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REVIEW

Control measures for neglected tropical diseases: vaccine updates

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ABSTRACT

Introduction: Infectious diseases like neglected tropical diseases (NTDs) have seen a rapid surge in recent times, threatening public health. These diseases impose a significant global health burden, affecting individuals, particularly in tropical locations characterized by low-income populations. The comprehensive compilation of NTDs includes an array of bacterial, viral, and parasitic infections. The prioritization of 20-NTD action plans in 2020 was undertaken by the WHO to acknowledge their importance. Infections such as leishmaniasis, schistosomiasis, and human African trypanosomiasis exhibit high rates of mortality. This highlights the pressing need for collaborative initiatives aimed at addressing these diseases and minimizing their detrimental impact on susceptible populations.

Areas covered: The etiology, types of NTDs, and management strategies, particularly vaccinations are discussed. The limitations of the available vaccines and the scope of development of novel formulations are also covered.

Expert opinion: The emergence of vaccines for NTDs poses significant challenges, mostly arising from the complex developmental phases of diverse diseases, inadequate resources for research, minimal involvement from the pharmaceutical industry, and the wide spectrum of infections, impeding vaccine development. Advancements in technology have improved vaccine quality, which could lead to the development of personalized vaccines tailored to individual susceptibility to specific NTD pathogens.

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Neglected tropical diseases; vaccination; adjuvant; immune response; recombinant vaccines; leishmaniasis; dengue fever; Chagas disease

1. Introduction

Neglected tropical diseases (NTDs) are a class of bacterial, parasitic, viral, and fungal infections that are common in many developing tropical and subtropical regions, particularly among the low-income population. In the WHO[1] 2020 agenda, NTDs[2] were given priority, which includes, Chagas disease, dengue fever, echinococcosis, human African trypanosomiasis (sleeping sickness), leprosy, rabies, Buruli ulcer, cysticercosis/taeniasis, dracunculiasis (guinea pig disease), lymphatic filariasis (onchocerciasis river blindness), alimentary trematodiasis, leishmaniasis, and others [1]. These diseases are endemic in low-resource areas of Africa, Asia, and South America and affect millions of people worldwide. In addition to having an adverse effect on health, NTDs also add to the enormous social and economic cost brought on by stigmatization, physical impairment, deformities, blindness, racism, loss of social value, poverty, growth retardation, and cognitive retardation. Many of these interconnected consequences make it harder for those affected, to live fulfilling lives and have a detrimental effect on families, communities, and society as a whole, which serves to perpetuate poverty [1].

The term 'neglected' is used, because those affected are predominantly from low-economic strata, and over the years there have been very minimal attempts to control or manage the transmission of the diseases due to a lack of prioritization. According to the WHO, it is estimated that about one-sixth of the global population experience at least one NTD in their lifetime [2]. NTD treatments are divided into two categories by the WHO, (i) innovative and intensified disease management and, (ii) preventative chemotherapy and transmission [2].

The most common NTD is hookworm infection, whereas leishmaniasis, schistosomiasis, and human African trypanosomiasis, all lead to a great number of fatalities [3]. These diseases are endemic in low-resource areas of Africa, Asia, and South America and affect millions of people worldwide. The anti-retroviral medicines, anti-malaria drugs, and insecticide-treated nets are being provided to millions of people as part of global health projects [4].

NTDs affect over one billion individuals, accounting for one-eighth of the global population, which interferes with physical and cognitive growth, leading to disease and death in adults and children. Almost 149 countries and territories in

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Article highlights

- NTDs occur mainly in rural areas, conflict zones, and hard-to-reach regions.
- Affects poor communities and is prevalent in developing countries.
- NTDs include Chagas disease, dengue fever, echinococcosis, human African trypanosomiasis (sleeping sickness), leprosy, rabies, Buruli ulcer, cysticercosis/taeniasis, dracunculiasis (guinea pig disease), lymphatic filariasis, alimentary trematodiasis, leishmaniasis, and others.
- Vaccination is crucial for NTD control and management.
- The objective is to advance a generation of vaccinations that possess enhanced safety, stability, and cost-effectiveness, with a specific focus on populations residing in low-income nations.
- Developing innovative and economically viable treatments for NTDs

the world are threatened by at least one NTD. Using safe and effective medications in large quantities in addition to other interventions including, vaccinations, some NTDs can be reduced or even completely eradicated. Although aware of their significance in the field of public health on a worldwide scale, vaccine development lags more than it should because of difficulties with the method and the fact that the majority of infections are reported in low-income populations [5]. Scarce funding has been cited as an important challenge in vaccine development for NTD. Another serious concern is that the live attenuated vaccines of the parasites can lead to the manifestation of the infection in immunocompromised individuals [6]. The complex morphological characteristics of the disease-causing parasites also present a critical obstacle to vaccine development. Some existing vaccines like Pasteur vaccines against NTDs reportedly exhibit risks attributed to using live viruses in the formulation. It could also lead to adverse effects due to the occurrence of myelin in the nervous system which act as a reservoir of viruses. Several new vaccines require regular doses to stimulate antibody production. The cost of vaccines is also significantly high resulting in a lack of vaccine availability in low-income countries [7].

The first generation of NTD vaccines was developed in the twentieth century and consisted of whole organisms that were either weakened (usually by radiation) or destroyed by heat or formalin [5,8]. Additionally, both killed and live egg-derived whole-cell vaccines against chlamydial infections have been developed, but sometimes these vaccinations can have adverse consequences [5]. Moreover, controlling NTDs in the lack of vaccinations remains a difficult task. Herein, we discuss the current scientific and technical advancements in the development, formulation, production, and efficacy of several vaccines against NTDs.

2. Neglected tropical diseases

The epidemiology of NTDs is complicated and frequently linked to environmental factors [9]. Different pathogens of parasitic, viral, helminth, protozoan, and bacterial origin follow different transmission routes (Figure 1). Many are vector-borne, have an animal reservoir, and have a complicated life cycle. Table 1 depicts several NTDs, along with their pathogenic agents, demographic information, transmission, mechanism, susceptibility, and severity.

2.1. Awareness and influence of NTDs

NTDs influence food, work, income, health, communities, and economies [52]. An unprecedented number of pharmaceutical companies, endemic countries, and national, international, and nonprofit organizations are initiating the most comprehensive and coordinated NTD effort through innovative partnerships [53]. There is an immediate necessity to develop proper monitoring technologies and strategic solutions to change the priority from management to eradication [54]. Further research will improve strategies, develop new methods, and advance scientific understanding of each disease. The enhancement of proactive monitoring of disease transmission hotspots and the molecular characterization of genetic variants and population dynamics contribute to the improvement of early diagnosis, prompt treatment, and the effectiveness of medications [54]. Furthermore, an optimal testing procedure should be quick, point-of-care, require minimal technical competence, and adhere to standards of good clinical and laboratory practice. Moreover, rapid diagnostic tests are now available for all of the high-prevalence diseases, such as tuberculosis, HIV[3] infection, and malaria. Thereby revolutionizing how these diseases are managed in the process of case management [55].

In addition, research and innovation are important for driving progress and mitigating risks such as antimicrobial resistance, environmental changes, etc. A global environment and effective health systems are required to achieve and sustain the targets for NTDs. However, reinforcement of the healthcare system is a long-term goal, and increasing potential in specific technical areas will be beneficial. Furthermore, the NTDs program will pool the efforts of several countries to combat a group of diseases and thus, save the lives of billions of people worldwide.

3. Approaches to control NTDs

The two prominent sectors involved in taking responsibility for the prevention of diseases are NTD control and WASH.[4] NTD control contains multi-laterally organized stakeholders at various levels of government. These include non-government organizations, donors, and pharmaceutical companies that provide natural therapies for NTDs to achieve global elimination and manage the targets. They are in charge of distributing drugs to high-risk groups regularly to prevent morbidity. The WASH sector is a diverse community of stakeholders, including national governments, international and local NGOs,[5] and multilaterals, who work directly to increase access to water, sanitation, and hygiene education in global, national, and sub-national regions. The stated goals are varied, but they include achieving the human right to water and sanitation as well as improving health, education, gender equality, and economics. Governments and bilateral donors provide the majority of the funding [56].

