. The current methods of diagnosing these infections are expensive and time-consuming and they require trained personnel. Moreover, neither technique is amenable to miniaturization [121–126].

Kim et al. (2019) [127] showed a new method for the development of an electrochemical biosensor, in which synthetic affinity peptides were immobilized to a gold electrode surface modified with 1-mercaptoundecanoic acid (MUA) and activated with a solution of EDC and NHS for detection of the DENV antigen, NS1. The sensor performance was monitored via square wave voltammetry (SWV) and electrochemical impedance spectroscopy (EIS). The repeatability of the sensor was also investigated, and it was observed that the sensor with synthetic peptides DGV BP 1 was stable up to third regeneration with good reproducibility. The developed electrochemical biosensor showed high sensitivity, stability, and specificity, being able to detect and quantify NS1.

Tancharoen et al. (2019) [128] report the development of a new type of electrochemical biosensor ZIKV based on surface-printed polymers and graphene oxide compounds. The biosensor was used to detect ZIKV by measuring changes in the electrical signal with changes in virus concentrations in the buffer and serum using standard electrochemical techniques. The detection limit of the method is similar to the detection limit of the quantitative reverse transcription PCR method in real-time.

Singhal et al. (2018) [129] reported the development of the first electrochemical biosensor based on molybdenum disulfide nanosheets (MoS_2 NSs) for the point-of-care diagnosis of CHIGV by a voltammetric signal. The proposed genosensor exhibited a wide linear range of 0.1 nM–100 μM towards the chikungunya virus DNA. A simple, sensitive, and inexpensive platform has been developed for the detection of the target DNA of chikungunya virus DNA (CHIKV). The authors used paper for mass production with the capability to be converted to commercial use.

Lectin and glycan-based biosensors are devices that use the ability of this kind of protein (lectin) to strongly bind carbohydrates, such as viral glycoproteins (glycan). These systems were used for arboviruses determination. Wasik et al. (2017) [130] developed a chemiresistive sensor using glycan heparin to directly interact with the cell surface of the whole Dengue-type 1 virus. On the other hand, Simão et al. [131] developed a lectin biosensor for the distinctly label-free determination of the three arboviruses through EIS measurements. Concavalin A was the lectin immobilized over a zinc oxide nanoparticle-modified gold electrode, as seen in Fig. 6 Through a tridimensional approach using the EIS response from three circuit elements (n, Rct, and Q), the authors could differentiate Dengue, Zika, Chikungunya, and even the Yellow fever viruses (inset Fig. 6). Andrade et al. (2011) [132], in previous work using a different lectin (Bauhinia monandra), proved that this analysis was effective to differentiate the three main Dengue serotypes (1, 2, and 3). The work of this research group proves the diversification on the type of biosensor applied with multiple determination of important viruses using two biomarkers. These publications are excellent examples of research allying simplicity with effective label-free, cost-effective devices to be applied in the health system.

Herein, Table 5 shows examples of electrochemical biosensors

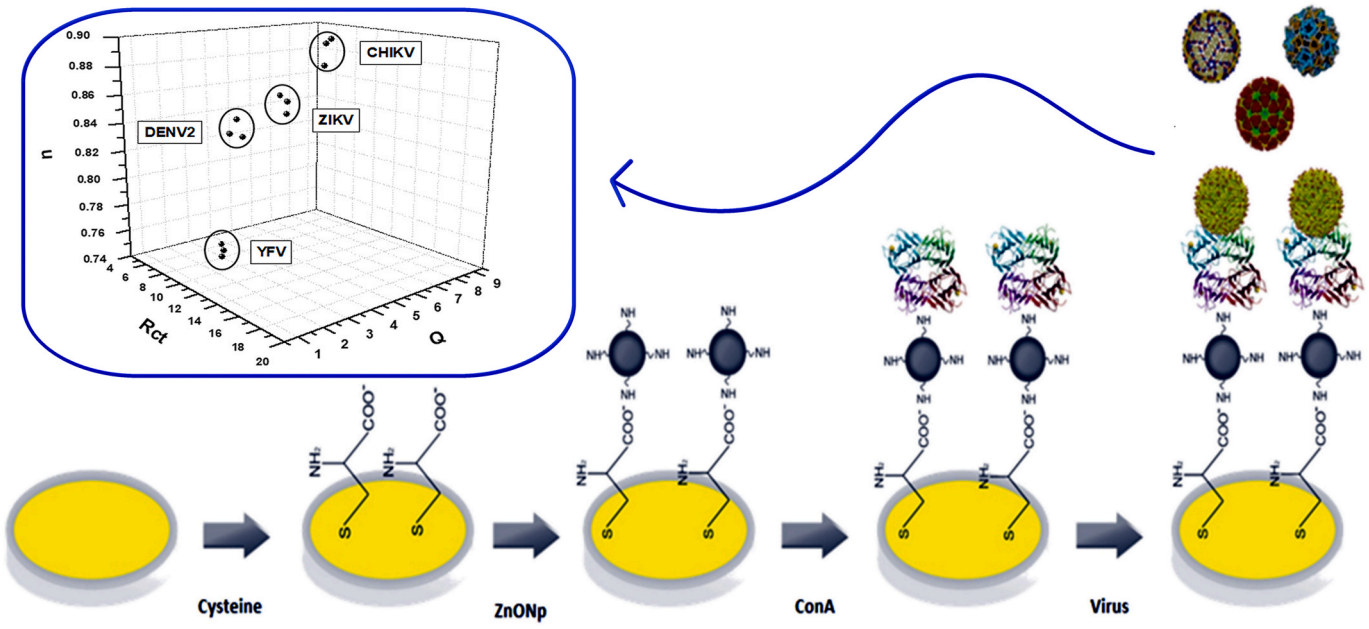

Fig. 6. Schematic representation of the surface modification. Inset: Three-dimensional plot for values of Rct, Q, and n. Adapted and republished from Ref. [131]; permission conveyed through Copyright Clearance Center, Inc, License Number 5083630431742.

developed to diagnose Dengue, Zika, and Chikungunya through different methodologies.

