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Neglected Tropical Diseases in India: Enhancing POC based Diagnosis towards Elimination

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Abstract:*Neglected tropical diseases (NTDs) represent a significant global health challenge, particularly in regions with limited access to healthcare and sanitation facilities. India, with its vast population and diverse landscape, faces a substantial burden of NTDs, including lymphatic filariasis (LF), visceral leishmaniasis (VL), and dengue along with other coinfections. The Government of India has undertaken various initiatives to eliminate these diseases, aligning with global objectives. However, challenges persist, including the need for accurate disease burden estimation, resource allocation, and disease diagnosis.Efforts to eliminate NTDs in India require comprehensive strategies, including mass drug administration and vector control programs. Thus, accurate and accessible diagnostic tools are essential for disease surveillance and treatment monitoring. Point-of-care testing including molecular and serological-based techniques facilitates swift diagnosis and disease surveillance, particularly in resource-limited settings. Thus, by prioritizing investments in innovative diagnostic and therapeutic strategies, India can make significant strides toward improving patient survival and decrease mortality rates.*

Keywords: Neglected Tropical Disease, Leishmaniasis, Filariasis, Elimination Programs, Point of Care, Lateral Flow Assay

INTRODUCTION

Neglected tropical diseases (NTDs) are a group of infectious diseases reported in underdeveloped or developing nations due to poor sanitation, impacting over two billion people, including over 500 million children, and causing 200,000 deaths annually. Despite

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being labelled as "neglected," these diseases result in illness, suffering from fever, rash, sores, swelling of lymph nodes or at the site of the infection, social stigma, impeding education, productivity, and perpetuating cycles of poverty resulting in significant public health challenges. While NTDs were reported in 179 countries and territories in 2021, 16 nations accounted for 80% of the global burden. Globally, an estimated 1.65 billion individuals require treatment for NTD. In 2022, eight countries were certified or validated as having eliminated at least one NTD. The prevalence of NTDs in tropical and subtropical regions, persists due to poor sanitation, contact with vectors and livestock, and limited healthcare services in developing nations. (1)

NTDs comprise various pathogens like viruses, bacteria, parasites, fungi, and toxins, with profound health, social, and economic implications, predominantly affecting impoverished communities. India, the leading world with a population of 1.3 billion, faces a significant NTD burden despite being the seventh-largest economy by GDP (2). The World Health Organization (WHO) recognizes 20 NTDs (**Fig 1**), including 17 major infections, highlighting the substantial impact on India's public health landscape (3).

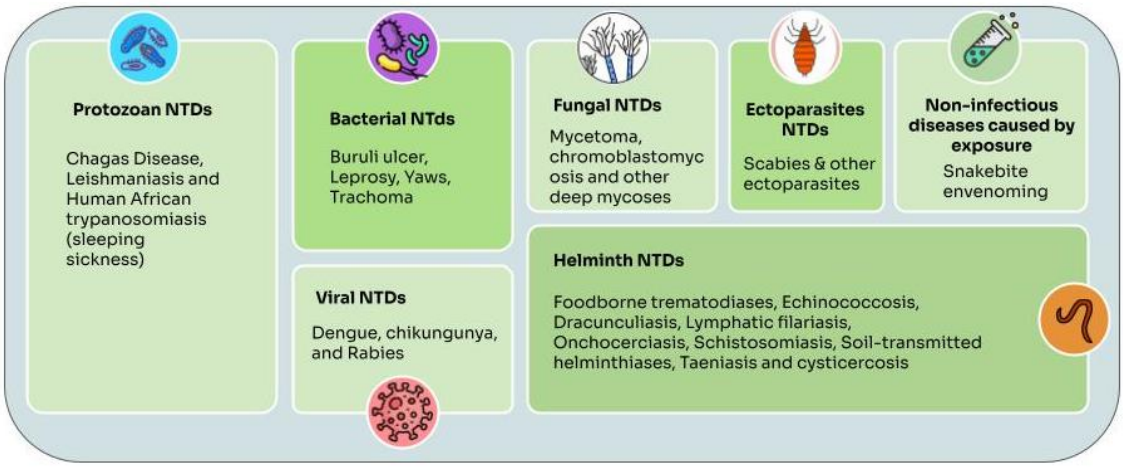

Fig 1: **20 NTDs Identified As per WHO (2,4)**

METHODOLOGY

For this review, publications were obtained from open-access repositories such as Elsevier, PubMed, Scopus, and Google Scholar, employing the search criteria: 'diagnosis', 'elimination program', 'NTD test', 'Point of care testing', and 'India'. We exclusively incorporated original research papers, case studies, and reports from the WHO portal pertaining to neglected tropical diseases in Indian contexts, published between 2010 and January 2024, available in English with unrestricted full-text access.