In the case of, trachoma, it is transmitted via an infected individual by immediate contact. Azithromycin has long been the preferred treatment for due to its favorable safety profile in young individuals [57]. Preventive measures include promoting face washing, using good-quality water, and

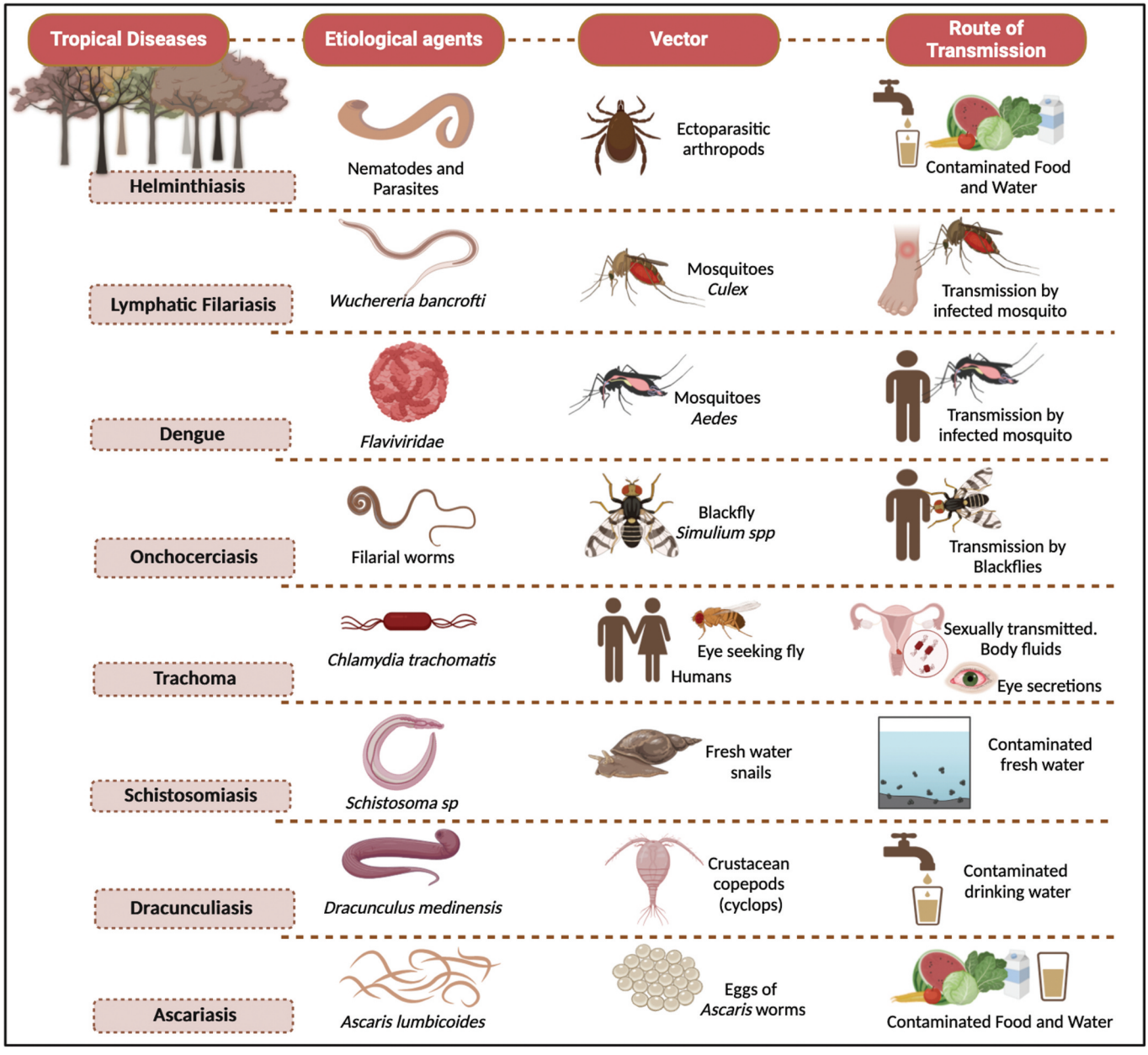

Figure 1. Illustration of neglected tropical diseases, etiological agents, vector, and their route of transmission (Figure created using BioRender.com).

adequate sanitation [56]. A novel generation of anthelminthic therapies may emerge quite soon as a result of recent advancements in molecular and medical helminthology which aids in eradicating the diseases caused by helminths [44]. Schistosomiasis can be prevented by good personal hygiene, chemotherapeutic usage, and preventing contact with surface water [56]. Moreover, for dracunculiasis protecting primary water sources from contamination and using filtration methods would be a preventive action. Poor construction of washrooms and increased standing water increase the risk of chronic diseases such as lymphatic filariasis. Therefore, adequate water volume and clean water management can reduce the mosquito population [56]. Furthermore, dengue virus and onchocerciasis can be prevented by controlling the breeding action of mosquitoes, using insecticidal sprays, etc.

4. Advancements and development in vaccines against NTDs

The advancements and development in techniques have paved the way for the development of vaccines for several infectious diseases that result in a high global burden. Vaccination is an essential approach for the control and management of NTDs, however, the development of efficient vaccines for NTDs is a challenging task. Currently, the focus is on the production of efficient, stable, safer, and cost-effective vaccines that could be accessed by all groups of the population including people from low-income countries (Table 2) [81].

Several strategies have been used in developing vaccines against infectious diseases, as well as for cancer and autoimmune disorders. Some of the emerging strategies include

Table 1. Overview of neglected tropical diseases.

Neglected Tropical Diseases	Demographics	Class of infection	Pathogenic Organisms	Transmission	Mechanism of infection	Susceptible population groups	Severity	Ref
Buruli ulcer	Found in Africa, America, Asia, and Western Pacific countries. Buruli ulcer has also been identified in Australia	Bacterial infection	Agent-environmental *Mycobacterium ulcerans*	The bacteria's mode of transmission remains unclear but it can be transmitted through aquatic insects, arthropods, water bugs, and mosquitoes.	Mycolactone, a unique toxin developed by the organism, leads to tissue damage and thereby inhibits immune responses.	Most Susceptible: In people aged 15–49 years, females were more likely than males	In addition to having a low death rate, the condition has a significant socioeconomic impact on the communities it affects and is a public health concern in terms of functional limitations, treatment, and morbidity	[10,11]
Chagas disease	Prevalent in Mexico, Central, and South America	Parasitic infection	Parasite *Trypanosoma cruzi*	Disseminated through contact with contaminated feces/urine of the Reduviid bug.	• Trypomastigotes-infected triatomines (bugs) ingest blood and expel it close to the bite wound. From the wound, trypomastigotes enter the host. • Near the site of the injection, trypomastigotes infect nearby cells and transform into intracellular amastigotes. • Trypomastigotes are produced when amastigotes multiply and differentiate, and they are subsequently discharged into the bloodstream. • As a result, different cells and tissues become infected. It can also be transmitted through transfusions, transplantation, and other means.	Most Susceptible: Adults between 25–44 years	At birth, newborns infected with Trypanosoma cruzi may exhibit significant morbidity and have a greater chance of mortality. Infants who are not treated may eventually acquire chronic Chagas disease.	[12,13]
Dengue and chikungunya	Prevalent in Asia, Africa, Europe, America, Tropical, Subtropical, Urban, and Semi-urban areas	Viral infection	• Mosquito-borne viral disease (*Aedes aegypti* or *Aedes albopictus* mosquitoes) • RNA virus • Caused by the alphavirus (genus-*Togaviridae*)	The primary vectors of transmission for the viral infections of dengue and chikungunya are Aedes mosquitoes, most especially *Aedes aegypti* and *Aedes albopictus*.	Mosquitoes infected with dengue or chikungunya virus transmit the virus to the host.	Most Susceptible: Infants and adolescents	Dengue and chikungunya viruses have fatality coefficients of 0.08% and 0.35%, respectively.	[14,15]
Dracunculiasis	Prevalent in Asia Africa and Ethiopia	Parasitic infection	• Crippling parasitic disease • Guinea worm	It can be spread through parasites	The parasite is spread primarily through the consumption of stagnant water contaminated with water fleas (parasite-infected).	Most Susceptible: young adults aged 15–45 years	The case fatality rate of dracunculiasis is 0.1% or less, according to research conducted in India using medical records.	[16,17]
Echinococcosis	South America, Asia, Central America, Europe	Parasitic infection	Parasitic disease caused by tapeworms (genus-*Echinococcus*)	The parasitic infection known as echinococcosis, or hydatid disease, is transmitted by tapeworms belonging to the Echinococcus genus, mainly *Echinococcus granulosus* and *Echinococcus multilocularis*.	Humans can become infected via contact with animal hosts or consuming contaminated food, water, or soil that contains parasite eggs.	Most Susceptible: Individuals < 18 or > 60 years of age	Patients without therapy had a greater mortality rate. However, there are other factors, primarily age, that might have affected this outcome.	[18]

(*Continued*)

Table 1. (Continued).

