Crucial role of biosensors in the detection of helminth biomarkers in public health programmes

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Helminthiases are highly prevalent but neglected infections that affect more than 1·5 billion people worldwide. Considering the worldwide prevalence of helminthiases, WHO has declared them a public health concern since 2001, necessitating rigorous control and elimination efforts. However, only a few reliable point-of-care diagnostic tests are available for assessing the effectiveness of public health interventions targeting helminthiases, thus increasing the risk of suboptimal outcomes, misallocation of resources, and emergence of drug-resistant helminths. This Review provides an introduction on helminthiases and strategies to achieve control, elimination, interruption in transmission, and eradication of these infections. The Review then comprehensively details the existent biosensors that can be used to detect these infections in human samples, focusing on their target biomarkers, the bioreceptors used, and the sensing readouts. The Review concludes with an in-depth discussion on the persistent challenges related to helminthiases, aiming to encourage the development of much-needed diagnostics specific to these neglected infections.

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Introduction

Neglected tropical diseases (NTDs) are a diverse group of conditions that mainly occur in tropical and subtropical regions of the planet, affecting the most clinically vulnerable populations.[1,2] Among all NTDs, those caused by helminths are the most prevalent.[3–7] Over 18% of the global population is estimated to be living with at least one of the various helminth infections; this large proportion could still be an underestimate, owing to the complex epidemiology of helminth infections and the scarcity of robust surveillance systems in many regions.[7] Although helminthiasis infections are mostly asymptomatic, they can produce severe symptoms and be life threatening in some cases.[2] These infections have strong social and economic consequences,[1,7] resulting in an estimated loss of more than 9 million all-age disability-adjusted life-years annually (table).[8]

Global landscape of helminth control

In the WHO road map for 2021–30, NTDs are classified into four groups according to the target(s) expected to be achieved by 2030: control, elimination as a public health problem, interruption of transmission, and eradication. Helminthiases appear in all of the four groups (table).[1] The helminthiases in the control group, including taeniasis or cysticercosis, foodborne trematodiases, echinococcosis, and strongyloidiasis, require intensified control in highly endemic areas.[1,18] The helminthiases in the elimination as a public health problem group[19] include schistosomiasis, lymphatic filariasis, and soil-transmitted helminthiases.[1] In this group, the targets vary depending on the specific disease: for schistosomiasis, the target is to reduce the prevalence of heavy infections to less than 1% by 2030; for lymphatic filariasis, to maintain low transmission for 4 years after chemotherapy in 58 countries; and for soil-transmitted helminthiases, to reduce the prevalence of moderate and heavy infections to less than 2% in 96% of the endemic countries.[1] Onchocerciasis is the only helminthiasis in the interruption of transmission (ie, reduction of the incidence of infection to zero with minimal risk of reintroduction) group, which has set a target of 12 countries to achieve this goal by 2030.[1] Finally, dracunculiasis (or Guinea worm disease) is included in the eradication group, and by 2030, all countries are predicted to be transmission-free for this disease condition.[1] In this Review, we focus on diseases in the control, elimination as a public health problem, and interruption of transmission groups. Dracunculiasis will not be included for being an outlier in terms of diagnostic techniques.

Public health strategies

Different intervention strategies have been implemented over the years to mitigate the effect of helminthiases. Preventive chemotherapy, which relies on mass drug administration (MDA) campaigns, is the main and most cost-efficient public health intervention for neglected helminthiases.[5,20] WHO's strategy for controlling helminth infections involves assessing the baseline prevalence of the infection and implementing MDA in at-risk populations, which consist of population groups with higher prevalence or risk of severe morbidity in endemic areas (ie, school-aged children or women of reproductive age), wherever thresholds are met. The frequency and duration of preventive chemotherapy depend on initial prevalence, and accurate diagnostics are crucial for monitoring the prevalence trends and deciding whether to continue MDA. Unfortunately, existing diagnostics for neglected helminthiasis are often inadequate, costly, and restricted to small population samples, thereby reducing their effectiveness as a monitoring tool in public health strategies.[1,21]

Tools for monitoring and evaluation

The current diagnostic tools for helminthiases can be classified into three main categories, as described below.

Conventional microscopy is mostly considered as the gold standard. However, its use in large-scale assessment of intervention strategies is hampered by limitations such as

	Global prevalence	DALYs[8]	WHO target by the year 2030[1]	WHO indicator[1]	Number of countries expected to achieve the WHO target by the year 2030[1]	Diagnostic requirements for target achievement
Taeniasis or cysticercosis	Neurocysticercosis 2·56–8·30 million[9]	1 610 000 years (cysticercosis)	Control	Number of countries with intensified control	17	Low cost High sensitivity
Foodborne trematodiases[10] (clonorchiasis, opisthorchiasis, fasciolasis, and paragonimiasis)	67·4–82 million[11]	1 870 000 years	Control	Number of countries with intensified control	11	Low cost High sensitivity
Echinococcosis	Greater than 1 million[12]	100 000 years (cystic echinococcosis)	Control	Number of countries with intensified control	17	Low cost High sensitivity
Strongyloidiasis	Greater than 600 million[13]	Not known	Control	Coverage with ivermectin for individuals older than 5 years and in areas with prevalence of infection ≥5% among school-aged children	Not known	Low cost High sensitivity
Soil-transmitted helminthiases	1·5 billion[14]	1 920 000 years	Elimination as a public health problem	Less than 2% of moderate to heavy intensity infections	96	High specificity
Schistosomiasis	240 million[15]	1 430 000 years	Elimination as a public health problem	Less than 1% of heavy intensity infections	78	High specificity
Lymphatic filariasis	120 million[16]	1 360 000 years	Elimination as a public health problem	4 years of no evidence of transmission after preventive chemotherapy	58	High specificity
Onchocerciasis	19·1 million[16]	1 340 000 years	Interruption of transmission	Number of countries verified for interruption of transmission	12	High specificity
Dracunculiasis	27[17]	0·55 years	Eradication	Number of countries certified free of transmission	194	High sensitivity and specificity

DALYs=disability-adjusted life-years.