A first look at Table 5 reveals the enormous number of papers describing the development of biosensors for Dengue and just a few for Zika and Chikungunya. As informed before, Dengue is the oldest disease and has been affecting millions of people worldwide. In Brazil, there are reports of Dengue since 1846 [186]. However, Chikungunya and Zika were only identified in 2014 and 2015, respectively [187]. This fact, associated with the historical profile of Dengue alongside the number of deaths annually, could be the reason that drives this many authors in developing Dengue biosensors. The majority of the papers worked with the EIS technique and biomolecule immobilization through adsorption, which shows the efforts for label-free determinations, the decrease in the development steps, thus increasing the simplicity and cost-effectiveness of the devices. However, the traditional use of carbodiimide and succinimide for covalent bonding is recurrent, as it ensures the orientated binding between the biomolecule and the transducer. Two types of sensors stand out: immunosensors (most of them targeting the virus non-structural protein) and genosensor (targeting specific oligonucleotides designed for virus's genome fragments). However, some interesting choices of the assembly were performed as the use of SIP [128] and MIP [159], whole-cell-based biosensor [151], aptasensor [175], and glycan-based biosensor [130]. It is worth noting that, despite the efforts for the development and use of novel biomarkers, knowledge is needed, as it is shown by the high limit of detection (in micrograms range) obtained using a phage-based biosensor [164] and a peptide-based biosensor [127]. In this review, flaviviruses are, by far, the most studied NTDs regarding the development of biosensors. There is no reason not to take advantage of the novelties presented regarding the electrode types, electrode modifications, electrochemical techniques, immobilization strategies, and analysis in other NTDs' research.

3.5. Schistosomiasis

Schistosomiasis is a neglected tropical disease caused by trematodes worms of the genus *Schistosoma*. It is the second most prevalent parasitic disease in the world. The main disease-causing species are *S. haematobium*, *S. mansoni*, and *S. japonicum*. It affects up to 300 million people annually and 779 million people are at risk of infection in regions of South America, Southeast Asia, the Middle East, Mediterranean Europe, and sub-Saharan Africa, and can also occur in nonendemic areas. Human schistosomiasis is among the most prevalent human parasitic infections. The transmission cycle involves contamination of surface water by excreta, as well as specific freshwater snails acting as intermediate hosts [188–190].

The methods to control schistosomiasis are prevention and treatment. Improving sanitation and eliminating snail hosts are essential methods to prevent schistosomiasis. Sensitive and specific diagnostic procedures are required to monitor the success or failure of schistosomiasis control programs as well as to determine whether control efforts have resulted in elimination. The identification of eggs in urine (*S. haematobium*) or stool (*Schistosoma mansoni* and *Schistosoma japonicum*), is the most commonly used diagnostic method, but is time-consuming, has a poor positive test rate and it is difficult to apply in areas with relatively less severe infection levels [191–193].

Early diagnosis of schistosomiasis in endemic areas is essential to support the patient, evaluation of treatment response, and checking of control programs. The diagnostics involving molecular or immunological techniques can be expensive, time-consuming, offer poor sensitivity, particularly when the parasite burden is low, required specialized facilities to need skilled personnel and it is difficult to apply in areas with relatively less severe infection levels. Moreover, as there is no affordable sensitive and rapid standard test for schistosomiasis, there is an imminent need for a gold standard technique with high sensitivity to attend principally the people in endemic areas. The vaccines for schistosomiasis are unavailable, therefore the best way to avoid this disease is prevention [194,195].

Santos et al. (2019) [196] developed an impedimetric biosensor able to recognize the *S. mansoni* genome. The electrochemical platform was based on self-assembled layers of 3-mercaptopropyltrimethoxysilane and electrosynthesized gold nanoparticles, as seen in Fig. 7. The biosensor was characterized by electrochemical impedance spectroscopy and cyclic voltammetry. The developed genosensor was able to detect small concentrations of *S. mansoni* DNA in urine, cerebrospinal fluid, and serum with a limit of detection of 0.6 pg μL^{-1}.

Several examples of electrochemical biosensors constructed for Schistosomiasis detection are summarized in Table 6.

As the world's second most prevalent parasitic disease,

Table 5
Electrochemical biosensors to Chikungunya, Dengue and Zika.