After initially screening over 200 articles, 39 were evaluated for eligibility. Four articles meeting the inclusion criteria were included in this review. Government guidelines, screening programs, elimination initiatives, major NTD lists, and disease management information, along with implementation strategies, were sourced from the official websites of the National Health Mission (NHM) and the National Centre for Vector Borne Diseases Control (NCVBD).

RESULTS

India's Major NTDs

A significant burden of NTDs is contributed by India and other South Asian countries approximating upto one-quarter of global soil-transmitted helminth infections, over one-third of global rabies deaths, and more than half of the global burdens of Lymphatic Filariasis (LF), Visceral Leishmaniasis (VL), and leprosy. The region also faces challenges from the emergence of three significant arbovirus infections: Dengue, Japanese encephalitis, and Chikungunya. However, disease burden estimates for several other significant NTDs such as strongyloidiasis, toxocariasis, leptospirosis, and amebiasis are currently unavailable. Estimating the total burden of all NTDs in India is difficult due to the absence of a single organization or government agency mandated to do so. This lack of reliable data diminishes the evidence base for policies, thereby affecting their effectiveness. Moreover, many NTDs emerge in resource-limited areas where appropriate diagnostic tools are unaffordable and therefore unavailable. Presently, India carries the greatest absolute burden of at least 11 major NTDs. The table below outlines the causative agents, clinical symptoms, and reported case numbers for each respective NTD. (5)

NTDs are a diverse group of illnesses caused by various pathogens, posing a significant public health concern in India and affecting millions annually. Ascariasis, hookworm disease, trichuriasis, and lymphatic filariasis are prevalent, impacting millions with symptoms like abdominal discomfort, itching, rashes, and limb swelling. Additionally, diseases such as cysticercosis, cystic echinococcosis, visceral leishmaniasis, dengue, rabies, trachoma, and leprosy contribute to the complex NTD landscape in India. Efforts in prevention, diagnosis, and treatment are vital to address these diseases and mitigate their impact on public health (2,5).

The Government of India is committed to eradicating NTDs such as lymphatic filariasis and kala-azar, aligning with global elimination and control objectives. Notably, India has eliminated leprosy in 82% of cities and districts, along with infectious trachoma and chronic yaws. To accelerate NTD elimination efforts, the Indian government has launched several initiatives, including the Accelerated Plan for Elimination of Lymphatic Filariasis (APELF). The Kala-azar Elimination Programme (KEP) and the Filariasis Elimination Programme (FEP)

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are operated under India's National Vector Borne Disease Control Programme (NVBDCP). (6,7) In line with these efforts, focusing on diseases like Lymphatic Filariasis (LF), Leishmaniasis and Dengue becomes crucial.

Lymphatic Filariasis

Lymphatic filariasis (LF), is caused by parasitic worms transmitted through mosquito bites, primarily *Wuchereria bancrofti, Brugia malayi,* and *Brugia timori*. These worms infect the lymphatic system and trigger an immune response, producing microfilariae that circulate in the bloodstream and are transmitted through mosquito bites. While many infections show no symptoms, chronic cases can lead to damage to the lymphatic system and kidneys, affecting over 40 million people worldwide and causing symptoms such as limb lymphoedema. Although diethylcarbamazine (DEC) is an effective treatment, its use is limited in regions where co-infections with diseases like onchocerciasis and loiasis occur, leading to the adoption of alternative strategies such as mass drug administration (MDA) of ivermectin. (8)