Neglected Tropical Diseases	Demographics	Class of infection	Pathogenic Organisms	Transmission	Mechanism of infection	Susceptible population groups	Severity	Ref
Fascioliasis	Prevalent in South America, Asia, Africa, Europe	Parasitic infection	Parasitic flatworms. Foodborne trematode. Zoonotic disease	Fascioliasis is transmitted by liver fluke *Fasciola species* and also by consuming raw or undercooked aquatic plants that are infected with metacercariae	The life cycle of fascioliasis involves a carrier (plants), an intermediate (worm development), and a final host (adult worm), which affect the host tissue and organs	Most Susceptible: Adult males more likely (68.8%) than females (57.1%)	The effects on people have been particularly severe, as human fascioliasis is frequently ignored and misdiagnosed, resulting in delayed treatment, particularly in situations of ectopic parasitism.	[19]
Foodborne trematodiases	Predominantly in Asia and America	Parasitic infection	lung flukes, liver fluke, intestinal flukes, Echinostomes	Humans become infected by eating raw or uncooked food	• A molluscan (first) and freshwater fish, crustaceans, aquatic vegetables, or freshwater or brackish water gastropods and bivalves as a (second) intermediate host are involved in their life cycle. • Humans become infected by eating raw or uncooked food. • Foodborne trematodes can cause serious complications such as brain damage, spinal cord damage, skin damage, and liver cirrhosis	Most Susceptible: Pregnant women, children under the age of 5, and adults.	Foodborne trematodes can cause serious complications such as brain damage, spinal cord damage, skin damage, and liver cirrhosis	[20,21]
Hantaan viral infections	Prevalent in East Asia, specifically in areas of China, Korea, Russia, and certain areas of Southeast Asia.	Viral infection	Hantaan virus along with Seoul virus and Dobrava-Belgrade virus, is classified in the Hantavirus genus of the Bunyaviridae family.	Infrequent instances occur when bites from infected rodents or ingestion of contaminated food or water results in infection.	• Humans can contract the virus by inhaling aerosolized virus particles released from rodent urine, droppings, or saliva. • Infrequent instances occur when bites from infected rodents or ingestion of contaminated food or water results in infection.	All age groups can be affected, but severe cases are more common in young, older adults and those with weakened immune systems.	Severe cases are more common in young, older adults and those with weakened immune systems.	[22]
Human African trypanosomiasis	Africa and Uganda	Parasitic infection	• Parasitic disease • Vectorborne disease • Transmitted by infected tsetse flies • Parasites of (genus-*Trypanosoma*)	Transmitted by infected tsetse flies	• The disease is largely spread by the bite of an infected tsetse fly. • Trypanosome growth in subcutaneous tissues, blood, and lymph is characteristic of the first stage, also referred to as the haemo-lymphatic stage. • The second stage is the neurological stage, which includes symptoms like headaches, swollen lymph nodes, fever, and itching.	Most susceptible: Young adults, children, mothers.	Human African trypanosomiasis also referred to as African sleeping sickness, has an almost 100% fatality rate if left untreated.	[23–25]

(*Continued*)

Table 1. (Continued).

Neglected Tropical Diseases	Demographics	Class of infection	Pathogenic Organisms	Transmission	Mechanism of infection	Susceptible population groups	Severity	Ref
Japanese encephalitis	Japanese encephalitis primarily occurs in rural and agricultural areas of Asia and the western Pacific. The disease is prevalent in many countries, encompassing regions of China, Southeast Asia, the Indian subcontinent, and the Pacific Islands.	Viral infection	Japanese encephalitis virus (JEV) is a flavivirus that falls under the same genus as the yellow fever virus and dengue virus.	The viral illness known as Japanese encephalitis (JE) is mostly found in South East Asia and is frequently linked to transmission through pigs, and the mosquito *Culex tritaeniorhynchus*.	• The primary mode of transmission is by the bite of infected mosquitoes, particularly *Culex tritaeniorhynchus*. • The breeding grounds of these mosquitoes include rice fields and other agricultural areas characterized by stagnant water	Individuals who have not received the Japanese encephalitis vaccine are at risk of contracting the disease, particularly during the transmission season, when traveling to endemic regions.	The severity of Japanese encephalitis (JE) determines the death rate of individuals with severe symptoms may have a fatality rate of up to 30%.	[26]
Leishmaniasis	Prevalent in regions of Africa, America, the Eastern Mediterranean region, Asia, and Europe	Parasitic infection	• It is caused by protozoan parasites • Female phlebotomine sandflies	Diversity and complexity are hallmarks of vector-borne parasitic illness. It is transmitted by over 20 Leishmania species and disseminated to people by more than 30 kinds of phlebotomine sandflies.	• When sandflies bite or take a blood meal from the human body, these protozoa enter the body. • If the sandfly is infected, the infective form (metacyclic promastigote) enters the human body and enters the bloodstream; in the blood, a macrophage engulfs the infective form (promastigote is resistant to macrophage destruction). • In these cells, prostigotes change into the parasite's tissue stage (amastigotes), where they spread the infection to other mononuclear phagocytic cells via simple division.	Most Susceptible: People aged 10–19 years, adults.	In more than 95% of cases, kala-azar, another name for leishmaniasis, is lethal if left untreated.	[27]
Leprosy	Prevalent regions of Brazil, Asia, Pacific and United states	Bacterial infection	Caused by a bacillus, *Mycobacterium leprae*	Droplets of moisture from an infected individual with leprosy can spread the disease through the air.	• Leprosy is primarily transmitted through frequent contact with an untreated person or droplets (from the nose and mouth). • If untreated, leprosy can permanently damage the eyes, skin, nerves, and limbs	Susceptible: Children < 15 years and adults	The average annual mortality rate for leprosy was 0.43 deaths/100,000 population (95% CI 0.40–0.46), which indicates that the disease is rarely lethal.	[28,29]
Lymphatic filariasis	Prevalent in Pacific islands, Africa, and Asia	Parasitic infection	• Parasite worm • nematodes (roundworms) of the family Filariodidea • Filarial worms (*Wuchereria bancrofti*, *Brugia malayi*, *Brugia timori*) • Transmitted by different types of mosquitoes (Culex and *Aedes* mosquitoes)	Transmitted by different types of mosquitoes (Culex and *Aedes* mosquitoes)	• When a mosquito bites an infected person, the mosquito becomes infected with the same disease (Microfilariae) • Microfilariae evolve into infectious larvae inside the insect and following a mosquito bit to a person, the parasite larvae enter the body through the skin, move to lymphatic veins, and mature into adult worms. • The lymphatic system of the host is hampered by these worms.	Most Susceptible: Adults and adolescents	Lymphatic filariasis is not generally deadly, but it can significantly lower the quality of life.	[30,31]

(*Continued*)

Table 1. (Continued).