Disease	Technique[a]	Electrode[b]	Modification[c]	Analyte	Sensor	Sample	Limit of detection	Reference
Chikungunya	CV EIS	ePAD	Fe_3O_4@Au/ oligonucleotide probe	Oligonucleotide target	Genosensor	Serum	1×10^{-10} M	[133]
Chikungunya	CV DPV	SPGE	MoS_2 NSs/ oligonucleotide probe	Oligonucleotide target	Genosensor	Human serum	3.4×10^{-9} M	[129]
Chikungunya	EIS	Au	SAM/11-MUA/6-MH/ anti-CHIKV-nsP3	CHIKV-nsP3	Immunosensor	Human serum	8×10^{-9} g/mL	[134]
Chikungunya	DPV	GCE	QDs-liposome@MB/anti-Chikungunya virus	Recombinant Chikungunya virus E1 protein	Immunoassay	Real	3.27×10^{-14} g/mL	[135]
Dengue	EIS	IDE	BST/SAM/APTS/DENV-2	anti-DENV-2	Immunosensor	Human serum	nd	[136]
Dengue	EIS	Au	AuNpPANI/BmoLL	Glycoproteins	Lectin biosensor	Sera	1:150 dilution	[132]
Dengue	EIS CV	Au	AuNpPANI/ oligonucleotide probe	Genomic DNA target sequence	Genosensor	Human genome	7×10^{-12} M	[137]
Dengue	EIS CV	Au	PVB–Fe_3O_4–CramoLL	Glycoproteins	Lectin biosensor	Human serum	nd	[138]
Dengue	DPV	Gold CD-trode	Protein A/anti-NS1	NS1	Immunosensor	Human serum	3.3×10^{-10} g/mL	[139]
Dengue	CV	CF	CFE/anti-DENV	Dengue virus	Immunosensor	Human serum	9.4×10^{-10} g/mL	[140]
Dengue	DPV	Pt	NPAE/anti-DENV-2	DENV-2	Immunosensor	Dengue virus	1.0 pfu/mL	[141]
Dengue	EIS	NPA	NPAE/anti-DENV-2	DENV-2	Immunosensor	Dengue virus	1.0 pfu/mL	[142]
Dengue	CA	CNT-SPE	EDA/anti-NS1	NS1	Immunosensor	Human serum	1.2×10^{-8} g/mL	[143]
Dengue	EIS	Pt-AME	Pt-AME/2H2	DENV-2	Immunosensor	Human serum	0.230 pfu/mL (Denv-2) 0.710 pfu/mL (Denv-3)	[144]
Dengue	EIS	Au	AuNp-PANI-CramoLL	Glycoproteins	Lectin biosensor	Human serum	80-dilution fold	[145]
Dengue	EIS CV	Au	Lipid-ConA	Glycoproteins	Lectin biosensor	Human serum	nd	[146]
Dengue	DPV	ITO	SiNWs/AuNPs/thiolated oligonucleotide probe	Oligonucleotide target	Genosensor	Synthetic	3.5×10^{-9} g/mL	[147]
Dengue	CV	SPCE	Thiophene/anti-NS1	NS1	Immunosensor	NS1 culture	1.5×10^{-9} g/mL	[148]
Dengue	EIS	GNP-AAO	SAM-CLEC5A	Dengue virus	Lectin biosensor	Dengue virus	nd	[149]
Dengue	EIS	Au	MUA/6COH/EDC/NHS/ anti-NS1	NS1	Immunosensor	Human blood serum	3×10^{-8} g/mL	[150]
Dengue	EIS	SPCE	PLL/BHK-21 cells	DENV-2	Cell-based biosensor	Infected BHK-21 cells	Early as 30 h post-infection	[151]
Dengue	EIS	Au	Cysteamine/GA/IgY-NS1	NS1	Immunosensor	Commercial	9×10^{-8} g/mL	[152]
Dengue	EIS	Au	Cysteine/EDC/NHS/ MBA/AuNP/anti-DENV	Dengue viruses	Immunosensor	Dengue virus	1:100 dilution	[153]
Dengue	DPV	PCGE	DENV-3 oligonucleotide probe	DENV-3 oligonucleotide target	Genosensor	Human serum	3.09×10^{-9} M	[154]
Dengue	DPV	SPGE	SiNW/APTES/DTPA/ AuNP/oligonucleotide probe	Oligonucleotide target	Genosensor	Synthetic	1.63×10^{-12} M	[155]
Dengue	EIS	ITO	SP/TMAP/PPD/ diazonium/AuNP/EDC/ NHS/IgG-NS1	NS1	Immunosensor	Human serum	5×10^{-9} g/mL	[156]
Dengue	EIS	Pt	SiO_2APTES-GO/RNA or DNA oligonucleotides	DNA and RNA targets	Genosensor	Infected mosquito cell lines with serotype 2 Dengue	1×10^{-15} M	[157]
Dengue	EIS	SPGE	MUA/EDC/NHS/IgG-NS1	NS1	Immunosensor	Synthetic	5×10^{-10} g/mL	[158]
Dengue	EIS	Au	PMC/GO	Dengue viruses	MIP biosensor	Infected mosquito cells	0.12, 0.10, 0.50 and 0.46 pfu/mL (DENV-1, DENV-2, DENV3 and DENV4, respectively)	[159]
Dengue	AP	IDE	APTES/EDC/NHS/ oligonucleotide probe	DENV-2 oligonucleotide target	Genosensor	Synthetic	1.7×10^{-8} M	[160]
Dengue	QCM QCM-D	GQC	PEE/CN/EDC/NHS/IgG-NS1	NS1	Immunosensor	Blood serum	1×10^{-7} g/mL for QCM-D and 3.2×10^{-7} g/mL for QCM	[161]
Dengue	CV	FTO	ZnO/Pt–Pd/chitosan/ GA/oligonucleotide probe	Oligonucleotide target	Genosensor	Synthetic	4.3×10^{-5} M	[162]
Dengue	DPV	GE	MNF/MPA/EDC/NHS/ oligonucleotide probe	Oligonucleotide target	Genosensor	Blood serum	1.2×10^{-19} M	[163]
Dengue	LSV	IDE	SWNT/Pyr-NH_2/EDC/ NHS/heparin	DENV-1	Glycan biosensor	Infected Vero cells	8.4×10^2 $TCID_{50}$/mL	[130]

(*continued on next page*)

Table 5 (*continued*)