Table: **Epidemiological characteristics of neglected helminthiases targeted for action in the WHO road map for neglected tropical diseases for 2021–30**

poor sensitivity, complex protocols, and the need for trained microscopists.[22–24]

The detection of specific biomarkers (antibodies or antigens) is generally conducted in the laboratory using ELISA and in the field using lateral flow assays (LFAs). These techniques allow for the diagnosis of some neglected helminthiases (when detecting antigens) and the detection of exposure to a specific helminth (when detecting helminthiasis-specific antibodies),[25] and are commonly applied for onchocerciasis,[26,27] lymphatic filariasis,[28–30] schistosomiasis,[31–38] and echinococcosis.[39–42] However, these techniques often suffer from low sensitivity and cross-reactivity.[43–45]

Molecular tests detect nucleic acid sequences specific to helminthiases with high sensitivity and specificity but require substantial infrastructure and specialised personnel, which limits their use in low-resource settings.[24,46,47] Insufficient standardisation also hampers the implementation of molecular tests in public health strategies. To tackle this challenge, efforts have been made to implement shared laboratory protocols of DNA extraction and real-time PCR procedures, as well as an international external quality-assessment scheme.[47,48]

In this context, WHO identified the development of more accurate point-of-care (PoC) diagnostic methods that can be implemented in situations in which health-care services are provided and in large-scale interventions as a top priority.[1]

The realm of PoC diagnostics comprises different technologies that have varied properties depending on the situations in which they need to be deployed. That is, the general definition of PoC includes technologies designed for use at the bedside in tertiary hospitals, as well as those that should be deployed in field settings. With respect to the technologies for field settings, the REASSURED criteria clarify the characteristics that diagnostic methods should have for them to be easily implementable and provide maximum benefits in such scenarios:[49] specifically, they should have real-time connectivity, ease of specimen collection, and be affordable, sensitive, specific, user-friendly, rapid and robust, equipment-free and environmentally friendly, and deliverable to the end-users (REASSURED).[49,50]

Notwithstanding the importance of such guidelines, the complexity of lengthy public health interventions aiming at the control, elimination, and interruption of diseases should also be highlighted. To provide a proper assessment of such interventions, the performance of the diagnostic tools needs to be tailored to the prevalence of the disease (table). Specifically, interventions for controlling helminthiases require sensitive diagnostics to assess its baseline prevalence in an area for routine monitoring.[21] To guarantee their large-scale application, such technologies should also be cost-effective and suited for use at the PoC. Helminthiases in both the elimination as a public health problem and interruption of

transmission groups require highly specific diagnostics for two main purposes: demonstrating the absence of infection after the commencement of a public health strategy and assessing the effectiveness of the preventive chemotherapy, especially when low prevalence is being reached. Therefore, considering these specific applications, diagnostic technologies with higher costs and longer protocols are acceptable, particularly because they are intended for smaller-scale applications in which higher costs can be justified.[21]

Detection of helminth-specific biomarkers

In the development of a diagnostic device, the identification of sensitive, specific, and recombinant biomarkers (expressed by genetically engineered organisms using recombinant DNA technology) is crucial to obtain the desired analytical and clinical performance of the test, because the use of crude extracts often introduces additional challenges, particularly during the scale-up phase.[51] Although research on helminth-specific biomarkers began decades ago, and several of these biomarkers have been incorporated into biosensors (as discussed in the following paragraphs), there remains a pressing need to identify new biomarkers that provide better performance, especially for use in monitoring and evaluation strategies.

In the present work, we have focused on helminth-specific antigens and antibodies, as these can be easily integrated into PoC biosensors. Specifically, biosensors are devices with biological sensing elements that measure the analyte of interest in a specific sample.[52] Biomarkers that enable antigen-antibody reactions and have already been used in commercial and non-commercial biosensors for human helminthiases are listed in the appendix p 2. Several of those biomarkers have been identified and incorporated into newly developed diagnostic tools, especially for schistosomiasis,[53–56] onchocerciasis,[57] lymphatic filariasis,[28,30,57] and echinococcosis.[58,59] For example, both circulating cathodic antigen (CCA) and circulating anodic antigen (CAA) have been used extensively for the detection of schistosomiasis in serum and urine samples.[34,38,54–56,60] Ov16, a glutathione-S-transferase fusion protein from *Onchocerca volvulus*, has been the most used biomarker in the diagnosis of onchocerciasis, whereas the circulating antigens and the Wb123 antigen from *Wuchereria bancrofti* as well as BmR1 and BmSXP from *Brugia malayi* are the most used biomarkers for detecting lymphatic filariasis.[26,27,57,61–65] The enriched antigen 5 and antigen B have been used in multiple studies for the detection of echinococcosis.[39–42,66]

Biosensors for neglected helminthiases

Over the past two decades, rapid advances in technological miniaturisation and automation have led to the development of several PoC biosensors for the detection of neglected helminthiasis infections.[49,67–70] Some studies have reported proof-of-principle results, whereas others have evaluated the performance of working prototypes using clinical samples and even in field settings.[69] Using an adapted technology readiness level scale,[69] the majority of the developed biosensors are ranked with a maximum of a technology readiness level-4, and are, therefore, not ready for commercialisation, with the exception of a few devices for schistosomiasis,[53–56] lymphatic filariasis,[28,30,57] onchocerciasis,[57] and echinococcosis,[58,59] which have reached the readiness required for commercialisation. This section provides an overview of publications on biosensors using antigen-antibody reactions (classifying them as immunodiagnostic techniques) for diagnosing human helminth infections.

We searched PubMed for peer-reviewed articles in English without publication year restrictions, using keywords related to neglected helminthiases and biosensors as per the WHO road map for NTDs for 2021–30. This search yielded 5559 articles for the duration between 1993 and 2023. After excluding irrelevant studies, duplicates, and those involving non-human samples, 109 articles were selected for analysis (appendix p 22).

The main diseases covered were schistosomiasis (38 of 109 articles), neurocysticercosis and cysticercosis (16 of 109), lymphatic filariasis (15 of 109), foodborne trematodiases (11 of 109), onchocerciasis (11 of 109), strongyloidiasis (nine of 109), and echinococcosis (nine of 109). We could not identify studies reporting the development or validation of biosensors for soil-transmitted helminthiases, most likely due to the absence of reliable biomarkers. This challenge arises from factors such as the complex lifecycles of soil-transmitted helminthiases;[16,71] substantial antigenic variation between and within species;[16,71] sophisticated immune evasion mechanisms that weaken immune responses;[72] environmental factors;[16,71] high cross-reactivity among species;[72,73] and the paucity of comprehensive genomic data.[71] In the present work, we grouped the selected studies on the basis of the type of biosensor used, such as immunochromatographic (90 of 109), electrochemical (13 of 109), optical (four of 109), and piezoelectric (two of 109) biosensors.