Neglected Tropical Diseases	Demographics	Class of infection	Pathogenic Organisms	Transmission	Mechanism of infection	Susceptible population groups	Severity	Ref
Murray Valley encephalitis	The primary geographic distribution of Murray Valley encephalitis virus is in Australia and Papua New Guinea. The virus is has been detected in northern and western Australia, where mosquito vectors that transmit the virus are common.	Viral infection	The Murray Valley encephalitis virus belongs to the Flavivirus genus, which includes other viruses such as Zika virus, West Nile virus, and Dengue virus.	Mosquitoes acquire the virus when they consume the blood of birds that are infected, and subsequently transfer the virus to humans through their bites.	• The disease is predominantly transmitted by mosquito vectors, specifically Culex mosquitoes. • The virus is sustained in a cyclic relationship between avian species and mosquitoes, with people and horses serving as secondary hosts. • Mosquitoes acquire the virus when they consume the blood of birds that are infected, and subsequently transfer the virus to humans through their bites.	Most susceptible children and > 70 years of age.	Mortality rates vary during epidemics, from 18% to 80%, and 30% to 50% of survivors experience long-term neurological damage.	[32]
Mycetoma	Predominantly in Africa, Asia, Europe, Latin America	Bacterial and fungal infections	It is brought on by different species of bacteria or fungi	A causative organism is more likely to be transmitted through trauma or a penetrating injury to the body.	• A causative organism is more likely to be transmitted through trauma or a penetrating injury to the body. • Mycetoma is associated with people who walk barefoot and work with their hands.	Most Susceptible: males aged 15–30 years	Patients who had eumycetomas had a 40% post-operative recurrence rate and a 1% mortality rate.	[33,34]
Onchocerciasis	Found in the sub-Saharan region of Africa, America and Brazil	Parasitic infection	• Parasitic worm *Onchocerca volvulus*. • Filarial worm • Transmitted by repeated bites of infected blackflies	Transmitted by repeated bites of infected blackflies	• When a blackfly bites human skin, the larva from the blackfly's gut is transmitted into the host, where it matures and transforms into an adult (male and female) worm within a month. • Mating between them occurs, resulting in the production of microfilariae, which affects human tissue and organs.	Most Susceptible: Adults in the 35–44 age range	Blindness and serious defects in vision can result from infection with the parasitic filarial worm *Onchocerca volvulus*.	[35,36]
Rabies	Occurs in the region of Asia and Africa	Viral infection	Zoonotic, viral disease caused by dogs. Lyssa viruses	The fatal virus known as rabies is transmitted to humans through the saliva of animals that are infected	• People typically acquire the rabies virus through the bite of an animal carrying the virus, such as rabid dogs that frequently transmit the disease to people.	Most Susceptible: Children aged 5–15 years	Rabies has a near-100% case-fatality rate, making it one of the most perilous infectious illnesses.	[37,38]
Scabies and other Ectoparasitoses	Prevalent in low/middle-income countries	Parasitic infection	Caused by *Sarcoptes scabiei var hominis*	Scabies can be transmitted directly from skin to skin or indirectly by contact with infected substances (fomites).	The infection is transmitted via physical, or skin contact and affects the host	Most Susceptible: Children aged 5–9 years and > 70 years of age	It can result in higher mortality and fatality rate	[39,40]

(*Continued*)

Table 1. (Continued).

Neglected Tropical Diseases	Demographics	Class of infection	Pathogenic Organisms	Transmission	Mechanism of infection	Susceptible population groups	Severity	Ref
Schistosomiasis	China, Africa, Brazil, Indonesia, Philippines	Parasitic infection	Blood flukes (genus-*Schistosoma)*	Schistosomiasis, commonly known as bilharzia, spreads by direct contact with polluted waterbodies.	• Parasites found in freshwater snails. • The infectious form of the parasite emerges from the snail and enters the water bodies. • Skin contact with contaminated freshwater can result in infection.	Most Susceptible: School-aged children and adults.	Katayama fever, also known as acute schistosomiasis, may increase the death rate by as much as 25%.	[41,42]
Snakebite envenoming	Prevalent in Africa, Asia, Latin America	Snakebite venom infection	Causative agent: snakes	Snakes	• The venomous snake bites prevent breathing and result in paralysis. • It can also lead to hemorrhage, kidney failure, and tissue and organ damage.	Most Susceptible: Ages between 10–40 years	In India, the overall mortality rate was 4.4 per 100,000, with higher rates among women and in rural regions.	[43]
Soil-transmitted helminthiasis	Found in Brazil, Africa, America, and Asia	Parasitic infection	It is brought on by various parasitic worm species. • *Ascaris lumbricoides* (roundworm), • *Trichuris trichiura* (whipworm) • *Necator americanus Ancylostoma duodenale* (hookworms)	Infection Spreads through eggs found in the feces of infected people.	• Infection Spreads through eggs found in the feces of infected people. • Adult worms lay thousands of eggs per day in human intestines, and these eggs contaminate the soil in areas where sanitation is inadequate.	Most Susceptible: Toddlers aged 36–47 months and pregnant women	The average annual crude mortality rate was 0.38 deaths per million people.	[44,45]
Tick-borne arboviruses	North America, Russia, Europe, Asia	Viral infection	Tick-borne arboviruses, including Powassan virus, Tick-Borne Encephalitis virus, Crimean-Congo Hemorrhagic Fever virus, and Heartland virus	Tick-borne arboviruses are spread when infected ticks bite and feed on a host.	• Tick-borne arboviruses are spread when infected ticks bite and feed on a host. • Ticks become infected with the virus when they consume blood from vertebrate hosts that are already infected, such as small mammals, birds, or larger mammals like livestock. • Humans are mostly accidental hosts but can get an infection if they are bitten by a tick that is carrying the disease.	All age groups, but severe cases are more common in > 60-year-olds and those with weakened immune systems	In India, the overall mortality rate of Tick-borne arboviruses was 80%	[46]
Trachoma	America, Asia, sub-Saharan Africa, Australia	Bacterial infection	Caused by bacterium *Chlamydia trachomatis*	Trachoma is more prone to spread in regions with poor cleanliness, close contact with contaminated objects, overcrowding, and restricted access to medical care.	• Chlamydia trachomatis infection of the ocular surface begins in childhood. As a result, conjunctival scarring and recurring chronic inflammatory episodes occur. • Entropion and trichiasis are caused by scar tissue contracture.	Most Susceptible: Prevalent in preschool-aged children and adults.	According to the WHO, Trachoma affects an estimated 150 million individuals globally, with 6 million of them are prone to blindness	[47,48]

(*Continued*)

Table 1. (Continued).

Neglected Tropical Diseases	Demographics	Class of infection	Pathogenic Organisms	Transmission	Mechanism of infection	Susceptible population groups	Severity	Ref
Yaws	Prevalent in Africa, Pacific, Asia, and Latin America	Bacterial infection	Causative agents are *Treponema pallidum*	Spread through physical contact.	• Spread through physical contact. A small percentage of patients experience an acute phase followed by a chronic, relapsing course. • The disease has distinct stages, including early, latent, and late yaws, which manifest as nodules, scarring, and destructive bone	Most Susceptible: Children < 15 years of age	The overall average number of deaths was 35.38 each year.	[49,50]
Yellow Fever	It is prevalent in endemic tropical areas of Africa and Central and South America.	Viral infection	Yellow fever is caused by an arbovirus (a virus transmitted by vectors such as mosquitoes, ticks, or other arthropods)	Transmitted through bite of infected mosquitoes	The primary route of transmission is via the biting of infected mosquitoes, specifically Aedes aegypti in urban areas and Haemagogus or Sabethes insects in the jungle or forest settings.	In all age groups, however, severe instances are more prevalent among elderly people and individuals with compromised immune systems.	Approximately 15% of symptomatic people acquire severe illness and the average mortality rate is 30 to 50%	[51]

nanoparticle-based vaccines [82–84], internalizing peptides [85,86], dendrimers [87], *ex vivo* monocyte-derived dendritic cell-based vaccines [88,89], hapten-linker conjugated vaccines [90,91], and glycol-conjugate tri-component vaccines [92]. There is a plethora of vaccine design approaches, each of which shows promise. Several vaccines against NTDs have been formulated and tested with varying degrees of immune stimulation and/or protection. These vaccine formulations will undoubtedly assist in protection against NTDs (Tables 2 and 3).

4.1. Vaccine for African trypanosomiasis

African trypanosomiasis is highly contagious and caused by the unicellular parasites of the genus Trypanosoma, is contracted through the sting of a diseased tsetse fly [102]. The progression of the infection is influenced by the characteristics of the host and parasite type and strain. Even though the situation of human African trypanosomiasis has progressed, still there is an urgent need for novel treatments and vaccinations to treat African trypanosomiasis [103]. The formulation of vaccines for African trypanosomiasis in mice models is shown in (Figure 2).

4.2. Amoebiasis vaccine development

The Gal-lectin antigen is the most extensively studied in vaccine formulation against amoebiasis. It is an appealing vaccine candidate due to its antigenicity and relevance in disease origination and development of a disease, where it plays critical roles in parasitic adhesion to MUC2 mucin and target cells, ultimately resulting in contact-dependent apoptosis and phagocytosis [104]. Gal-lectin has also been demonstrated to stimulate the progression of dendritic cells and the synthesis of the T helper (Th)-1 pro-inflammatory cytokines IL-12 and interferon (IFN)-gamma both *in vitro* and *in vivo*. Gal-lectin in its native or recombinant forms has been used in vaccine studies in humans with positive results. Recombinant proteins, in contrast, can be manufactured in high quantities. A recombinant version of the cysteine-rich region of the Gal-lectin 170 kDa subunit, known as LC3, was shown to be effective against *E. histolytica*. As such, the development of vaccines against *E. histolytica* will continue to gain insight from ongoing research into the pathogenesis of the disease, with the ultimate goal of eradicating amoebiasis [105].