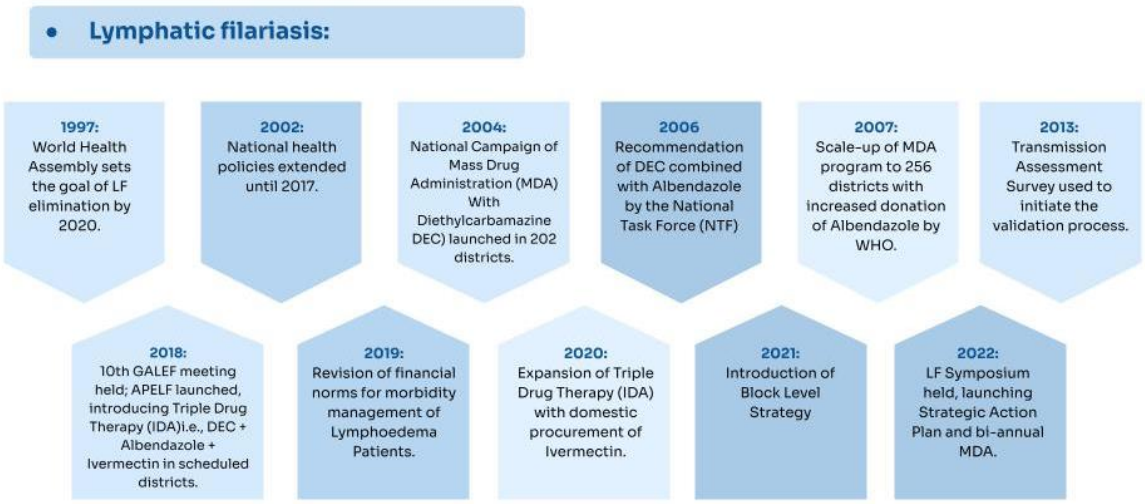

Fig 2: Programs held by the government for the elimination of Lymphatic Filariasis

Leishmaniasis

Visceral leishmaniasis (VL), or kala-azar or black fever, is a severe form of leishmaniasis marked by symptoms such as fever, weight loss, enlarged spleen and liver, and profound anemia. While VL is not confined to a specific endemic area, most new cases are reported in countries such as Brazil, China, Ethiopia, India, Iraq, Kenya, Nepal, Somalia, South Sudan, and Sudan. If left untreated, VL can progress to post-kala-azar dermal leishmaniasis (PKDL), which serves as a reservoir for the parasites for months to years following treatment. Liposomal

amphotericin B (AmBisome®) is the preferred treatment for VL, typically administered through intravenous infusion. However, miltefosine may be used as an alternative in cases where AmBisome® is unavailable or cost-prohibitive. (8)

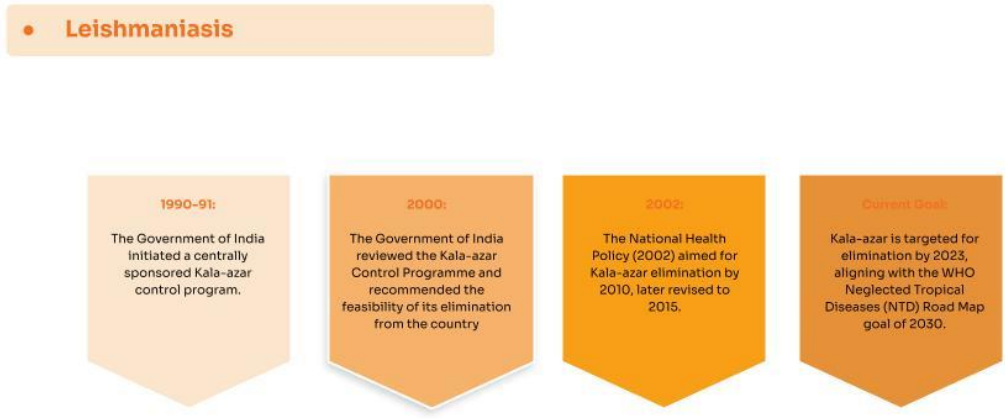

Fig 3: Programs held by the government for the elimination of Leishmaniasis

Dengue

Dengue, like chikungunya, is an acute arboviral illness primarily spread by infected female Aedes mosquitoes, though instances of non-vector transmission have been documented. While sexual and breast milk transmission have been discounted, vertical transmission from viremic mothers to fetus is plausible. The disease progresses through phases, starting with a febrile phase marked by headache and malaise, and advancing to a critical phase characterized by plasma leakage and severe complications like dengue shock syndrome. The global prevalence of dengue imposes substantial socioeconomic and healthcare burdens, with around 400 million infections annually resulting in 3 million disability-adjusted life years (DALYs). Its rapid dissemination is aided by international travel, leading to cases even in temperate regions. Efforts are ongoing to develop vaccines and control transmission, although no specific treatment exists beyond symptom management using medication. (8)

India has committed to eliminating VL, commonly known as kala-azar, and LF, commonly known as elephantiasis, by 2020, through World Health Assembly (WHA) resolutions. Despite

facing previous obstacles, India remains dedicated to controlling and eradicating these diseases, as evidenced by the implementation of various governmental initiatives (6).