See Online for appendix

Immunochromatographic tests (ICTs)

Of the 109 manuscripts selected for this Review, the vast majority (83%, n=90) pertain to ICTs. ICTs rely on the use of a nitrocellulose membrane on which the presence of specific antigens and antibodies leads to the accumulation of a colorimetric reporter, whose signal indicates the presence or absence of the biomarker (figure 1A).[74,75] ICTs mostly provide qualitative colorimetric results, which are coloured bands in the case of LFAs or coloured dots in the case of dot-blot assays. Owing to their ease of use and low cost, ICTs based on naked-eye detection are the most widely developed and characterised, with most LFAs and dot-blot assays allowing for qualitative naked-eye detection, and the latest efforts aim to make these assays more quantitative and sensitive.[75] For helminthiasis biosensors, these advancements include the use of spectroscopic, fluorescence, and magnetic readers (discussed in the following sections). In terms of WHO's REASSURED criteria, ICTs typically fulfil

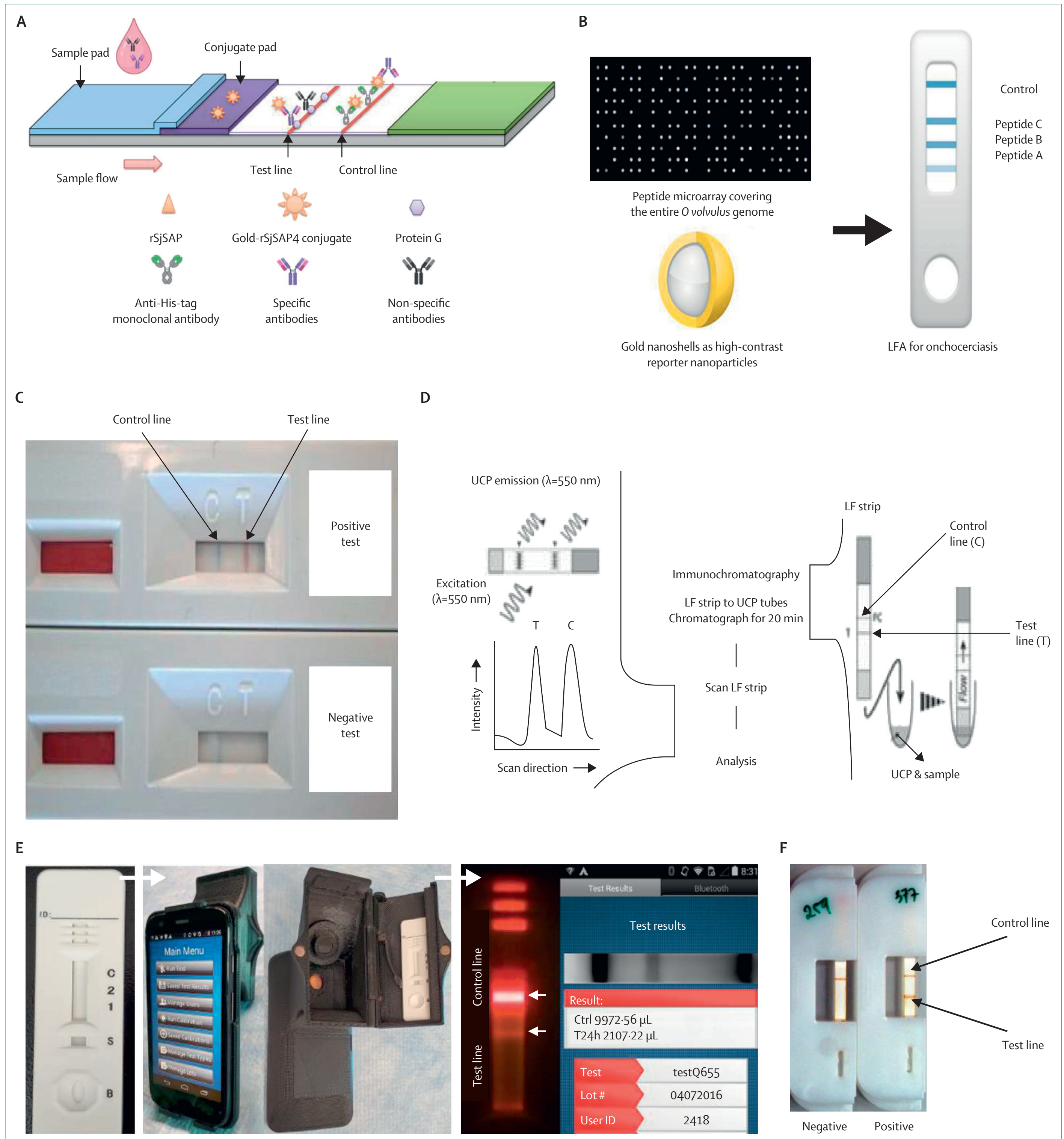

Figure 1: **Novel immunochromatographic tests for the diagnosis of neglected helminthiases**
(A) Single-antigen LFA using gold nanoparticles for diagnosis of *Schistosoma japonicum* infection (modified from Mu and colleagues[78]). (B) Multiple-antigen reading and naked-eye reading LFA for the detection of *Onchocerca volvulus* (modified from Gonzalez-Moa and colleagues[81]). (C) Dual-label reading and naked-eye reading LFA for the diagnosis of neurocysticercosis; test line appears in red and control line in blue (modified from Fleury and colleagues[84]). (D) UCP technology-based LFA scheme for the detection of *Schistosoma* circulating anodic antigen or circulating cathodic antigen, or both (modified from Corstjens and colleagues[55]). (E) LFA with quantum dots label for the detection of antibodies against *Taenia solium* and portable reader to measure fluorescence intensity (modified from Lee and colleagues[108]). (F) Magnetic LFA for antibody detection in taeniasis (ES33 antigen) and neurocysticercosis (T24H antigen) infections (2010 American Society for Microbiology. Adapted with permission from Handali and colleagues.[111] No further reproduction or distribution is permitted without the prior written permission of American Society for Microbiology). LF=lateral flow. LFA=lateral flow assay. UCP=up-converting phosphor.

the requirements of affordability, rapid and reliable performance, deliverability to end-users, and in some cases, are equipment-free and offer real-time connectivity. However, these tests often require health professionals to collect samples and mostly use single-use plastic, which makes them less user-friendly and environment-friendly.