4.3. Vaccines targeting Buruli Ulcer

The skin condition known as Buruli Ulcer is brought on by the *Mycobacterium (M) ulcerans* bacterium and can afflict patients with conspicuous scars and permanent disabilities [11]. A vaccine made from live, attenuated microbes is a well-proven approach for inducing broad immune defenses against several antigens. DNA[6] vaccination is a potential immunization approach because *M. ulcerans* vaccine target genes may be efficiently cloned into DNA vectors and vaccines can be manufactured on a massive scale. This is an affordable vaccination technique and does not require any refrigeration [58].

4.4. Vaccines to combat Chagas disease

Chagas disease, or American trypanosomiasis, is endemic to 21 countries in Latin America and is primarily transmitted by vectors and brought on by the protozoan parasite *Trypanosoma cruzi* [106]. The live attenuated virus vaccines can elicit cellular and humoral responses. In addition, the trans-sialidase family's ASP-1, ASP-2, and TSA-1 genes stimulate low levels of antibodies and cytotoxic T cells [107]; and can be boosted with co-administration of genes for interleukin (IL-12)[7] , granulocyte-macrophage colony-stimulating factor (GM-CSF[8]). These results demonstrate the viability of preventive and therapeutic DNA vaccines to control the *T. cruzi* infection [93]. Further, the 45 and 68 kDa antigens isolated from the cell surface membrane of *T. cruzi* epimastigotes isolated using affinity chromatography and used immunized in combination with Quil-A adjuvant, a saponin derivative, resulted in strong humoral and cellular immune responses and protection against trypomastigotes in mice.

4.5. Preventive vaccine for cholera

There are several cholera vaccines available, including Dukoral, Shanchol, Euvichol (all oral vaccines containing killed Vibrio cholerae strains), and Vaxchora (a live attenuated oral vaccine), each offering protection against cholera for varying durations and used in different contexts such as travel or outbreak response. Clinical trials have demonstrated Dukoral's efficacy, showing protection rates ranging from 50% to 85% against cholera caused by *V. cholerae* O1 for approximately 2 years in adults [108]. It is generally well-tolerated with mild gastrointestinal side effects reported. The US FDA[9] licensed the CVD[10] 103-HgR (Vaxchora vaccine) in 2016 as an oral, live attenuated vaccine for individuals aged 18–64 years who are traveling to locations where the disease is common. The selection was based on clinical trials conducted on human volunteers, which showed that the vaccine was well tolerated and provided 90% protection after 10 days. Additional clinical trial data has contributed to the growing body of evidence supporting the effectiveness of the Vaxchora vaccine. These trials specifically included elderly individuals (aged 46–64 years) and children (aged 2–17 years) and showed that the vaccination elicits a robust vibriocidal antibody response [109].

4.6. Vaccines to prevent Japanese encephalitis

These vaccines are efficacious in preventing Japanese encephalitis and are advised for those residing in or traveling to areas where the disease is widespread. There are 4 types of vaccine available: inactivated mouse brain-derived vaccines, inactivated Vero cell-derived vaccines, live attenuated vaccines and live recombinant vaccines [110]. The following vaccines are available for the prevention of Japanese encephalitis: an inactivated Vero cell-derived vaccine that is administered in a two-dose series with a booster, an inactivated mouse brain-derived vaccine that has been phased out due to safety concerns, and a live attenuated SA 14–14–2 vaccine that is administered as a single dose and is commonly used in specific Asian countries.

Table 2. Reported available vaccines for neglected tropical diseases.

Neglected Tropical Disease Vaccine	Status	Advantages	Disadvantages	Comments	Ref
Buruli ulcer Bacillus Calmette–Guerin (BCG)	The vaccine has been actively used against tuberculosis since 1921. Currently, it is being studied against the SARS-CoV-2 virus and is in phase 2/3 human clinical trials. The only vaccine in randomized controlled trials	Prevents tuberculosis and is being tested for COVID-19.	Lower efficiency	Vaccination is the best prevention method. Modern foam and hydrogel dressings are used on Buruli ulcers with antibiotics to kill mycobacteria to clean and treat wounds without the discomfort and bleeding of gauze bandages.	[58–60]
Dengue Dengvaxia CYD-TDV TAK-300	DNA immunization offers superior defense against the dengue virus. Approved for use in populations in endemic areas and those susceptible to the infection. The vaccines were pre-qualified by the World Health Organization against dengue. TAK-300 is currently undergoing phase 3 trial	Prevention of dengue infection brought on by serotypes 1, 2, 3, and 4. With increasing incidence in the case of dengue infection, the development of new vaccines is essential to combat the disease. CYD-TDV is the sole licensed tetravalent vaccine developed against dengue. Provides prolonged safety for 3 years on the administration the TAK-300 vaccine.	It may increase a patient's risk of developing a severe infection. The varying efficiency of vaccines against different serotypes is reported. An imbalance in the virologically confirmed dengue between the vaccinated and placebo individuals was observed.	The vaccine is presently only recommended for individuals between the ages of 9 and 16 who are inhabitants of regions where the dengue virus is endemic. The vaccine belongs to the class of live attenuated vaccines. And can be administered to children in the age group of 6–16 years.	[61,62] [63,64]
Leprosy LepVax BCG Vaccines	This recombinant vaccine is found to be efficient against Leprosy. The vaccine is in Phase 1b/2a of a clinical trial. Major trials were conducted in 1960 in Karimui, Burma, India, and Uganda. However, the results of protection varied in different geographic locations. For instance, the trials reported 80% protection in Uganda and 20% protection in Burma.	The recombinant protein adjuvant vaccine is notable in its capability to be safely administered to immunocompromised individuals. The BCG vaccine exhibited higher protection against leprosy in younger populations. Protection can last for 10–30 years.	There is a gap in studies focusing on pre-sensitization of mycobacterium which can potentially improve, mask, or diminish immunogenicity.	Leprosy prevention is another area in which the BCG vaccine has been studied. Several strategies like recombinant technologies have been used to increase the efficacy of BCG vaccines for providing protection against Leprosy.	[65,66] [67,68]
Rabies Imovax Fermi and Semple vaccines	m-RNA vaccination These are Pasteur vaccines with chemical modifications developed by Fermi in 1908 and Semple in the year 1911.	The immune system produces antibodies after the Rabies vaccine. These proteins can detect and kill viruses. These vaccines were successful in protecting from the rabies virus.	Pain at the injection site skin discoloration swelling induration, or hardening or thickening of the skin at the injection site. There have been reports of sensitization in vaccinated people which also cause fatal encephalitis. This is attributed to the high levels of myelin. Conditions such as Guillain-Barre Syndrome and Transmissible Spongiform Encephalopathies were reported as serious side effects of these vaccines.	Pre-exposure immunization, Imovax may be used alone or with other medications. Protection can last from 6 months to 2 years. Fermi and Semple vaccines were obtained from infected sheep and goats as well as suckling mouse brains.	[69] [70,71]
Echinococcosis EG95	Immunization of livestock, especially sheep could be one of the most efficient preventive measures against echinococcosis. Small-scale trials show safety and efficacy in those immunized with EG95.	After immunization, invading oncospheres are lysed by antibodies and complement. This vaccination is safe and efficacious in pregnant sheep, cattle, and young small ruminants.	Challenges in correct administration of vaccines to sheep on the field. The social practice of the regions and communities.	Based on the discovery of certain oncosphere components that incite host-protective immune responses in sheep, Eg95 (16.6 kDa protein) was developed. Protein variants include protein isoforms. Recently, research was done with the new goal of developing a multi-epitope vaccination that contains both T and B cell epitopes.	[72–75]

(*Continued*)

Table 2. (Continued).