Disease	Technique[a]	Electrode[b]	Modification[c]	Analyte	Sensor	Sample	Limit of detection	Reference
Dengue	CV EIS SWV	Au	Phage	DENV-2 NS1	Phage-based biosensor	Infected *E. coli* strain	1.5×10^{-6} g/mL	[164]
Dengue	EIS	SPCE	BSA/EDC/NHS/Dengue NS1 antibody	NS1	Immunosensor	Human serum	3×10^{-10} g/mL	[165]
Dengue	EIS	GCE	MWCNT/poly(pyrrole-NHS) Dengue virus NS1	anti-DENV-2 NS1	Immunosensor	Bovine blood plasma	1×10^{-12} M	[166]
Dengue	EIS	SPCE	poly(4-APA)/ recombinant NS1	anti-NS1	Immunosensor	Human serum	1:1280 serum dilution	[167]
Dengue	EIS	Au	PEG-thiol/11Fc/EDC/ NHS/anti-NS1	NS1	Immunosensor	Human serum	6.1×10^{-10} g/mL	[168]
Dengue	EIS	Au	PEG-thiol/11Fc/EDC/ NS1	anti-NS1	Immunosensor	Human serum	6.1×10^{-9} g/mL	[168]
Dengue	CV	SPGE	MUA/EDC/NHS/IgG-NS1	NS1	Immunosensor	Human serum	5×10^{-8} g/mL	[169]
Dengue	SWV EIS	Au	MUA/EDC/NHS/NS1 peptide	DENV-2 NS1	Peptide biosensor	Dengue virus culture broth	1.49×10^{-6} g/mL	[127]
Dengue	EIS	GE	Electrosynthesized polymers/Dengue recombinant NS1	anti-NSI	Immunosensor	Human blood serum	Nd	[170]
Dengue	EIS	SPCE	MIP-PSNF/dopamine/ NS1	NS1	MIP biosensor	Human serum	3×10^{-10} g/mL	[171]
Dengue	DPV	PCGE	4-CDS/EDC/NHS/anti-NS1	NS1	Immunosensor	Human serum	5×10^{-10} g/mL	[172]
Dengue	CV	GCE	Polyaniline/GA/anti-NS1	NS1	Immunosensor	Infected *E. coli* strain	1×10^{-10} g/mL	[173]
Dengue	DPV	Au	MWCNT/AuNP/ Cysteamine/EDC/NHS/ anti-DENV2	DENV-2 NS1	Immunosensor	Human serum	3×10^{-13} g/mL	[174]
Dengue	CV	PCGE	AuNP/PEI/aptamer	NS1	Aptasensor	Human serum	3×10^{-10} g/mL	[175]
Dengue	EIS	SPCE	poly(4-ABA)/ recombinant NS1	Anti-NS1	Immunosensor	Human serum	1:1280 serum dilution	[176]
Dengue	EIS	Au	MCH/MHA/ oligonucleotide probe	DENV-1 RNA fragments	Genosensor	DENV1 suspension	20 pfu/mL	[177]
Zika	EIS SWV	SPCE	CN-PPhy-EDIII or NS1	anti-NS1 and anti-EDIII	Immunosensor	Specimens human	17,714.700 dilution	[178]
Zika	EIS	IDE-Au	Zev-Abs	ZIKV envelope protein	Imunosensor	ZIKV	1×10^{-11} M	[179]
Zika	SWV	PCGE	poly(3-4-AHBA)/ oligonucleotide probe	Zika virus RNA	Genosensor	Enriched human serum	2.54×10^{-11} M	[180]
Zika	CV	Au	ZnO NRs/anti-ZIKV NS1	ZIKV NS1	Imunosensor	Urine	1×10^{-12} g/mL	[181]
Zika	EIS	Au	Thiolated oligonucleotide probe	Oligonucleotide target	Genosensor	Synthetic	2.5×10^{-8} M	[120]
Zika	EIS	ox-GCE	AuNPs-SiPy/thiolated oligonucleotide probe	Oligonucleotide target	Genosensor	Human serum	8.2×10^{-13} M	[182]
Zika	EIS CV	SPGE	SIP	Zika virus	SIP-Biosensor	Serum	0.002 pfu/(1% serum) and 0.05 pfu/mL (10% serum)	[128]
Zika	CA	SPGE	sP-STV-MB/ oligonucleotide probe	Oligonucleotide targets	Genosensor	Specimens human	7×10^{-13} M for target probe 1 and 3×10^{-12} M for target probe 2	[183]
Zika	DPV	SPGE SPCE/Au	AuNP/oligonucleotide probe	Oligonucleotide targets	Genosensor	Human serum	2×10^{-16} M (SPGE) 3.3×10^{-14} M (SPCE/Au)	[184]
Zika	SWV	Au	UDH	Fragment of ZIKV genome	Aptasensor	Synthetic	1.11×10^{-12} g/mL	[185]
Chikungunya Dengue Zika	EIS	Au	Cys-ZnONp-ConA	Chikungunya, Dengue and Zika viruses	Lectin Biosensor	Human serum	0.062 pfu/mL 0.0382 pfu/mL 0.0421 pfu/mL	[131]

[a] **CV:** Cyclic voltammetry; **EIS:** Electrochemical impedance spectroscopy; **DPV:** Differential pulse voltammetric; **CA:** Chronoamperometry; **AP:** Amperometry; **QCM:** Quartz crystal microbalance; **QCM-D:** Quartz crystal microbalance with energy dissipation; **LSV**: Linear sweep voltammetry; **SWV:** Square-wave voltammetry.

[b] **ePAD:** Electrochemical paper analytical device; **SPGE:** Screen-printed gold electrodes; **GCE:** Glassy carbon electrode; **IDE**: Interdigitated electrode; **CD-trode:** Gold film electrode obtained from a recordable compact disk; **CF:** Carbon fiber sheet; **NPA:** Nanoporous alumina electrode; **CNT-SPE:** Carbon nanotube-screen printed electrodes; **Pt-AME:** Platinum coated alumina membrane; **ITO:** Indium tin-oxide coated glass slide; **SPCE:** Screen-printed carbon electrodes; **GNP-AAO:** Electrode of gold nanoparticles deposited nano-hemisphere array of the anodic aluminum oxide; **PCGE:** Pencil carbon graphite electrode; **GQC:** Gold quartz crystal; **FTO:** Fluorine tin oxide; **GE:** Carbon graphite electrode; **GCE**: Glassy carbon electrode; **IDE-Au**: Interdigitated microelectrode of gold array; **ox-GCE:** Oxidized glassy carbon electrode; **SPCE/Au:** Screen-printed carbon electrode decorated with hierarchical gold nanostructures.

[c] **Fe_3O_4@Au**: Iron oxide@gold nanocubes; **MoS_2 NSs:** Molybdenum disulphide nanosheets; **SAM/11-MUA/6-MH**: Self-assembled monolayer comprising of 11-mercaptoundecanoic acid and 6-mercapto-1-hexanol; **QDs-liposome@MB**: Fluorescent quantum dots embedded and methylene blue–encapsulated liposomes; **BST/SAM/APTS:** Sol–gel derived barium strontium titanate thin film modified with organic self-assembled monolayer formed by 3-aminopropyltriethoxysilane; **AuNpPANI**: Gold nanoparticles-polyaniline hybrid composite; **PVB–Fe_3O_4-CramoLL:** Fe_3O_4 nanoparticles and polyvinyl butyral as an occlusive layer with *Cratylia mollis* lectin immobilized; **CFE:** Chitosan-modified carbon fiber electrode; **NPAE:** Nanoporous alumina-modified electrode; **IgG**: Immunoglobulin G (IgG); **EDA:** Ethylenediamine film; **AuNp-PANI-CramoLL**: Gold nanoparticles-polyaniline hybrid composite with *Cratylia mollis* lectin immobilized; **Lipid-ConA:** Concanavalin A and lipid membranes; **SiNWs/AuNPs:** Silicon nanowires decorated with gold nanoparticles; **SAM-CLEC5A:** Self-assembled monolayer of mercaptoundecanoic acid with C-type lectin domain family 5, member A; **MUA:** Mercaptoundecanoic acid; **6COH:** 6-mercaptohexanol; **EDC**: Ethyl-3-dimethylaminopropyl carbodiimide; **NHS**: N-