ICTs usually incorporate gold or carbon nanoparticles as optical labels, and the whole operation requires less than 15 min.[76–80] To improve the performance of ICTs for helminthiasis detection without losing the simplicity of naked-eye detection, some research groups have used novel labels, specifically gold nanoshells[81] and latex nanoparticles.[82–85]

Gold nanoshells are reporter particles that consist of a thick gold shell deposited around silica spheres. Because of their unique optical behaviour, gold nanoshells substantially increase the analytical sensitivity of the ICTs.[81] To develop a multiplexed and sensitive biosensor, Gonzalez-Moa and colleagues[81] performed a peptide microarray covering the entire *O volvulus* genome, with the three most promising peptides (OvOC9384, OvOC198, and OvOC5528) incorporated into an ICT for diagnosis of onchocerciasis using serum samples (figure 1B). Therefore, the final ICT had four different lines: the first three lines corresponded to the detection of the three different *O volvulus* antigens, and the fourth line corresponded to the control. The test was considered to be positive for *O volvulus* infection when any of the three antigen lines appeared together with the control line. However, the authors themselves reported some limitations such as cross-reactivity with other species and the need for optimising the peptides incorporated into the ICT.[81]

Another ICT was developed by Toribio and colleagues[82] for detecting circulating cysticercosis antigens in the urine of patients with subarachnoid neurocysticercosis. The ICT incorporated blue latex microspheres in the conjugate pad, and the presence of the target led to their accumulation on the test line.[82] Therefore, the appearance of a blue test line was seen as a positive diagnosis for taeniasis. Moreover, the authors used a predefined standard scale to evaluate test line intensities, making an effort towards obtaining semi-quantitative results. Scale-use for semi-quantification has huge potential in ICTs, but standardisation efforts and defining what the obtained intensities correspond to are challenging tasks without the use of a dedicated reader.

Similarly, Fleury and colleagues[84] reported the development of an ICT for the detection of the HP10 antigen from *Taenia solium* for the diagnosis of neurocysticercosis (figure 1C). The test was evaluated using cerebrospinal fluid from patients with neurocysticercosis. The researchers used an ICT in which red latex nanoparticles modified with anti-HP10 antibodies accumulated on the test line in the presence of the target. In this case, the appearance of a red line indicated the presence of the HP10 antigen in the cerebrospinal fluid of individuals with neurocysticercosis. However, obtaining cerebrospinal fluid samples requires medical interventions, such as a lumbar puncture. Owing to this challenge, the authors later tested their ICT using serum samples and reported lower sensitivity compared with that obtained with cerebrospinal fluid.[82–84]

To deliver quantitative and more sensitive results, some researchers have developed ICTs paired with various readers. Spectroscopic ICTs for detecting helminths in human samples were primarily published between 1990 and 2010.[86–100] These tests produced positive results through the enzymatic activities of peroxidase and alkaline phosphatase, which catalyse chemical reactions that result in a visible colour change detectable by spectrophotometry. However, the development of these tests has slowed over the past decade due to the rise of cheaper, portable fluorescent readers and smartphones.

In contrast, fluorescence-based ICTs have emerged as a new, more sensitive technique for detecting helminth analytes, as evidenced by a surge in scientific publications of late.[55,56,60,101–109] The majority of these use up-converting phosphor nanoparticle-based LFA (UCP-LFA) for their studies (figure 1D). The unique feature of up-converting phosphor nanoparticles is their ability to be excited by infrared light and emit visible light, which produces a superior fluorescent signal with minimal background interference from other components of the ICT.[110]

Corstjens and colleagues[101] were the first to develop a UCP-LFA for neglected helminthiases, which aimed to detect the *Schistosoma* CAA in serum samples obtained from international travellers in the Netherlands. The authors reported a good correlation between UCP-LFA signal intensity and infection intensity when the test was evaluated with 40 well characterised samples. Moreover, more CAA-positive samples were identified using UCP-LFA than using their in-house CAA-ELISA when testing 166 serum samples obtained from Dutch residents (immigrants and travellers) with suspected schistosomiasis. The same research group also adapted the UCP-LFA into a more user-friendly version by incorporating dry reagents, making it more suitable for PoC applications.[102] This modified UCP-LFA was evaluated using a portable reader developed by Ampath Laboratories (Pretoria, South Africa). Testing of the modified UCP-LFA with 2000 clinical samples concluded that the newly developed UCP-LFA matched or exceeded the performance of CAA-ELISA in terms of sensitivity and specificity, with a limit of detection (LOD) of 30 pg CAA/mL serum, and showed improved applicability. The authors emphasised that the use of dry reagents allowed for sample testing in South Africa at ambient temperature. Combined with the development of a portable reader, this advancement brought their UCP-LFA closer to being applicable at the PoC level. The same research group, in collaboration with Markwalter and colleagues,[60] reported the development of an alternative CAA concentration method from large-volume urine samples, which requires minimal laboratory equipment. This method uses poly (amidoamine)-coated magnetic particles to capture the CAA antigens through electrostatic interactions, allowing the CAA concentrate to be directly used in the UCP-LFA,

thereby improving its performance and achieving an LOD of 0·05 pg CAA/mL.

Lee and colleagues[108] developed a different type of fluorescent ICT using quantum dots as a label for the detection of antibody responses against *T solium* in serum samples (figure 1E). Quantum dots were coupled to the *T solium* antigen T24H, and in the presence of anti-T24H antibodies in the serum, they interacted with the T24H sprayed on the test line, resulting in a fluorescence signal. Fluorescence signals emitted by positive tests were quantified using a mobile phone reader approximately 30 min after sample testing.

In all cases in which fluorescent labels were included in the ICT for helminth detection, the authors emphasised their higher sensitivity in comparison with that of traditional ICTs and the elimination of individual interpretation.[101,106,108] Although current studies on fluorescent ICTs have shown potential for PoC applications, some improvements are still needed, such as the use of direct whole blood instead of serum samples and a reduction in the assay duration, as it currently takes more than 1 h to obtain results.