Neglected Tropical Disease Vaccine	Status	Advantages	Disadvantages	Comments	Ref
Trachoma Recombinant CTH522 protein with adjuvants CAF01 liposomes or Aluminium hydroxide is in the clinical phase.	Sub-unit vaccine, which stimulates both humoral and cellular immune responses, could be an alternate approach to preventing chlamydial infections. Phase 1 completed	The vaccine has the potential to treat urogenital Ct infection. The results of Phase 1 demonstrate the safety and effective immunogenicity of the vaccine.	Absence of immunological correlations of protection. Considerable complexity in the identification of effects associated with disease conditions in the urogenital tract.	While the trachoma vaccine has yet to be tested in clinical trials, these results show that it is indeed possible for the vaccine to generate an ocular immune response. Data is very encouraging for vaccines against pathogens that infect the eye.	[48,76]
Helminthiasis Ancylostoma secreted protein 2 (ASP-2) HHVI (Human Hookworm Vaccine Initiative)	Irradiated helminth vaccines, subunit vaccines, and combining recombinant proteins with novel adjuvants strategies were employed. The trial was halted at the first phase of clinical trials due to the development of urticarial reactions in individuals with prior exposure to *N. americanus*. Following the development of manufacturing processes, A recombinant recombinant Na-GST-1/ Alhydrogel vaccine has been shown to exhibit significant antigen-specific IgG in both hookworm-naive and hookworm-exposed adults in a Phase 1 clinical trial.	HHVI includes a group of effective vaccines for helminth infections. ASP-2 exhibited efficiency in pre-clinical and animal studies. The Na-GST-1/Alhydrogel vaccine shows a significantly lower inhibition percentage of Na-GST-1's catalytic activity in immunized humans compared to animals vaccinated with the same Na-GST-1/Alhydrogel vaccine.	Adults with pre-existing levels of Na-ASP-2-specific IgE experienced generalized urticaria following a single vaccination. Synthesis of greater concentration of IgE antibodies in the host body. Na-GST-1/Alhydrogel was well tolerated by both hookworm-naïve and hookworm-exposed adults. The most frequent side effects included nausea, minor headaches, and mild to severe discomfort and tenderness at the injection site. There were no notable or severe side effects linked to the vaccination.	HHVI is now focusing on adult hookworm candidate antigens, particularly antigens involved in parasite blood feeding. Recombinant Na-GST-1 vaccination produced considerable antigen-specific IgG responses in individuals who had never been exposed to hookworms as well as those who had been administrated. It was effective and well-tolerated. These findings will drive the vaccine's advancement into pediatric clinical trials and ultimately increase the effectiveness of the research.	[45,77,78]
Lymphatic Filariasis BmALT-2 and BmHSP	Chemotherapy in conjunction with vaccination is a great way to manage this infection. The preclinical studies have demonstrated the efficacy of the vaccine in the treatment of lymphatic filariasis as a multivalent vaccination approach.	When given as a DNA, protein, or prime-boost vaccine, each of the candidate vaccine antigens provided variable degrees of protection.	Comparatively not effective vaccines	The effectiveness of the vaccine is examined when administered as a monovalent or multivalent formulation. In mice, the multivalent vaccine significantly increases protection.	[79,80]

4.7. Vaccines against leishmaniasis

The vaccines against leishmaniasis are available for veterinary purposes, however, there is still a lack of commercial-use vaccines approved for human infection [111]. Different species of Leishmania cause different clinical forms of leishmaniasis, namely, cutaneous, mucocutaneous, and visceral leishmaniasis. The mechanism involving Th1-type immune reaction driven by IL-12 plays an important role in the protection of the host. Various studies have focused on the development of live, attenuated, subunit, recombinant, and chimeric-peptide-based vaccines. The ancient practice of vaccination against leishmaniasis is called leishmanization which involves inoculation of low doses of virulent and live *L. major*, intradermally. The technique is no longer in practice because of safety issues concerning transmission of HIV, administration of immunosuppressants, ethical issues, persistence of skin lesions [112].

4.8. Leprosy vaccine immunization

The classic disease leprosy, commonly known as Hansen's disease, is brought on by the acid-fast bacterium *Mycobacterium leprae*. Drug therapy has drawbacks, and it takes time to undo the damage brought on by the bacterium. To lower illness occurrence and encourage eradication, an effective vaccination would be beneficial. An indigenous leprosy vaccine known as *Mycobacterium indicus pranii* has been shown to reduce the number of new leprosy cases by 60% in three years and, it is efficacious for 7–8 years before the requirement for a booster dose to sustain immunity [113].

4.9. Vaccine against lymphatic filariasis

A multivalent DNA-based lymphatic filariasis vaccination using BmALT-2 and BmHSP, as well as a prime-boost strategy, is 90%

Table 3. A list of neglected tropical diseases that currently have no vaccines or are in the early stages of vaccine development.

Neglected Tropical Disease Vaccine	Status	Advantages	Disadvantages	Comments	References
Chagas disease Currently, no vaccine is available.	There is a lack of vaccine for Chagas disease. However, drugs (benznidazole or nifurtimox) are available for the effective treatment of the disease.			Protective clothes, topical insect repellents, insecticide spraying infested homes, avoiding possibly contaminated meals, and wearing protective garments are frequent Chagas disease prevention methods.	[13,93]
Chikungunya No vaccine Virus-Like Particles (VRC-CHKVLP059-00-VP) and Measles vector vaccines (MV-CHIK) have been tested.	Inactivated and subunit, live attenuated, recombinant virus vector vaccination strategies were employed.	Expression of viral structural proteins cannot replicate or infect, however self-assemble to form structures resembling the original virus.	Poor responses due to the presence of preexisting anti-measles immunity	There are now feasible approaches to combat this debilitating disease because of several discoveries that have entered phase I and II human clinical trials.	[94,95]
Guinea-worm disease No vaccine	No vaccination strategy is available.			For the worm to contract and release larvae, submerge or soak the infected body part in water.	[96]
Human African trypanosomiasis No approved vaccine or drug	The DNA vaccination technique can boost the humoral immune response and protect against infection.			There were no differences between the vaccinated and unvaccinated controls; thus, no proper vaccination is available till now. Congopain, a cysteine protease present in the parasite can be targeted.	[69,97]
Food borne trematodiasis.	No vaccines are currently available.			Recent gene discoveries may lead to the development of vaccines. However, 2 next-generation trematocidal drugs (praziquantel and triclabendazole) are found to be effective.	[98,99]
Leishmaniasis No vaccine	The development of the live-attenuated, anti-leishmanial vaccine currently remains in the very early stages. In a mouse model, vaccination with dihydrofolate reductase thymidylate synthase (dhfr-ts) knockout parasites resulted in protection against leishmaniasis, but it was unable to shield monkeys from an infectious stimulus. Despite tremendous efforts, no vaccination is currently available for human use.	Live attenuated mutants have been successfully utilized to induce protection against various parasite illnesses, including malaria, and this procedure is not exclusive to leishmaniasis vaccinations.	Nevertheless, vaccination has typically only produced partial protection and full resistance has not yet been attained.	Considering the tremendous advancements in parasitic immunology and genetic engineering, a viable anti-Leishmania vaccine should be developed more rapidly rather than in the future.	[100,101]

successful in mouse models. pVAX1 encodes either Bmhsp or Bmalt-2 for monovalent DNA vaccination, or both for multivalent vaccination. Plasmids were propagated in *E.coli* Top10Fc cells. The vaccines were successful in preventing lymphatic filariasis, particularly in case of infection caused by *B. malayi* [79]. However, there are no vaccines approved to prevent the infection in humans, at present.

A vast majority of lymphatic filariasis cases (90%) are caused by *Wuchereria bancrofti*, but the clinical studies have been focused on *B. malayi* and *B. pahangi* due to the difficult maintenance of the life cycle of *W. bancrofti* in labs. Studies have found that non-human primates can be used as an efficient model where the infection by *W. bancrofti* and *B. malayi* is similar to human infection. Some candidate antigens that have been focused on for vaccine development include thioredoxin peroxidase (TPX^{11}), tetraspanin (TSP^{12}), abundant larval transcript 2 ($ALT2^{13}$), heat shock protein (HSP^{14}), glutathione S-transferases (GST^{15}), collagen 4 ($Col4^{16}$), and vespid venom allergen (VAH^{17}). A multivalent vaccine targeting multiple antigens is considered to have better efficacy [114].

World Health Organization (WHO) has reported that around 880 million population in 52 countries are at risk of developing

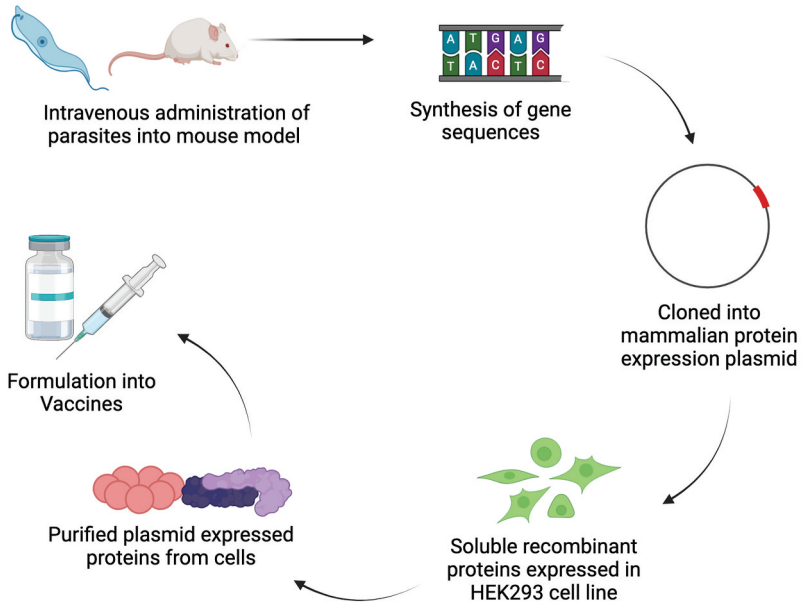

Figure 2. The formulation of vaccines for infectious agents in mice (Figure created using BioRender.com).

lymphatic filariasis infection. Currently, the mitigation of the disease greatly relies on mass drug administration (multidrug therapy) and vector control strategies. The development of a prophylactic vaccine is a critical requirement to control the transmission of infection. An effective vaccine should provide robust and prolonged protection in the vaccinated population [114].