hydroxysuccinimide; **PLL:** Poly-L-lisine; **BHK-21**: Baby hamster kidney; **GA:** Glutharaldehyde; **MBA:** 4-mercaptobenzoic acid; **AuNP:** Gold nanoparticles; **SiNW:** Silicon nanowire; **DTPA:** Dithiopropionic acid; **SP:** 4-sulfophenyl; **TMAP:** 4-trimethylammoniophenyl; **PPD:** 1,4-phenylenediamine; **IgG-NS1:** Immunoglobulin G-non-structural protein 1; **SiO_2@APTES-GO**: Graphene oxide sheets functionalized with 3-aminopropyltriethoxysilane (APTES) coated with silica nanoparticles; **PMC:** Polymer matrix composite composed by acrylamide, methacrylic acid, methylmethacrylate and N-vinylpyrrolidone; **GO**: Graphite oxide; **PEE:** Polyethylenimine; **CN:** Cellulose nanocrystals; **Pyr-NH_2**: 1-pyrenemethylamine; **SWNT:** Single walled carbon nanotubes; **PBASE:** 1-Pyrenebutyric acid N-hydroxysuccinimide ester; **MWCNT**; Multi walled carbon nanotubes; **poly(4-APA):** poly(4-aminophenylacetic acid); **MIP-PSNF**: Molecular imprinted polymer based on polysulfone nanofibers; **4-CDS:** 4-carboxyphenyl diazonium salt; **poly(4-ABA):** poly(4-aminobenzoic acid); **ZnONp:** Zinc oxide nanoparticles; **ConA:** Concanavallin A; **MCH:** 6-mercapto-1-hexanol; **MHA:** 6-mercaptohexanoic acid; **CN-PPhy-EDIII or NS1:** Carbon-nanotubes modified with p-phenylenediamine and recombinant forms of ZIKV non-structural protein 1 (NS1) and the domain III of the envelope protein (E-DIII); **Zev-Abs/SAM**: Zika-virus-envelop protein antibody onto self-assembled monolayer of dithio-bis(succinimidyl propionate) deposited on IDE-Au; **ZnO NRs:** Zinc oxide nanorods; **poly(3-4-AHBA):** 3-Amino-4-hydroxybenzoic acid; **AuNPs-SiPy:** Silsesquioxane-functionalized gold nanoparticles; **SIP:** Surface imprinted polymers; **sP-STV-MB:** Specific biotinylated capture probe immobilized at streptavidin-coated magnetic beads; **UDH:** Universal DNA-Hairpin; **AuNP/ssDNA:** gold nanoparticles linked to single-stranded DNA; **Cys-ZnONp-ConA:** Cysteine - zinc oxide nanoparticles - Concanavalin A lectin film; **Anti-CHIKV-nsP3**: Chikungunya virus non-structural protein 3 antibody; **DENV-1**: Dengue virus type 1; **DENV-2**: Dengue virus type 2; **DENV-3**: Dengue virus type 3; **BmoLL**: *Bauhinia monandra* lectin; **CramoLL:** *Cratylia mollis* lectin; 2H2: Mono-clonal anti-dengue complex antibody.

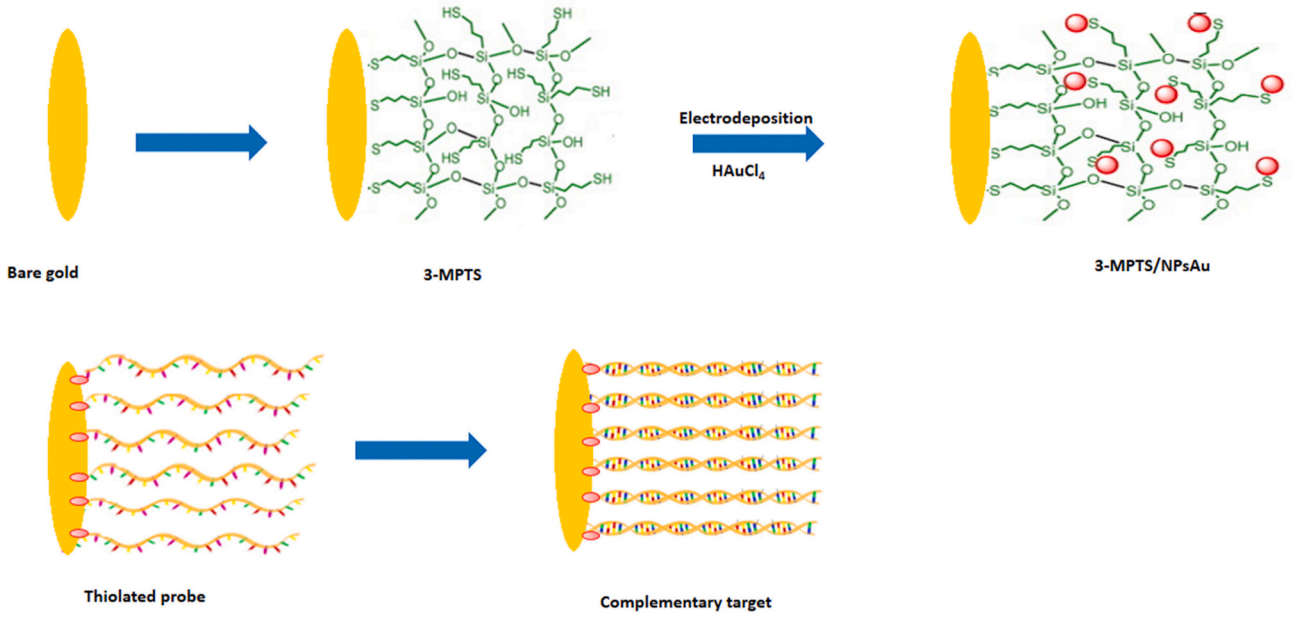

Fig. 7. Schematic representation of the fabrication process of the biosensor. Republished from Ref. [196]; permission conveyed through Copyright Clearance Center, Inc, License Number 5083640066535.

Schistosomiasis is also neglected regarding the efforts for early diagnosis through biosensor development. Few papers addressing this subject were found, and most of them are incomplete regarding optimization and figures of merit. The works wander between using immunologic and genetic assays based on biological material obtained mainly from *S. mansoni* and *S. japocunium*. Only one paper by Mach et al. (2015) [193] reported a genosensor for *S. haematobium* detection from RNA prepared from adult worms as the analyte. However, different researcher groups have worked and proved the capability of such development, as the systems do not differ experimentally from the observed for other most-evident diseases. The detection systems were even more versatile when compared, with different techniques such as EIS, QCM, ASV, DPV, and AP, and specific electrochemical markers such as ferro/ferricyanide, ferrocene, tetramethylbenzidine, and silver, that paves the road for novel and improved devices.