Finally, two magnetic ICTs were developed by Handali and colleagues[111] to detect specific antibodies present in serum samples from individuals with taeniasis and neurocysticercosis (figure 1F). To achieve this, the authors sprayed the antigens ES33 (for taeniasis) and T24H (for neurocysticercosis) in the test lines. Serum samples were mixed with the ES33 or T24H antigens conjugated with superparamagnetic particles, and the mixture was added to the ICTs. If taeniasis and neurocysticercosis antigens were recognised by specific antibodies, the resulting complexes were retained in the test line, and the emitted signals were quantified using a magnetic assay reader. Since the publication of this study in 2010, no additional articles have been found that use magnetic ICTs for helminthiasis identification.

Electrochemical biosensors

In electrochemical biosensors, biochemical reactions are converted into measurable electrical signals using redox reporters or impedimetric measurements.[112] Overall, electrochemical biosensors are considered to be quantitative, user-friendly, and inexpensive, and therefore, suitable for use at the PoC.[113] Electrochemical biosensors successfully meet the REASSURED criteria of real-time connectivity, affordability, rapid and reliable performance, and accessibility to end-users. However, these biosensors require a potentiostat to measure signals; although potentiostats can be portable for PoC use, they prevent the biosensors from being completely equipment-free. Furthermore, efforts are being made to enhance the environmental friendliness of these biosensors by using substrates such as paper-based and carbon-based electrodes.

A majority of electrochemical sensors for the diagnosis of neglected helminthiasis have focused on identifying *Schistosoma* and *Strongyloides*.[114–124] Traditionally, gold has been the main material used for working electrodes in electrochemical biosensors for the detection of neglected helminthiases.[115,116,118] However, carbon-based electrodes, particularly graphite, have emerged as sustainable materials for working electrodes of late.[114,117,119,121–124] For example, Deng and colleagues[117] used a disposable 16-channel screen-printed carbon electrode array, with every channel containing working, reference, and auxiliary electrodes (figure 2A). They coimmobilised two antigens from *Schistosoma japonicum* on the surface of all working electrodes and used a secondary anti-human IgG antibody modified with a redox reporter. The recombinant calcium-binding protein (SjE16) was used as the principal antigen, and the soluble egg antigen was used as the minor antigen, at a ratio of 8:1.[117] The biosensor thus developed was evaluated for antibody detection in serum samples obtained from schistosomiasis-infected and non-infected individuals. A portable detector was used for reading the electrochemical signal (using cyclic voltammetry), which showed high sensitivity (>90%) and minimal cross-reactivity.[117] However, the protocol required multiple steps and at least 1 h to obtain the results, making it less suitable for PoC applications. In addition, further evaluations were needed due to the low number of samples used.

Similarly, Melo and colleagues[114] used commercially available graphite screen-printed electrodes in which epitopes from *Strongyloides stercoralis* and the non-helminth species *Leishmania infantum chagasi*, *Leishmania amazonensis*, and *Mycobacterium leprae* were deposited to construct a multiplexed electrochemical biosensor (figure 2B). The study aimed to evaluate whether addition of the compound 4-dimethylaminoantipyrine to the biosensor thus developed promoted higher electrochemical signals for immunological detection. Although the authors confirmed this hypothesis, the assay duration takes around 2 h to reach a diagnostic result, making it less suitable for PoC use[114] when compared with that of ICTs for strongyloidiasis diagnosis, which require only a few minutes.[125–127]

Other material and sensing strategies were also implemented for the fabrication and modification of electrodes. In a biosensor developed by Lin and colleagues,[128] the electrode surface was sequentially electroplated with nickel and gold in an interdigitated microelectrode shape (figure 2C). This biosensor used alternating current electrokinetics (ACEK, a technique that uses oscillating electric fields) capacitive sensing to enhance specific antibody detection against *T solium* infection in serum samples.[128] The application of the ACEK effect on the biosensor allowed for both the enrichment of target antibodies and enhanced measurement of the capacitance changes induced. Specifically, the *T solium* rT24H antigen was immobilised onto the interdigitated microelectrode surface of the biosensor. Serum samples were added, and with the application of sinusoidal alternating current (<350 mV), an ACEK flow