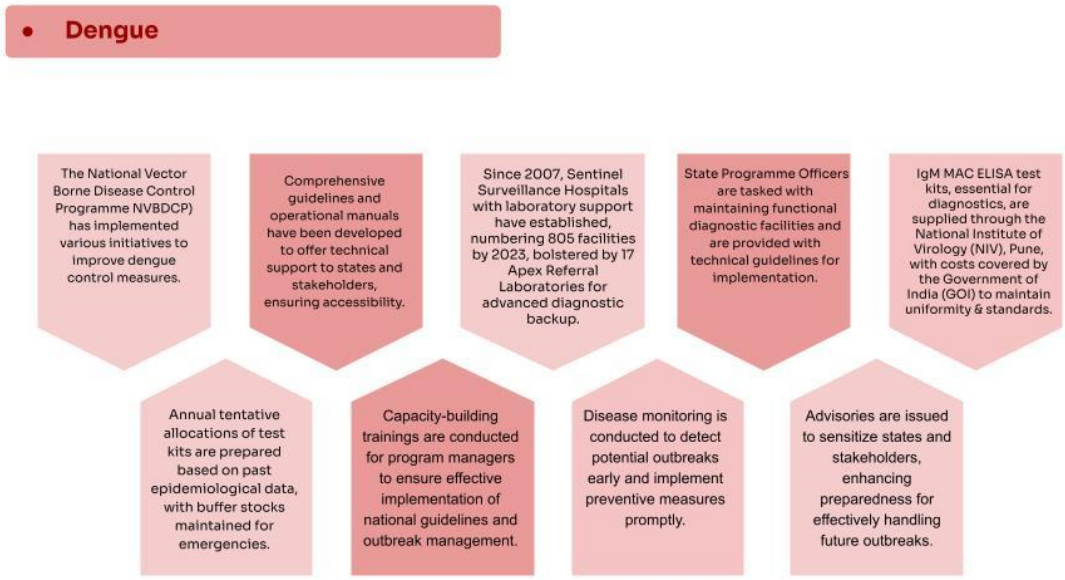

Fig 4: Programs held by the government for the elimination of Dengue

Need to eliminate NTDs:

The eradication of LF and VL in India would not only reduce illness and mortality rates but also align with the attainment of Sustainable Development Goals. This would involve shortening the duration of illness, thereby improving overall health outcomes, and potentially alleviating the economic burden associated with sickness, thus assisting families in escaping poverty.

Ensuring the accessibility of effective preventive measures and treatments, coupled with sustained efforts in disease control and elimination, is crucial for achieving these objectives and enhancing public health outcomes both domestically and globally.

The lack of reliable data undermines the basis of evidence for policies, hindering their effectiveness. The absence of a comprehensive medical registry for NTDs presents significant challenges for healthcare providers and public health authorities. Without an accurate understanding of the burden and prevalence of these diseases, it becomes challenging to

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allocate resources effectively for NTD prevention and control efforts. Additionally, the absence of an accurate registry hampers the development of new diagnostics and treatments, as well as the ability to identify optimal strategies for NTD control and elimination. Therefore, establishing a medical registry is essential to ensure that all stakeholders have access to the most current and accurate information on NTDs. (7)

Since India contributes significantly to the global burden of these diseases, reducing their prevalence in India would have a substantial impact on the global burden. The elimination of LF and VL will not only reduce illness and death but also contribute to achieving the Sustainable Development Goals. The reduction in days lost due to ill health will improve overall well-being, and the subsequent decrease in the financial burden of ill health will help lift families out of poverty. (6)

Fig 5: Operational Issues identified in India for the elimination of NTDs

In India, the KEP and FEP are administered by the National Vector Borne Disease Control Program (NVBDCP). A National Road Map for VL elimination was established in 2014, guided by global, regional, and local evidence. Joint missions conducted by WHO and ICMR have reviewed these programs and identified various operational issues hindering their effective implementation. (6)

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Coinfection of NTDs:

In regions where NTDs prevail, coinfections involving both NTDs and other diseases like HIV, malaria, and tuberculosis are common, exacerbating health challenges. Leishmania/filaria coinfections contribute significantly to the social, medical, and economic burdens in endemic areas. For instance, up to 5–7% of VL patients in India were found to be coinfected with HIV in 2022, with an even higher prevalence (2–7%) in Bihar state. This coinfection poses various challenges to healthcare systems, including resource allocation and service delivery, and significantly increases mortality rates, ranging from 4.6% to 16.6%. Moreover, NTD coinfections disproportionately affect communities with existing health and socioeconomic disparities, potentially leading to lifelong health consequences, particularly when experienced early in life. Understanding the complexities of NTD coinfections and their global health impact is crucial for achieving international health and development objectives. (9,10,11)