3.6. Leprosy

Leprosy or Hansen's disease is a chronic and potentially infectious disease caused by *Mycobacterium leprae* (*M. leprae*) or *Mycobacterium lepromatosis* (*M. lepromatosis*). Leprosy is primarily a disease that causes skin and nerve damage and mucosa particularly in the upper respiratory tract, often leading to lifelong handicaps [204–206]. This infection is one of the oldest human diseases, but up to now, there are no laboratory tests to diagnose it [207]. The diagnosis mainly relies on the detection of clinic symptoms, which can take many years to manifest. Moreover, the majority of infected individuals will never progress to disease but instead, will develop adequate immunity or will remain asymptomatically infected. It is a very worrying health problem worldwide, most prevalent in Asia, Africa, and Latin America, with accounts for approximately 200,000 new cases each year [208].

In endemic countries, treatment defaulting is still an important obstacle to effective leprosy control and elimination. Further, delays in leprosy diagnosis and inadequate treatment may lead to irreversible physical disabilities that can cause social disadvantages in affected people. Such problems can be circumvented by using low-cost tools, simple, and sensitive handling as biosensors. So, studies have developed some devices capable of detecting such a disease [206,209].

Afonso et al. (2010) [210] developed a new bioelectrode for gene detection of *Mycobacterium leprae*, produced by immobilizing single-stranded DNA on graphite electrode modified with poly (4-aminophenol). This biosensing platform was able to recognize complementary DNA molecules via the hybridization process. Hybridization between probe and target was monitored by voltammetry, using ferrocenecarboxaldehyde as an electrochemical DNA hybridization indicator. ssDNA hybridization with the DNA target was also investigated by electrochemical impedance spectroscopy, showing significant modification in Nyquist plot, by modification in electrode surface after addition of the complementary target. The effective immobilization of specific gene of *Mycobacterium leprae* onto graphite electrode modified

Table 6
Electrochemical biosensors to Schistosomiasis.

Technique[a]	Electrode[b]	Modification[c]	Analyte	Sensor	Sample	Limit of detection	Reference
ASV	MPPCPE	Fe_3O_4/Au/MCH/EDC/NHS/SEA	Coloidal gold-labeled rabbit anti-schistosoma	Immunosensor	Rabbit antibodies	1×10^{-8} g/mL	[197]
QCM	GQC	SPA/InRS or ImRS/NRS	SjCAg	Immunosensor	Rabbit and human sera	nd	[198]
QCM	GQC	MPA/ME/*Sj*Ag	Rabbit anti- *S. japonicum* SEA	Immunosensor	Rabbit serum	1:1800 dilution	[199]
DPV	SPCE	GA/SEA	*anti-S. japonicum*	Immunosensor	Human serum	nd	[200]
CV	SPCE-16	EDC/NHS/SEA/SjE16	anti- *S. japonicum* SEA	Immunosensor	Human serum	nd	[201]
AP	Au	Thiol/capture probe	RNA extracted from *S. haematobium* eggs	Genosensor	Human urine	30 eggs/mL	[193]
DPV	NCE	GA/CS/schistosomiasis antigen	*anti-S. mansoni*	Immunosensor	Synthetic antibodies	3.8×10^{-11} g/mL	[192]
EIS	Au	MBA/EDC/NHS/Fe_3O_4NPs/AuNPs/ thiolated oligonucleotide probe	Schistosoma DNA and genomic material	Genosensor	Human specimens	7.81×10^{-10} g/mL (serum) 6.85×10^{-10} g/mL (cerebrospinal fluid)	[202]
CV DPV	SPGE	AuNP- *Rabbit anti-schistosome*	Mouse Schistosome SEA	Immunosensor	Stool sample	8.3×10^{-11} g/mL	[203]
CV EIS	Au	MPTS/AuNPs/oligonucleotide probe	*S. mansoni* DNA	Genosensor	Human specimens	6×10^{-9} g/mL	[196]

[a] **ASV:** Anodic stripping voltammetry; **QCM:** Quartz crystal microbalance; **DPV:** Differential pulse voltammetric; **CV:** Cyclic voltammetry; **AP:** Amperometry; **EIS:** Electrochemical impedance spectroscopy.

[b] **MPPCPE**: magnetic porous pseudo-carbon paste electrode; **GQC:** gold quartz crystal; **SPCE**: Screen-printed carbon electrode; **SPCE-16:** 16-channel screen-printed carbonelectrode array; **NCE:** Nanocarbon-screen-printed electrode; **SPGE**: Screen-printed gold electrode.

[c] **MCH**: 6-mercapto-1-hexanol; **EDC:** 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide; **NHS**: N-hydroxysuccinimide; **SEA:** native soluble egg antigen; **SPA**: Staphylococcal protein A; **InRS:** Infected rabbit's sera; **ImRS:** Immunized rabbit's sera; **MPA:** Mercaptopropionic acid; **ME:** Mercaptoethanol; **GA**: Glutaraldehyde; ***Sj*Ag:** *Schistosoma japonicum* antigen; **SjE16**: *Schistosoma japonicum* calcium-binding protein; **MBA**: Mercaptobenzoic acid; **Fe_3O_4 NP:** Magnetite nanoparticles; **AuNPs:** Gold nanoparticles; **AuNP-IgG**: Gold nanoparticle-anti-bilharzia conjugate; **MPTS**: Mercaptopropyltrimethoxysilane; SjCAg: *Schistosoma japonicum* circulating antigens.

with poly(4-aminophenol) and the detection of the hybridization process with the DNA target, monitored by voltammetry and EIS indicate that this is a new and promising biosensing platform for gene detection of Hansen's bacillus.

Yotsumoto Neto et al. (2019) [211] described the development of a novel CdS/Ni(OH)$_2$/FTO photoelectrochemical platform for the diagnosis of leprosy based on the detection of antibodies of patients using a recombinant mimetic peptide (PGL1M3R) as a recognition element exploiting a peptide-based antigen of leprosy. The morphology and the photoelectrochemical response (concentration, and pH of the buffer) of the platform were optimized. The photoelectrochemical immunosensor is a low-cost platform for the discrimination of positive and negative leprosy human serum samples diluted from 1:40 up to 1:10,240. The sensor presented a high response to positive samples for leprosy, while it does not show significant responses for sera samples from tuberculosis and leishmaniasis patients, showing sensitivity and selectivity.