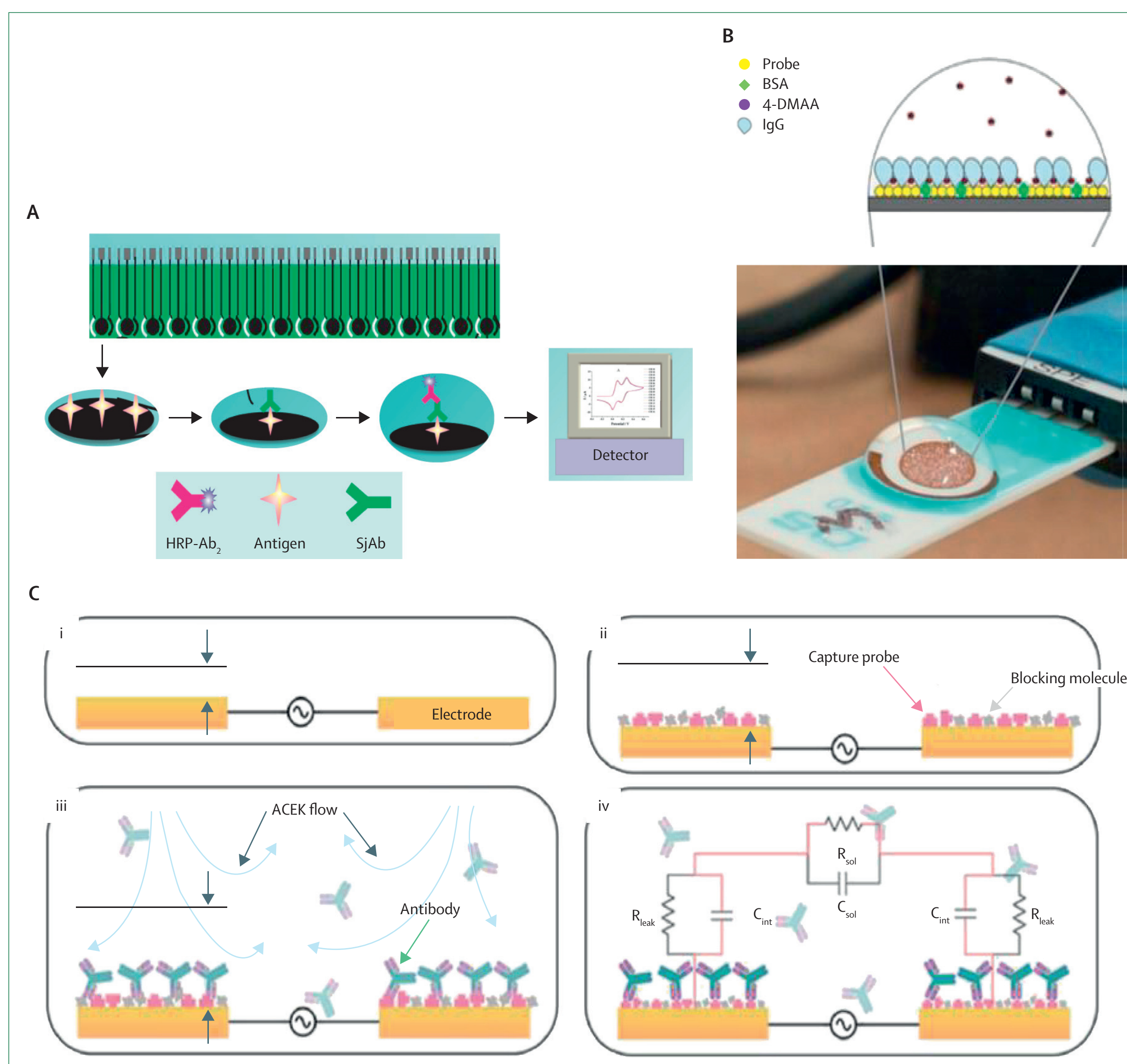

Figure 2: **Novel electrochemical biosensors for the diagnosis of neglected helminthiases**
(A) Schematic diagram of a portable 16-channel electrochemical biosensor for the detection of antibodies against *Schistosoma japonicum* antigens (modified from Deng and colleagues[117]). (B) Graphite screen-printed electrodes in which epitopes from *Strongyloides stercoralis, Leishmania infantum chagasi, Leishmania amazonensis,* and *Mycobacterium leprae* were deposited to construct a multiplex detection electrochemical biosensor (modified from Melo and colleagues[114]). (C) ACEK capacitive sensing by an interdigitated microelectrode biosensor for serological screening of *Taenia solium* cysticercosis infection: (i) representation of the interdigitated microelectrode with the bare surface; (ii) interdigitated microelectrode surface functionalised with *T solium* antigens and blocked; (iii) biosensor surface with antibodies specifically bound to the antigen; this process is assisted by the ACEK effect; (iv) scheme of the circuit on the interdigitated microelectrode biosensor surface in a sample fluid (modified from Lin and colleagues[128]). 4-DMAA=4-dimethylaminoantipyrine. ACEK=alternating current electrokinetics. BSA=bovine serum albumin. HRP=horseradish peroxidase.

was created. This flow enhanced the movement of serum antibodies, increasing the probability of antibodies being found on the interdigitated microelectrode surface, thereby promoting antigen-antibody recognition. The antigen-antibody binding events generated a conformational change in the biosensor surface, leading to a change in the interfacial capacitance of the biosensor, which can be electrically quantitated. This interfacial capacitance change had a strong correlation with the quantity of antigen-antibody binding, allowing for a quick response time (<1 min) and low LOD (24·1 fg/mL).

Other sensing strategies

Optical biosensors are devices that measure changes in the optical properties of propagated light when a binding interaction occurs.[112] These optical biosensors show rapid and reliable performance with reference to REASSURED criteria. However, compared with other biosensors used in the detection of neglected helminthiases, the technology of optical biosensors is less mature. Consequently, achieving affordability, user-friendliness, accessibility to end-users, equipment-free operation, and ease of specimen collection remain substantial challenges.