4.10. Vaccine for measles

The measles-mumps-rubella (MMR) Vaccine contains live attenuated measles virus, mumps virus, and rubella virus strains. Administered as a two-dose series, typically given at ages 12–15 months and 4–6 years. It is highly effective, with more than 95% protection against measles after two doses. Measles-Mumps-Rubella-Varicella (MMRV) Vaccine protects against measles, mumps, rubella, and varicella [115,116]. Vaccines are essential in avoiding measles, a highly transmissible viral illness that can lead to severe consequences, particularly in young children. Administering the MMR[18] or MMRV[19] vaccine not only safeguards individuals but also aids in establishing community immunity (herd immunity), hence diminishing the overall transmission of measles among groups.

4.11. Pneumococcal pneumonia vaccine development

Vaccines have a crucial role in public health efforts to prevent pneumococcal pneumonia and associated illnesses, particularly among susceptible groups such as young children, older adults, and individuals with preexisting medical disorders. Pneumococcal Conjugate Vaccines (PCVs) are a type of vaccination that combines the polysaccharide antigen of *S. pneumoniae* with a carrier protein through conjugation. PCV13 provides immunity against 13 different serotypes of *S. pneumoniae*, whereas PCV10 provides immunity against 10 serotypes. This vaccine is highly efficient in preventing invasive pneumococcal disease (IPD), pneumonia, and otitis media caused by the specific serotypes targeted by the vaccination. The Pneumococcal Polysaccharide Vaccine (PPSV) is a vaccine made up of pure capsular polysaccharides from 23 different serotypes of *S. pneumoniae*. Given as a solitary dosage to individuals aged 65 and above, as well as younger individuals with specific medical problems, this vaccine protects against pneumococcal pneumonia and other invasive infections caused by the included serotypes [117,118].

4.12. Vaccines targeting schistosomiasis

An effective strategy to control the transmission of infection is the sustainable development of vaccines. Numerous studies have focused on potential vaccine candidates with schistosome antigens for various Schistosoma species of clinical relevance like *S. mansoni*, *S. japonicum*, and *S. haematobium*, however, there is no licensed vaccine for animals or humans till date. Four important candidate vaccine antigens in different clinical phases of design and development (pipeline) include *Schistosoma mansoni* tetraspanin (Sm-TSP-2/Alhydrogel), *S. mansoni* with 14kDa fatty acid binding protein (Sm14/GLA-SE), *S. mansoni* calpain (Sm-p80/GLA-SE), and *S. haematobium* with 28kD glutathione S-transferase (Sh28GST/Alhydrogel) [119,120]. Sm-p80 formulation reportedly provides a reduction in worms, protection from acute *Schistosomiasis*, and an anti-fecundity effect [121].

4.13. Vaccine for soil-transmitted helminthiasis

Currently, the effectiveness of controlling Soil-transmitted helminthiases infections seems to be almost entirely dependent on mass anti-helminthic drug administrations of albendazole or mebendazole to at-risk communities in association with awareness in schools and better sanitation, including WASH

initiatives [45,122]. New strategies that enhance the safety, immunogenicity, and efficiency of vaccinations have been developed as a result of breakthroughs in vaccination and immunomics and some of these approaches have even been utilized to create helminth vaccines [123]. The involvement in generating vaccines or a pan-anthelminthic vaccine to offer a practical, long-term immunological method of controlling various helminth infectious diseases has also increased due to the emergence of anthelmintic-resistant parasites, which poses a risk to drug treatment programs. Moreover, the excreted and secreted parasitic substances are potential vaccine choices because they function at the host-parasite interface, modulating the host immune system and inducing Th2-skewed immune responses. The two most effective helminth recombinant vaccines against hookworm infections produced by *Necator americanus* are aspartic protease-1 (Na-APR-1) and glutathione-S-transferase-1 (Na-GST-1). Na-ASP-2 vaccine exhibited favorable outcomes in preclinical studies and animal models. The vaccine formulated with alhydrogel triggers a strong antibody reaction and the skewed immune reaction of Th2. The vaccine efficiently reduces the worm count as well as the clinical pathology in hosts. In addition to the benefits associated with the Na-ASP-2 vaccine candidate, it is also related to urticarial reactions with high IgE antibodies in response to helminth antigen, halting the vaccine trial in Phase 1 in 2008 [45].

4.14. Varicella and shingles vaccine development

A singular virus of the herpes family, the Varicella-zoster virus (VZV), is responsible for both chickenpox and shingles. Chickenpox is the primary infection expressed in immunocompromised hosts, while the reactivation of latent infection causes shingles. Following the primary infection, varicella gets localized in the dorsal ganglion cells of sensory nerves where it remains latent. Upon reactivation, it transitions into a clinically distinct syndrome called shingles [124]. The varicella vaccine is administered to children in two doses to prevent chickenpox. On the other hand, the zoster vaccine is administered to individuals over 50 years of age or immunocompromised people aged 18 years and above [125].

The development of global vaccination strategies for chickenpox and shingles is complicated attributed to the complex characteristics of VZV.[20] Therefore, balancing the health impacts of vaccination, including understanding the effect of an altered mean age of infection for both chickenpox and shingles, should be carefully evaluated before implementing any vaccination program [126,127].

The FDA has approved two types of vaccines for persons aged 50 and above to prevent shingles (herpes zoster). The Centres for Disease Control and Prevention (CDC) exclusively recommends the use of Zostavax, a live shingles vaccine that has been available since 2006, in persons aged 60 and above who have robust immune systems. Since 2017, a more recent recombinant vaccine called Shingrix has been authorized and is the recommended vaccine for individuals aged 50 and above. There is no upper age limit for receiving the vaccination [128]. Nevertheless, the existing vaccines for varicella and herpes zoster do not provide complete protection; they have an efficacy rate ranging from 70% to 90% in preventing varicella and over 95% in preventing severe varicella [129].

4.15. Vaccine to prevent yellow fever

Vaccination is the most important measure for preventing yellow fever. Yellow fever vaccine is safe and affordable, and a single dose provides life-long protection against yellow fever disease. The yellow fever vaccine provides immunity within one week in 95% of people vaccinated. The main vaccine utilized for the prophylaxis of Yellow Fever is a live attenuated vaccine produced from the 17D strain of the Yellow Fever virus. Stamaril, also known as YF-Vax,[21] is administered as a single subcutaneous dose and typically confers lifelong immunity to the majority of patients. Travelers aged 9 months and above who are visiting or living in places where Yellow Fever is common are advised to receive this vaccine [130].

5. Challenges

The three NTDs with the highest mortality rates, Chagas disease, African human trypanosomiasis, and visceral leishmaniasis, continue to pose numerous obstacles, despite the substantial advantages of current research. Despite its significant benefits, several challenges persist in addressing these three NTDs with the highest mortality rates. These diseases cannot be effectively controlled or reduced in prevalence and mortality through preventive drug treatments (chemotherapy) alone [25,131,132]. Vector control remains the most effective method for managing Chagas disease and African trypanosomiasis. However, sustaining successful vector management programs, such as those that have significantly reduced Chagas disease transmission in five South American countries and African trypanosomiasis using low-cost, impregnated tsetse-fly traps, remains a challenge due to limited resources and infrastructure [25]. Additionally, insufficient funding for research and vaccine development for neglected tropical diseases poses a major obstacle [133]. Another challenge is the human host's inability to mount a sustained immune response upon re-infection by these parasites, necessitating frequent vaccine administration or treatment [134].