Kushwaha et al. (2019) [212] developed a MIP-based electrochemical biosensor for the detection of M*ycobacterium leprae* bacteria. A solution containing a series of specific monomers were polymerized in the presence of a synthesized derived epitope of the bacteria and then immobilized over the surface of a quartz crystal gold electrode. The epitope template was extracted with buffer solution and the progress of the extraction was evaluated by a piezoelectric and fluorescence analysis. The MIP-based biosensor was able to detect the bacteria in a buffer with a LOD in the nM range, and in real blood samples with sensitivity and selectivity.

3.7. Human African trypanosomiasis (sleeping sickness)

Human African trypanosomiasis (HAT) or known as sleeping sickness is originated in the African continent and happen just in Sub-Saharan African. The first identification of the parasite in humans was in 1902 in a captain on the River Gambia. Todd and Dutton screened more than 1000 humans. Although they identified the presence of the parasite, they didn't associate it with the disease [213]. After that, research regarding Sleeping Sickness achieved better control conditions, like using the diagnose to reduce the contamination [214].

Around 60,000 people are at risk of developing the disease. This is the major mortality cause in humans and livestock that are directly related [215]. Due to attention given by WHO, the number of cases is being controlled in specific regions, but not on a global scale [216].

HAT is caused by a protozoan of the group of *Trypanosome* parasites. The specific two subspecies are *Trypanosome brucei gambiense* and *Trypanosome brucei rhodesiense*. The *T. b. gambiense,* responsible for around 90% of cases, provokes a chronic infection in people asymptomatically, with increased chances for the disease to reach advanced stages. When identified, the infected have the central nervous system affected and the cure or control of the disease is hindered [216,217].

On the other hand, when the infection occurs by *T. b. rhodesiense*, the symptoms can be observed in weeks or months after contact with the parasite. This species causes an acute infection that rapidly affects the nervous system. In both species, the symptoms variate with the patient's health conditions and treatment [217]. Some common traces are intermittent fever, pruritus, headache, lymphadenopathy, anemia, and hepatosplenomegaly. According to the literature, in the phase where the parasite crosses the blood-brain barrier (BBB), the meningoencephalitis stage begins, with symptoms like neuropsychiatric and sleep disturbances, abnormal movement, limb paralysis, hemiparesis, aggressive behavior, or psychotic reactions [214,218,219].

These parasites are usually presented in the Tsetse fly (G*lossina* genus), the vector of sleeping sickness. Generally, the fly has contact with human or animal blood contaminated with the human pathogenic *Trypanosome.* Then, it transmits the disease through the sting to another being. Tsetse fly survives in regions with hot and relatively big humidity, natural characteristics of Sub-Saharan African places. Moreover, these regions present a population who are agriculture subsistence dependents, so they need to live in rural areas without environmental and health care [220–222].

Electrochemical research has been trying to give solutions to diagnose the neglected diseases using the development of biosensors. Tweed-kent et al. (2012) [223] reported the development of a biosensor to identify HAT in human blood samples. The authors described a

methodology based on a glassy carbon cylindrical rod electrode (GCCRE) modified with carboxylated single-walled carbon nanotubes (CSWCNT) and an immobilized aptamer that was synthesized by an RNA of the *Trypanosoma brucei*. It is important to highlight the limit of detection of 4.0 fmol L^{-1} reached in real samples. The hybrid aptasensor described by the authors represent an advance in the use of modified ion-selective electrode and an alternative to diagnose HAT rapidly and more cost effective than other commercial tests.

HAT has a difficult diagnosis because of the different reactions according to a large number of parasite species, the symptoms, and the poverty of affected locations. The number of scientific research about electrochemical sensors is not satisfactory. To another hand, methodologies like optical sensors or using chromatographic techniques, are most common to this disease in the scientific literature [214,222] However, the work presented here [223] can be used not only to help diagnose HAT but also to encourage researchers to develop different approaches with new ideas.

3.8. Lymphatic filariasis

Lymphatic filariasis (LF), commonly known as elephantiasis, is a neglected tropical disease, mosquito-transmitted, that constitutes a serious public health issue in the tropical region [224]. The disease affects millions of people is endemic in more than 70 countries throughout the regions of African, the Americas, Eastern Mediterranean, South-East Asia, and Western Pacific [225].

This disease is caused by infection with parasites classified as nematodes (roundworms) of the family *Filariodidea* that are transmitted by blood-feeding insects. Mosquito-transmitted larvae are deposited on the skin from where they can enter the body [226]. The larvae then migrate to the lymphatic vessels where they develop into adult worms, thus continuing a cycle of transmission. New diagnostic tools are essential at every stage of monitoring this disease because the methods currently used are time-consuming and high cost [227].

Venkatesan et al. (2013) [228] designed an electrochemical DNA biosensor. Their method enabled the amplification of ssDNA that was suitable for direct hybridization in an electrochemical DNA biosensor. This method is reproducible and avoids many of the difficulties encountered in conventional methods of DNA detection, for example, the analysis time.

Prado et al. (2018) [227] used the interaction between the (Wb/ALT2-A5) peptide and circulating antibodies of serum human samples to construct an electrochemical immunosensor by cyclic voltammetry. The biologic material was successfully immobilized on the working electrode of a screen-printed carbon electrode by their amine groups via chitosan film by coupling with glutaraldehyde as a cross-linker, tested in human serum samples from infected and healthy patients. In the work, it was obtained a detection limit of 5.0 μg mL^{-1} for the synthetic peptides (Wb/ALT2-A5) and 0.002 μg mL^{-1} for human serum, with a sensitivity of 1.86 μA.

3.9. Rabies

Rabies is an ancient disease that constitutes one of the most dangerous viruses causing many death cases every year, especially in Asia and Africa, where canine rabies is enzootic [229]. This disease claims more than 55,000 human lives each year, with a high percentage of children. Most cases of human rabies are transmitted by dogs. Dog rabies control by mass canine vaccination campaigns combined with intensive surveillance programs has led to a decline of human rabies in many countries [230,231].

The mainly responsible for transmission is a bite of animals and saliva of infected main reservoirs for rabies: wildlife like raccoons, skunks, bats, and foxes. The precise and rapid diagnosis is important for early treatment, effective prevention, and control measures. Human rabies often has distinctive clinical features reflecting the early brainstem involvement, including hydrophobia. There is a progressive clinical course to coma and the disease is virtually always fatal [229, 232].

To fight this dangerous disease, many techniques are usually used for the diagnostic and direct immunofluorescent test is a gold standard test and most commonly recommended for diagnosis of rabies, but these techniques are usually complex, heavy, expensive, difficult to implement, requiring high-qualified personnel and this is the necessity of developing new detections processes [229,232–234].