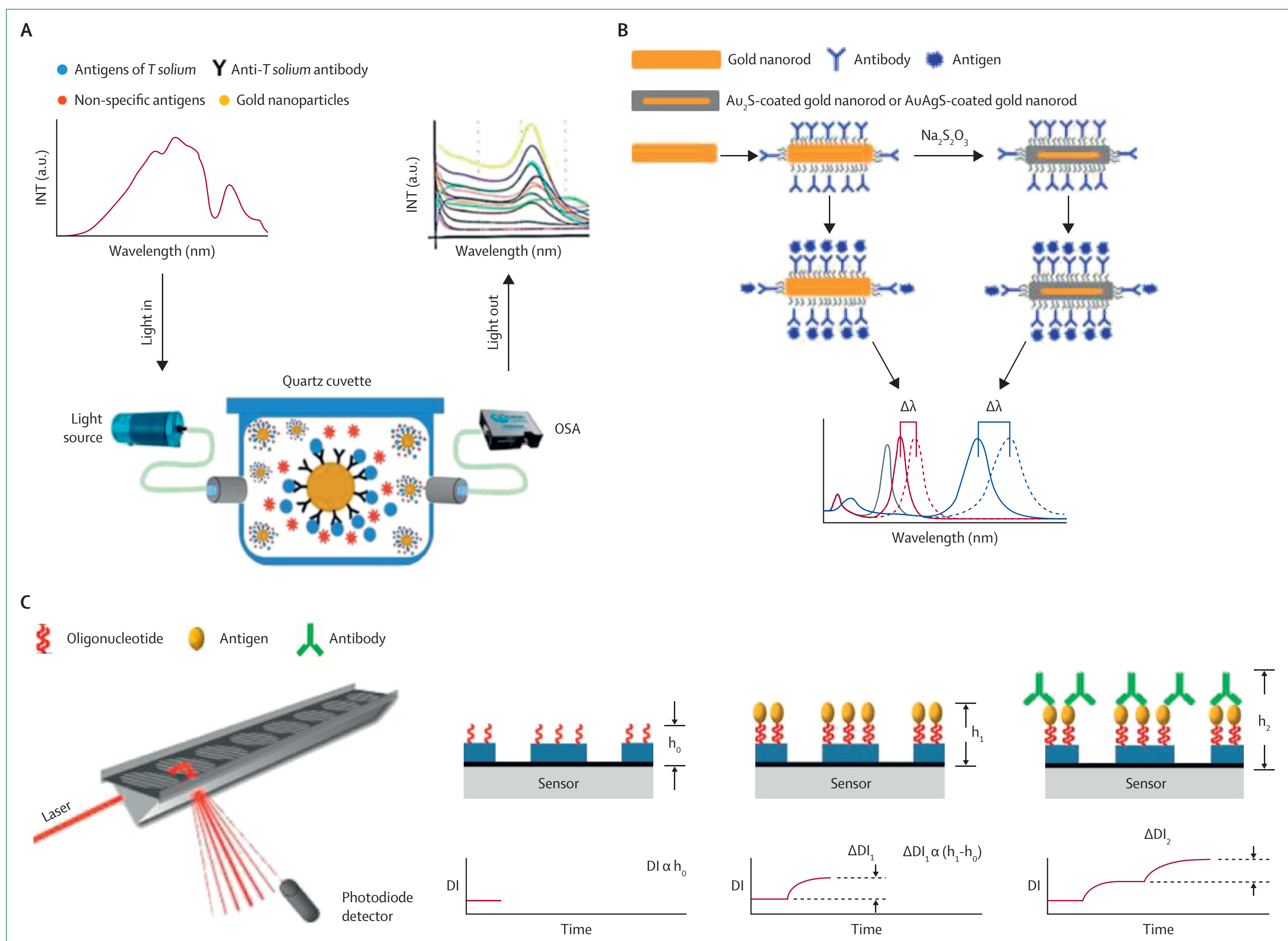

Figure 3: **Novel optical biosensors for the diagnosis of neglected helminthiases**
(A) Optical biosensor for the detection of *Taenia solium* using the localised surface plasmon resonance effect (adapted with permission from Optica Publishing Group from Arcas and colleagues[130]). (B) Detection of *Schistosoma japonicum* antigens through an optical biosensor using two types of gold nanorods and the localised surface plasmon resonance effect (modified from Huang and colleagues[131]). (C) Optical biosensor for the detection of antibodies against *Strongyloides stercoralis* antigens through generation of diffraction grating images (modified from Pak and colleagues[134]). DI=diffraction image intensity. INT=intensity. OSA=optical spectrum analyser.

In the studies included in this Review, authors have developed optical biosensors as potential diagnostic tools for the detection of schistosomiasis, strongyloidiasis, and neurocysticercosis in human serum samples. The majority of the published optical biosensors for helminth detection used the localised surface plasmon resonance effect generated by the interaction of light and gold nanoparticles.[129–131] In this effect, when light irradiates the gold nanoparticles, the electric field generated causes the electrons of the gold atoms to oscillate coherently. Consequently, characteristic absorption bands are generated in the visible range of the spectrum, which are detectable with a spectrophotometer.[130,131] When target biomarkers are detected, a change in the spectrum is found in comparison with the baseline.[131] Therefore, localised surface plasmon resonance can be effectively used to detect specific target-binding events.

Arcas and colleagues[130] compared two methodologies for gold nanosphere synthesis and their use in detecting *T solium* antigens in human serum (figure 3A). The authors reported rapid detection (within minutes), good sensitivity, and a LOD of less than 0·1 μg/mL.[130] On the other hand, Huang and colleagues[131] and He and colleagues[129] showed how gold nanorods (rod-shaped gold nanoparticles) have a superior optical behaviour (specifically using their longitudinal plasmon resonance) in comparison with the gold nanospheres, leading to a substantially enhanced sensitivity.[132,133] The authors used gold nanorods functionalised with antibodies specific for *S japonicum* antigens (figure 3B). In both cases, the authors showed superior analytical performance of their biosensors in comparison with that of the traditional techniques used for parasite detection; however, the LODs of the developed devices were not specified.

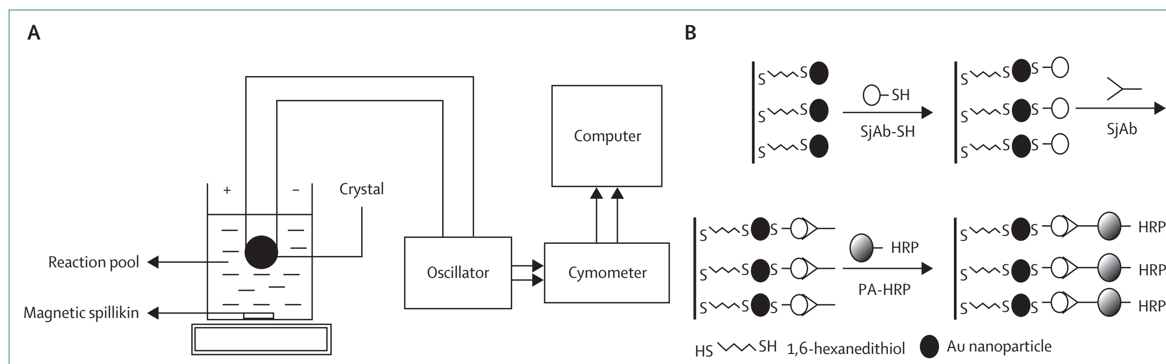

Figure 4: **Novel piezoelectric biosensors for the diagnosis of neglected helminthiases**
A schematic of (A) the piezoelectric biosensor for the diagnosis of schistosomiasis (modified from Wen and colleagues[137]) and (B) the assembly procedure of the antigen-antibody recognition in a piezoelectric biosensor (modified from Wu and colleagues[138]). HRP=horseradish peroxidase.

Another approach used by Pak and colleagues[134] created diffraction grating images when the optical biosensor was illuminated with a laser (figure 3C). The biosensor they developed consisted of a commercially available panel (dotLab mX System from Axela) onto which specific oligonucleotide sequences were attached and the biomarker of interest immobilised through complementary oligonucleotide hybridisation. The functionalisation of the surface of this biosensor with the NIE protein of *S stercoralis* allowed the recognition of strongyloidiasis-specific antibodies in serum samples. Furthermore, the use of the commercial panel allowed for either replicate analysis of the same biomarker or multiplexing with different biomarkers. The binding of specific antibodies to the NIE proteins immobilised on the biosensor can generate an increased intensity of the diffraction grating images, which can be monitored with a photodiode detector. Comparison of results obtained from testing human serum samples from strongyloidiasis-infected individuals and non-infected individuals with an in-house NIE-ELISA showed excellent agreement. Despite the relevance of confirming results using an in-house ELISA, the technique has not been validated by external users and agencies, thereby further highlighting the need for standardised methodologies for the detection of helminth infections.

Piezoelectric biosensors detect mechanical stress, such as an increase in mass because of antigen-antibody interactions, in terms of changes in resonance frequency on electrode surfaces.[112,135,136] However, with respect to the REASSURED criteria, piezoelectric biosensors meet only the desired characteristics of real-time connectivity and rapid performance, making them the least compliant with the REASSURED criteria among all the biosensors for neglected helminthiases discussed in this Review.