NTDs and Their Diagnostic Approach:

The surveillance response for NTDs focuses on gathering minimum essential data rather than collecting all possible data. Research priorities include developing new tools to detect low-transmission patterns and emerging pathogens effectively. (12)

The development of suitable diagnostics begins with defining target product profiles (TPPs), which describe the ideal specifications required for a product, considering patient needs and the characteristics of the relevant health system. (13)

Sr. No.	NTDs	Detection Methods	Diagnostic Test	Sample Types
1)	Leishmaniasis	Parasitological methods	Microscopic examination	Spleen, Bone marrow, Lymph, and Buffy coat from the peripheral blood
		Immunological methods	Montenegro test	Lesion (because of hypersensitivity)
			DAT	Serum/Plasma
			Fluorescent antibody test	Serum/Plasma
			Indirect hemagglutination assay	Serum/Plasma

			ICT	Blood/Saliva
			KAtex (Antigen detection)	Urine
			ELISA Crude soluble antigen, ESM antigen, rKLO8 antigen, rK39 antigen, rK28 antigen rK9 antigen rA2 protein LiHypA	Serum/Plasma/ Saliva
		Molecular Methods	Conventional PCR	Blood/serum/buffy coat cells/buccal swab/urine
			Nested and semi- nested PCR	
			RT-PCR and Multiplex PCR	
			NASBA-PCR	
			LAMP	
			RFLP and AFLP	
		Xenodiagnosis		Infected lesion or tissue
2)	Filariasis	Clinical	Ultrasonography	Scrotal
			Dreyer's clinical staging	Clinical features
			Portable scanning device	Limb
			Tissue tonometer	Skin and Tissue
		Parasitological	Microscopic Examination	Blood
		ELISA	Antigen:	Blood/ Serum/ Plasma
			Og4C3 filariasis antigen ELISA	
			Immunological	
			Antibody:	
			Bm14 ELISA	
			Wb123 ELISA	
			Wb-SXP-1 ELISA	
		Molecular	Multiplex PCR, LAMP	Blood/ Serum / Plasma

		Immuno-chromatographic test (ICT)	Antigen:	Blood/ Serum / Plasma
			BinaxNOW ICT (RDT)	
			Filariasis test strip (FTS) (RDT)	
			Antibody	
			Biplex Wb123/Ov16 (RDT)	
			Wb123 RDT	
3)	Dengue	Virus isolation.		Whole blood, serum, tissues
		Hemagglutination inhibition assay.		Serum, plasma, whole blood
		ELISA	IgM capture ELISA (MAC-ELISA)	Serum, plasma, whole blood
		Real-time RT-PCR.		Tissues, whole blood, serum, plasma

Table 1: Details of diagnostic techniques for Leishmaniasis, Filariasis and Dengue (14,15,16,17,18,19)

Conventional Methods:

Microscopy remains crucial for diagnosing various NTDs like lymphatic filariasis, leishmaniasis, and Dengue relying on skilled professionals and functioning laboratory equipment (20). For the detection of Lymphatic Filariasis, microscopic examination of blood samples to detect microfilariae is the gold standard for diagnosis. Diagnosis of VL typically involves microscopic examination of bone marrow, spleen, or lymph node aspirates to detect the parasite, which necessitates specialized medical skills and often involves invasive procedures. While highly specific, microscopy's sensitivity depends on infection intensity, requiring more sensitive tests as prevalence decreases during treatment efforts. However, the administration of this test requires trained clinicians and the interpretation of the result is subjective, leading to variability among readers. As elimination goals are near, more specific, and high-throughput tests are necessary to accurately identify pathogens. Various other methods for detecting FL such as Ultrasonography, Lymphoscintigraphy (21), leishmaniasis like in-vitro cultivation, inoculation in animals (mice or hamsters) Xenodiagnoses (22) and

Dengue like Virus Isolation, Hemagglutination-Inhibition test (HI), Complement Fixation test (CF), Neutralization Test (NT) are considered (23).

Molecular-based Techniques:

Nucleic acid-based tests detect the presence of the pathogen's genetic material (DNA or RNA) to diagnose specific diseases. While Nucleic Acid Amplification Tests (NAATs) enable specific amplification of the pathogen's genetic material for disease diagnosis, Next-Generation Sequencing (NGS) of the DNA/RNA is commonly used to map the pathogen sequence for diagnosis. Viral RNA detection using NAATs like RT-PCR, and the identification of viral antigens such as the NS1 antigen, which detects secreted proteins in blood samples (24).