Adnane (2011) [233] describes the development of a biosensor for rabies and H7N1 antigen detection using gold electrodes modified with a self-assembled monolayer of 11-mercaptoundecanoic acid. Through electrochemical impedance spectroscopy measurements, the authors obtain an affinity interaction of the antibody with specific antigen can be measured with a detection limit of 0.5 and 5 μg mL^{-1} for rabies and H7N1, respectively.

4. Ten-year view

Looking at the large number of studies found in the literature and presented here, we can see that biosensors are a growing use methodology. In most of them, the genosensors and immunosensors are prioritized. These two kinds of biosensors present advantages related to specificity and sensibility. As explained in the previous topics, part of the genetic material or specific biomarkers, like antibodies, are used to produce these sensors.

In terms of selectivity, immunosensors are the best biosensor produced over the years. The immunologic interaction is capable of produce high sensitivity and selectivity. The low detection limits seen in many works presented here can prove these characteristics. On the other hand, immunosensor limitation could be related to the specific biomolecules over the electrode surface. The limit thermal stability is difficult because of the aggregation and retention of binding affinities of the antibodies. However, new developments can improve these deadlocks [235,236].

Genetic material is the most accessible material compared to antibodies because of the easiness of their production processes, not requiring living organisms, which improves the accessibility and reduced price of these sensors. Therefore, it is possible to see the genosensor as the best alternative to diagnosis with comparable results with the immunosensors [235,236]. Although the specific characteristics of the immune and genosensors, the electrical biosensors are present as a promising technology. The advantages like a short time of detection, sensibility, specificity, and the portability of the systems could improve the conditions to take care of the poor regions that suffer from DTN.

In general, electrochemical biosensors have proven to be potent and future-directed analytical tools to detect neglected tropical diseases. Their sensitivities are comparable to immunoassay methods. Advantages such as low-cost, the possibility for real-time measurements, and miniaturization will probably bring these biosensors into the realm of practicability for diagnostics. Researchers have found electrochemical biosensors to be simple, sensitive, selective, and rapid and save costs compared with previous methods.

Some devices cannot quantify the number of analytes present, but they inform the presence or absence of these analytes. These devices are pivotal to perform qualitative tests, as in some cases, the determination of the disease (yes or no infection) is required and sufficient. Examples are situations in which it is not possible to measure antibodies or antigens in sera, when untreated samples are available, and when it is unnecessary to detect the analyte at a low detection limit. Therefore, a semi-quantitative or even qualitative test is more than enough for diagnosis. In this sense, some authors have opted for this approach. Serological diagnosis of these infections is important to obtain a methodology that detects infected individuals as really positive in a supposed test, including cases of lower reactivity. Thus, the obtained results to biosensors show to be similar to ELISA to detected samples with a higher dilution rate and fewer antibodies.

It is well-known that after infection by some protozoa such as *Trypanosoma cruzi* or *Leishmania chagasi*, the individual develops a specific antibody against the parasite produced by the host immune system. In this sense, patients might generate different amounts of antibodies due to several reasons, such as immunological background, the genetic variability of parasites, inoculum, or infection route. In general, the diagnosis of infected individuals is performed through antibody detection by immunological techniques, such as hemagglutination, indirect immunofluorescence, and enzyme-linked immunosorbent assay. It would be necessary to obtain a large quantity of an infected human serum or a serum immunized by the antigen of interest, once produced in response to infections, to isolate these antibodies and determine their concentration in serum. Then, complex, expensive, and low-yield purification techniques are required.

In clinical practice, diagnostics evaluations for these diseases are usually conducted with serum dilution as the analytical parameter, not with the absolute value of antibody concentration in the serum. When an infected serum is diluted, the number of antibodies in that sample is reduced, and vice versa. Thus, an adopted dilution factor associated with a determined cut-off value results in a dividing line between infected and not infected groups. In this context, many papers proposed to use infected sera samples containing antibodies or some other analyte produced by the immune system, similar to routine clinical practice for the diagnosis of the diseases. Such analytes are detected in the diluted patient's serum by using immunological assays. It is worth noting that diagnostic sensitivity is related to the ability of a diagnostic test to classify as positive as the true positive, and analytical sensitivity is the lowest amount of the element of interest that the test can detect.

The last ten years have proven important in the development of biosensors for NTD detection. The evolution of the systems is evident using different biomolecules such as aptamers or peptides. Also, novel assays were applied, such as molecularly imprinted polymers, creating a template for the analyte and magnetic nanoparticles to biomolecule immobilization, thus improving the washing steps and the attraction to the electrodes. However, even with the premise of point-of-care devices with high specificity, sensibility, sensitivity, robustness, and cost-effectiveness, there are only a few works for many neglected diseases.

5. Conclusion

Neglected tropical diseases negatively impact the whole world, and despite the many efforts from dedicated people, the numbers of new cases and deaths are still alarming. From reaching remote and insecure areas to the availability of drugs to assist entire populations, the difficulties are immense. The development of low-cost and miniaturized devices such as biosensors can be deployed in such areas to speed up the correct diagnosis and, therefore, the treatment.

The ongoing research in the biosensor field applied to neglected tropical diseases shows promising and interesting results. The high availability of biological material associated with different approaches is an interesting feature for more investments since portable devices can be arranged. However, some important and lethal diseases are still in need of further attention. Leprosy, Human African trypanosomiasis, lymphatic filariasis, and rabies are examples of diseases that lack electrochemical biosensors in the literature. Even Chagas disease resulted in few papers, mostly from Brazilian researchers. Few devices are under study, and no example could be found in a mass production stage for immediate use.

With the premise of simple devices and fast results, the next stage from proof of concepts to fully operated systems in the response to the growing demand in the poorest places in the world is needed. Investments in this next step of research are as crucial as the investments in the production and delivery of drugs and vaccines or on research in more efficient treatments. The employment of biosensors is one more tool in the combat against the proliferation and for the eradication of NTDs.

Credit author contribution statement

Taís Aparecida Reis Cordeiro: Writing – original draft. Mayra Asevedo Campos de Resende: Writing – original draft. Simone Cristina dos Santos Moraes: Writing – original draft. Diego Leoni Franco: Conceptualization, Writing – review & editing, Supervision. Arnaldo César Pereira: Conceptualization, Writing – review & editing, Supervision, Funding acquisition. Lucas Franco Ferreira: Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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