The only two studies that developed piezoelectric biosensors for detecting helminths in human samples targeted *S japonicum* and were published in 2006 and 2011 (figure 4).[137,138] These biosensors immobilised *S japonicum* antigens or specific antibodies on the electrode surfaces. One study evaluated serum samples from 180 participants, and the other evaluated the same from four. Although the easy regeneration properties of piezoelectric biosensors enhance their reusability, additional research is necessary to verify their sensitivity for biomarker analysis in human samples and their ease of use. Furthermore, piezoelectric biosensors require advanced infrastructure for sample testing, which limits their PoC application in regions where helminthiases are prevalent.

Current commercial landscape

So far, commercialised ICTs have been the only biosensors used in strategies to monitor and evaluate helminth control programmes, particularly for lymphatic filariasis[31,57,61,65,139,140] and onchocerciasis,[57,61,139] and, to a lesser extent, for schistosomiasis[141,142] and echinococcosis.[39,58,66] ICTs have proven to be cost-effective, and in some cases, have outperformed traditional serological techniques such as ELISA in terms of sensitivity.[101] Their development and availability for these neglected helminthiases have been driven by their high global prevalence (table), the support of international organisations and donors,[1] and the presence of well characterised antigens and antibodies crucial for the development of rapid tests (appendix p 2).

ICTs of lymphatic filariasis have been used extensively for mapping endemic areas, conducting baseline surveys, monitoring the effect of MDA, endpoint assessments, and research. A study by Washington and colleagues[143] found a reduction in lymphatic filariasis seroprevalence from 10·4% to 6·3% and a decrease in microfilaraemia from 0·9% to 0·4% after the first MDA with both diethylcarbamazine and albendazole. However, of note, ICTs showed cross-reactivity in areas with *Loa loa* endemicity.[43,45,144]

ICTs have been applied in various programmes and initiatives aimed at controlling and eliminating onchocerciasis, as well as in research studies, in several countries involved in the Onchocerciasis Control Programme, the African Programme for Onchocerciasis Control, the Expanded Special Project for Elimination of NTDs, and in efforts to achieve WHO's elimination goal by 2030. In a study conducted by Lipner and colleagues,[26] the field applicability of an ICT for onchocerciasis was evaluated and compared with microscopy techniques for assessing microfilaraemia

in two endemic villages in Côte d'Ivoire with no history of control measures. The results showed microfilariae prevalence rates of 82·8% and 65·1%, along with antibody seroprevalence rates of 73·1% and 62·1%. Although onchocerciasis ICTs showed good performance in hyperendemic and mesoendemic areas, their performance was less robust in hypoendemic regions.[139]

In the case of schistosomiasis, ICTs have been used at the national level in control programmes to assess disease prevalence and distribution, guide MDA efforts, and support research studies. Bärenbold and colleagues[145] conducted a comparative study of novel and standard diagnostic tools for detecting schistosomiasis in settings across Africa and the Americas. Their findings indicated that ICTs showed high specificity (>95%) and sensitivity (>95%) for moderate and heavy infection intensities, as well as moderate sensitivity (>75%) for light infection intensities, even for infections that are egg-negative but antigen-positive.

Finally, echinococcosis ICTs have been primarily used in research studies, with minor applications in specific programmes focused on controlling and surveillance. In a field study conducted by Manciulli and colleagues,[66] the performance of a commercially available ICT for the serodiagnosis of abdominal cystic echinococcosis was compared with that of ultrasonography in Peru. The prevalence of abdominal cystic echinococcosis determined using ultrasound, considered the gold standard technique, was 6%. ICT results showed similar sensitivity (76% *vs* 74%) but lower specificity (79% *vs* 96%). The study concluded that there was moderate to very good concordance between both diagnostic tools. However, ICTs for echinococcosis diagnosis are not reliable enough to be used independently[42,66] but can serve as complementary tools to ultrasound diagnosis, helping in clinical decision making.[42,66]

Considering the results obtained so far with commercially available ICTs, it is noteworthy that serology-based results commonly indicate helminth exposure but not necessarily active infection, as helminthiasis-specific antibodies can be detected in patients' samples months to years after the elimination of a disease. On the other hand, the presence of eggs and circulating antigen indicates viable worms and, therefore, active infections. In this context, control programmes and scientific studies should implement appropriate diagnostic tests to map active infections or exposure, or both.

Discussion

The choice of biosensors for neglected helminthiases depends on the goals of public health strategies: control, elimination as a public health problem, or interruption of transmission. In control scenarios, ICTs are favoured for their low cost and suitability for PoC, despite potential shortcomings in specificity and detecting current infections. For elimination and interruption targets, as defined by WHO, electrochemical and optical biosensors show promise due to their high sensitivity and specificity, although they still require additional research. Innovations, such as the use of carbon-based material in place of gold electrodes, enhance the cost-effectiveness and PoC applicability of electrochemical biosensors in control scenarios. These biosensors are expected to substantially improve the diagnosis of helminthiasis in upcoming monitoring and evaluation strategies. However, piezoelectric biosensors, with their low PoC usability, seem less viable for tackling neglected helminthiases in public health strategies.

Effective implementation of biosensors in endemic regions demands sustained access, availability, and technical training, along with sufficient national capacity to sustain these technologies.[139] Additionally, although some progress has been made towards meeting the REASSURED criteria,[50] including efforts to provide real-time connectivity and improve environmental friendliness, full compliance has not yet been achieved.

Despite the massive public health challenge posed by neglected helminthiases, which disproportionately affect the world's poorest communities and exacerbate poverty,[5] funding for the development of biosensors remains inadequate, amounting to less than 1% of the global research fund.[4,20] To overcome these barriers, intensified awareness and enhanced funding are crucial. Such efforts will encourage more research and development, leading to greater availability of biosensors, an urgent need in the current public health landscape.

Our expertise in LFAs and electrochemical sensors may have influenced the analyses in this Review; however, we endeavoured to provide an objective review by also including insights from medical doctors and researchers not involved in rapid diagnostic test development.

Contributors

MC-P researched the data for the Review, wrote the manuscript, and prepared the table, figures, and supplementary tables, with contributions from CP and JG. All authors thoroughly reviewed or edited the manuscript, or both, before submission.

Declaration of interests

We declare no competing interests. GraphenicaLab SL is a company that specialises in the development of electrochemical sensors based on graphene.

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