Commercially available POC NAATs typically utilize Polymerase Chain Reaction (PCR) in closed automated devices, employing prepackaged single-use integrated cartridges filled with reagents for nucleic acid amplification. Loop-mediated amplification assays show promise for diseases like visceral leishmaniasis, but advocacy and investment are needed for widespread adoption in NTD control programs. (25)

Serology Based Tests:

Immunodiagnostic is utilized for many NTDs through rapid Immuno-Chromatographic Tests (ICTs) and Enzyme-Linked Immunosorbent Assays (ELISAs).

The Direct Agglutination Test (DAT), identifies antibodies against the leishmania parasite (8)

Enzyme-Linked Immunosorbent Assays:

The typical procedure for employing the ELISA technique starts with applying a sample or calibrator containing the antigen (Ag) onto a solid-phase antibody (Ab) to allow binding. After washing, an enzyme-labelled antibody is introduced, forming a "sandwich complex" of solid-phase Ab-Ag-Ab enzyme. Excess, unbound antibody is washed away, and an enzyme substrate is added. The resulting product quantity is directly proportional to the antigen amount in the sample. ELISA encompasses four main variations: (i) Direct ELISA, which uses an antigen-coated plate and a screening antibody; (ii) Indirect ELISA, employing an antigen-coated plate and a screening antigen/antibody; (iii) Sandwich ELISA, which utilizes an antibody-coated plate and a screening antigen; and (iv) Competitive ELISA, which relies on a screening antibody (26). ELISA-based detection is applied to measure levels of anti-filarial IgG4 antibodies for LF detection, offering different levels of sensitivity and throughput. ELISA can also detect Dengue, typically 4-5 days after initial symptom onset. However, caution is necessary due to potential cross-reactivity with the Zika virus in all immunological assays and

the NS1 antigen test. Nevertheless, the current tests may lack uniformity and accessibility across different settings, thereby impeding surveillance efforts (8).

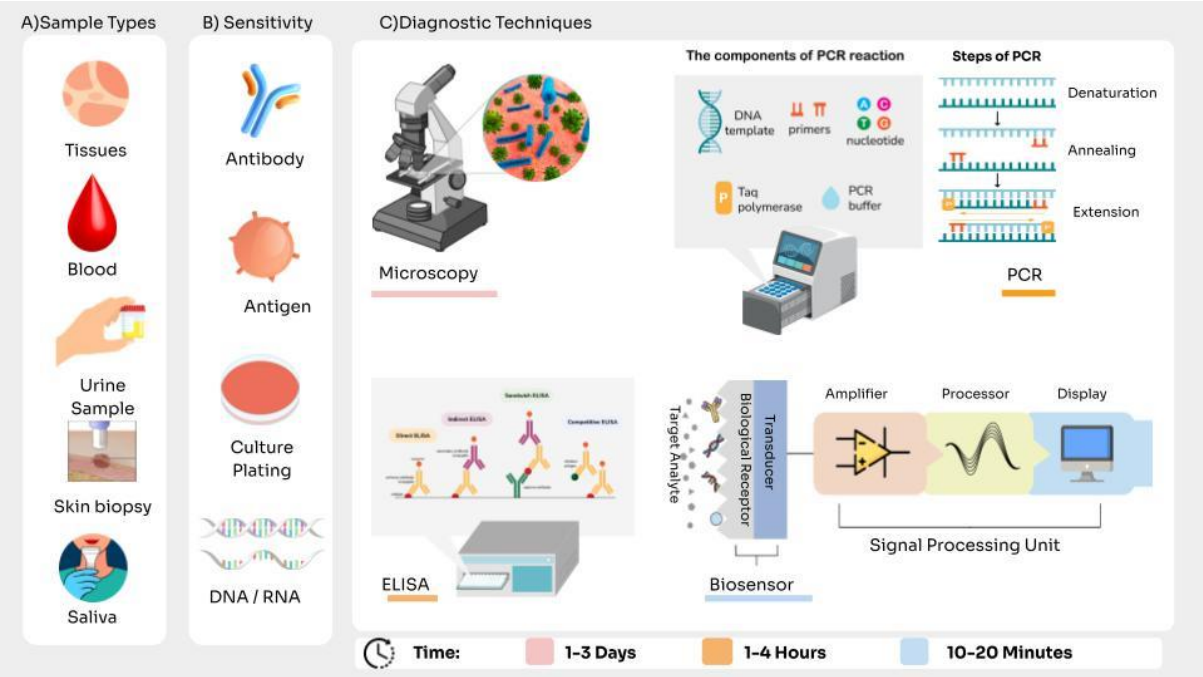

Fig 6: Diagnostics test available for the detection of Leishmaniasis, Filariasis and Dengue

Point of Care: The ultimate need to optimize NTDs Point of Care testing:

As per the International Organization for Standardization (ISO), POC diagnostic testing involves conducting tests near or at the patient's location, potentially impacting patient care. This method requires sensitivity, specificity, and robustness while minimizing steps and addressing limitations of current methods, such as the need for laboratory facilities, laborious, cost, the necessity of trained personnel, complex sample collection, reliance on expensive equipment, field suitability, and intricate protocols (8)

Lateral flow assays have emerged as promising PoC diagnostic tools, notably during the COVID-19 pandemic, where commercial self-testing kits have enabled early diagnosis (27). Similarly, rapid tests based on antigens or antibodies are utilized for various diseases like HIV, Malaria, Syphilis, HBB, HCV, HBsAg, SCD, and others within the diagnostic sector. This strategy can be extended to detect NTDs facilitating swift diagnosis, screening, and disease elimination.

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Lateral Flow Assay (LFA)

The LFA serves as a paper-based platform utilized to detect and measure analytes within complex mixtures, yielding results typically within 5–30 minutes (28). In this assay, the liquid sample containing the analyte travels through various zones of polymeric strips via capillary action (29). These strips comprise overlapping membranes affixed to a backing card for stability. The sample is applied to the strip's adsorbent sample pad, which primes it for interaction with the detection system. As the sample progresses through the strip, it traverses the conjugate release pad containing antibodies specific to the target analyte, bound to colored or fluorescent particles. Subsequently, the sample enters the detection zone, a porous membrane housing specific biological components immobilized in lines. Here, the analyte binds to the capture reagents, resulting in a response on the test line, while a response on the control line verifies proper liquid flow. The read-out, depicted by lines of varying intensities, can be visually analyzed using a dedicated reader. Additional test lines or multiple lines loaded with the same antibody can be employed for simultaneous detection of multiple analytes or semi-quantitative assays, respectively. An absorbent pad located at the strip's end sustains liquid flow by absorbing excess reagents and preventing backflow (28,30,31)

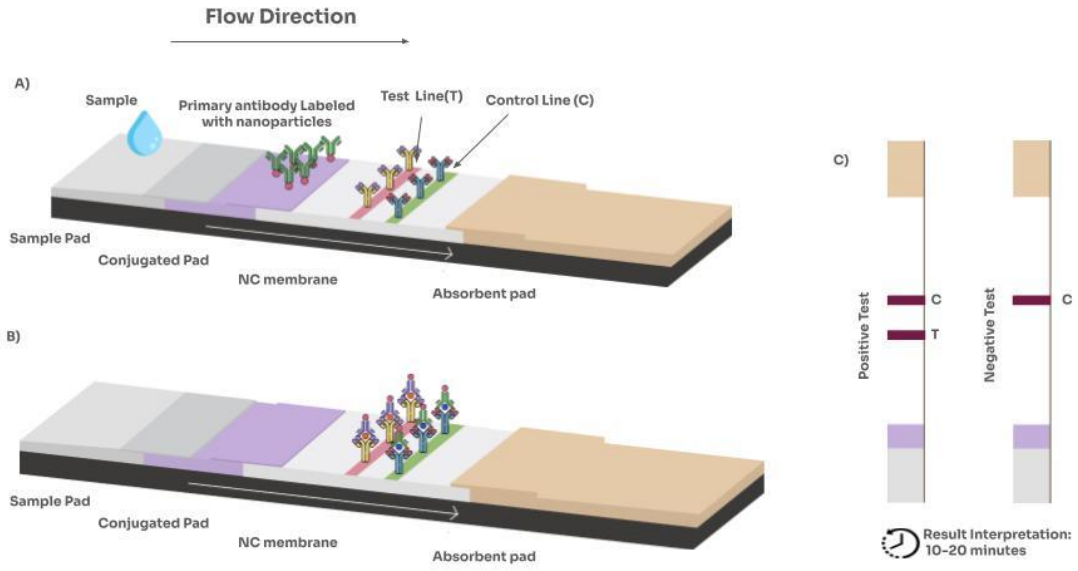

Fig 7: Diagrammatic representation of Lateral Flow Assay

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To support the (NTD)s roadmap for 2021–2030, which delineates global targets and milestones for preventing, controlling, eliminating, or eradicating 20 diseases and disease groups in alignment with the Sustainable Development Goals, POC testing will hold a crucial position (32).

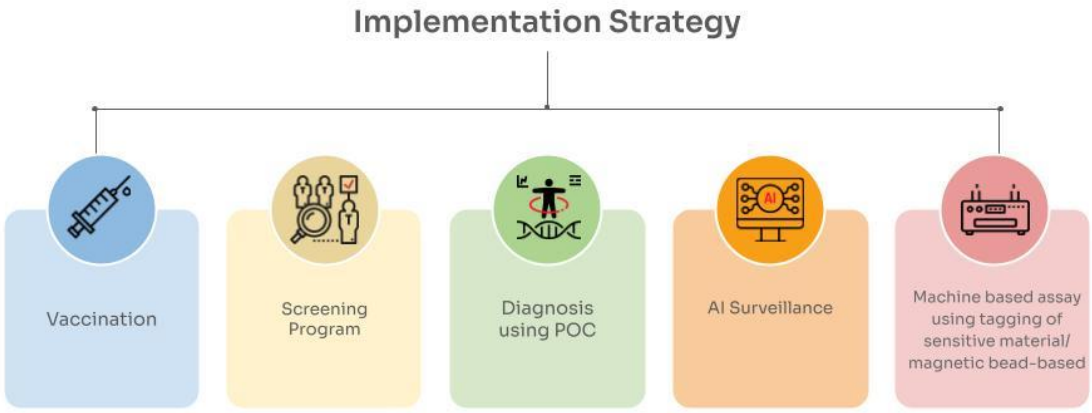

Fig 8: Implementation strategies to eliminate Leishmaniasis, Filariasis and Dengue

DISCUSSION

Despite advancements in point-of-care tests meeting the ASSURED criteria (Affordable, Sensitive, Specific, User-friendly, Rapid, robust, Equipment-free, and Deliverable) (33,34) quality assurance remains a concern, prompting the need for improved immunoassays like magnetic bead-based and microfluidic assays. (20). Cost-efficient implementation of novel technologies is crucial, particularly in resource-limited settings.

Diagnostics play a vital role in generating data for elimination programs, with point-of-care devices and molecular technologies offering opportunities for digitization and data transmission, potentially transforming disease surveillance. (20) However, effective digital data management requires carefully considering the necessary systems, software, and IT infrastructure. (35)

Artificial intelligence (AI) exhibits considerable potential in revolutionizing neglected tropical disease (NTD) diagnosis and augmenting clinical and public health services in resource-constrained settings. Leveraging AI-driven systems, the diagnostic process for NTDs can be optimized, expediting clinical decision-making at the point of care. Furthermore, AI offers the prospect of early outbreak detection, thereby mitigating disease dissemination. Moreover, AI methodologies can be harnessed for NTD mapping, facilitating enhanced public health surveillance and intervention strategies. Recent scientific inquiry has underscored the effectiveness of innovative diagnostic instruments like mobile phone-based microscopes, which have demonstrated notable enhancements in diagnostic accuracy and the breadth of pathogens detectable. These tools are presently undergoing rigorous field assessments and deployment in NTD-endemic regions (36).

For numerous NTDs, mass drug administration (MDA) is either impractical or ineffective for control or elimination purposes. Current chemotherapeutic options, while largely effective, often pose toxicity risks, high rates of drug failure, or rapid post-treatment re-infection, challenging MDA effectiveness. There's an urgent demand for alternative control measures, particularly vaccines, and a critical need for vaccines targeting zoonotic and vector-borne NTDs associated with severe morbidity. (37)

The focus on vaccine development, notably by the Infectious Diseases Research Institute (IDRI), underscores the importance of prophylactic vaccines, for controlling and eradicating lymphatic filariasis (LF) and leishmaniasis (VL). Despite the absence of a commercially licensed vaccine, the vast population at risk highlights significant potential for vaccine development. Recent progress in accessing genomes and proteomes of NTD pathogens, alongside the availability of new adjuvants and financial backing from organizations such as the Bill & Melinda Gates Foundation, has strengthened research and development initiatives for antipoverty vaccines. This support has facilitated the advancement of promising candidates into clinical trials. (38,39).

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