5.1. Therapeutics and vaccination challenges

War-torn and unstable regions will likely struggle to address these concerns. In the absence of novel disease prevention and environmental control methods, especially for benzimidazole anthelmintics like albendazole, mebendazole, and ivermectin, the same errors may be repeated [135,136]. To eradicate onchocerciasis, novel, effective anti-helminthic medications such as tribendimidine for soil-borne helminth infections, a novel macrofilaricidal, and anti-wolbachia-based therapy must be developed and tested [137]. Novel therapeutics targeting filarial parasites' Wolbachia bacterial endosymbionts reduce parasite reproductive capability and inflammation. The only hope for long-term management of

NTDs is vaccine development. Product development agreements have put hookworm, schistosomiasis, and leishmaniasis vaccines in phase 1 and 2 clinical trials [138]. New 'antipoverty vaccines' might be developed in theory to protect against all NTDs [139]. These could be used with 'vaccine-linked chemotherapy' for comprehensive prevention and treatment. Pharmaceutical and vaccine firms from supposedly inventive developing nations encourage cooperative efforts to create new tropical disease therapies. Brazilian, Chinese, and Indian emerging nations have the facilities and ability to generate cutting-edge drugs, vaccines, and medical testing [140–142]. More G8 aid would boost developing countries' innovation and health research.

A comprehensive approach is necessary to address the constraints in the way of developing vaccines for neglected tropical diseases (NTDs). Determining a Correlates of Protection (CoP), or immunological responses or biomarkers that signal a vaccine's efficacy, must be the first priority of study [143]. Extensive research in both preclinical animals and humans is required to establish significant markers of protection [144]. Data and expertise sharing can be facilitated by collaborative initiatives with foreign research organizations. Also, in circumstances where conventional trials are not practical, other testing techniques like surrogate endpoints or predictive models must be created to assess vaccination efficacy [145]. Additionally, adaptive trial designs can also be advantageous since they enable adjustments based on interim outcomes. Developing biopharmaceutical capacity is also considered to be essential, this entails investing in local manufacturing capabilities in areas where NTDs are common and partnering with businesses that can produce vaccines that meet GMP[22] standards [146]. The development of NTD vaccines can be accelerated by implementing the above strategies into practice, paving the way to efficient disease prevention and control.

6. Conclusion and future prospects

The group of illnesses known as NTDs is brought on by bacteria, parasites, viruses, helminths, protozoa, and fungi. The majority of those impacted are poor populations who live in tropical and subtropical climates, numbering over one billion people. The epidemiology of NTDs is complex, and environmental factors are frequently implicated. Many of them are vector-borne, have a reservoir of animals, and have a complicated life cycle. People most adversely affected by these illnesses are repeatedly detected in lower-middle-class economies, impoverished urban slum dwellers, far-flung rural areas, or war zones. Individuals are frequently affected by more than one parasite or infection. Infections are caused by contaminated water, unsanitary living conditions, and inadequate sanitation. Children are especially susceptible to these illnesses, which annually claim the lives of millions of people and frequently cause them to suffer for the rest of their lives. NTDs include Buruli ulcer, Chagas disease, cysticercosis/taeniasis, dengue fever, dracunculiasis (guinea pig disease), echinococcosis, alimentary trematodiasis, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, rabies, schistosomiasis, soil-borne helminthiasis, trachoma, yaws, etc. Novel and dependable treatment and vaccination approaches are being developed as a consequence of a diverse range of ongoing research and technological advancements in the domains of pharmaceutics and therapeutics. BCG,[23] Dengvaxia, LepVax, and Imovax are some of the vaccines available for NTDs. The production of these novel vaccinations provides better delivery methods and an improved understanding of immunological reactions. Furthermore, global initiatives to control as well as approaches to manage disease transmission are required. Furthermore, for effective disease containment and management, a global mass vaccination campaign is required. With improvement in technological understanding and research techniques, novel personalized vaccines could be developed, taking into account an individual's vulnerability to various NTDs. Continued investment in vaccine development, along with integrated public health initiatives, is critical for maintaining and expanding these advances, ultimately leading to the eradication of NTDs and promoting global health equality.

7. Expert opinion: emerging pathways

The NTDs encompass a collection of parasitic and associated infectious ailments, including but not limited to amoebiasis, Chagas disease, cysticercosis, echinococcosis, hookworm, leishmaniasis, and schistosomiasis. The management of NTDs in the absence of vaccination continues to pose a formidable obstacle. The advent of this new era signifies an important turning point in the expeditious advancement and authorization of vaccines, aimed at combatting the persistently substantial worldwide prevalence of ailments caused by various infectious pathogens, particularly in economically deprived regions. These infections have a significant impact on a vast number of individuals and are prevalent in regions with limited resources in Africa, Asia, and South America. The global prevalence of helminth infections has resulted in a substantial burden on public health. These parasitic organisms have emerged as the primary contributors to this widespread affliction. Within the realm of significant helminth infections, it is noteworthy to highlight the prevalence of soil-transmitted helminths (STHs) such as *Ancylostoma duodenale, Necator americanus, Ascaris lumbricoides*, and *Trichuris trichiura*. These specific STHs[24] collectively contribute to a substantial 50% of the overall disease burden

The need of the hour is the production of inexpensive vaccines against NTDs, accessible to all population groups. Plant-based vaccines are an efficient alternative that has a lower cost of production and can be effectively administered orally. Currently, studies are focusing on developing novel, efficient, cost-effective, and safer substitutes for conventional vaccines [147].

7.1. Collaborative strategies to control NTDs

The health goals of the WHO have been significantly advanced in several countries, but it is still unclear whether the available

funding and political commitments on a global scale are sufficient to achieve them. Despite the Assembly's lofty goals, further initiatives are expected to improve worldwide coverage and combine NTD control strategies. WHO is harmonizing and coordinating its operations to link partnerships to national health ministries to control or eliminate the most frequent NTDs. The geographic overlap and endemicity of these diseases support incorporating preventative chemotherapeutic treatments [139,148]. Parasites and NTDs impact these communities simultaneously. Thus, an immediate-effect pharmaceutical package is beneficial.

The 'fast-impact box' refers to community-based distributors' ability to quickly provide medication, which could reduce disability, promote well-being, and stop disease spread. This kit contains albendazole, mebendazole, praziquantel, ivermectin, and azithromycin [149]. Integrating partnerships to control NTDs and their public health infrastructures can deliver these medications at 26–47% cheaper costs [150]. The gift of four of the six rapid-impact drugs in sub-Saharan Africa estimates the annual cost per person at $0.40–$0.79 [149,150]. Thus, less than $400 million can treat 500 million at-risk people annually. This is a small fraction of the annual cost of treating TB with antiretrovirals or directly observed combo therapy. Hookworm infection and schistosomiasis, the most common NTDs, are often associated with malaria and HIV – AIDS and have synergistic effects. Thus, prophylactic chemotherapy may have serious side effects. Global Network for NTDs collaborates to tackle the most common NTDs and speed management strategy integration [139]. Another important approach to control NTDs includes efficient sanitation and hygiene strategies, as well as accessibility to clean water (WASH). It is effective in the control and prevention of multiple NTDs [151]. It is reported that countries like Benin in West Africa are endemic to several NTDs, due to lack of access to clean water and sanitation. Therefore, the prevention of pathogenic infections of NTD involves strategies like the implementation of WASH infrastructure, community awareness, and promotion of hygiene practices like the use of hand sanitizers and hand washes in all populations by making these products economical and accessible to all [152–154].

7.2. Innovative approaches

Myriad novel approaches have impacted the direction of NTD vaccine development [51,155]. Emerging vaccination platforms, including mRNA,[25] live attenuated, and vector-based technologies, provide rapid and flexible design possibilities, while genomic and proteomic research identifies novel antigens for targeted vaccines. Mucosal vaccinations and other enhanced delivery methods, such as those based on nanoparticles, are intended to boost immunological responses and accessibility [151]. Advances in adjuvant development, such as novel and combination adjuvants, will increase the efficacy of the vaccine. With fewer doses, multivalent and combination vaccines tend to provide greater protection against a variety of diseases [152]. Furthermore, the discovery of innovative and cost-effective therapeutic interventions aimed at addressing and eradicating various infectious diseases will undeniably enhance the efficacy of these medical procedures. In addition, it is imperative to conduct further research on the monitoring and evaluation of post-treatment reinfection rates as well as the emergence and development of anthelmintic medication resistance.

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Notes

1. WHO: World Health Organization.
2. NTDs: Neglected Tropical Diseases.
3. HIV: Human Immunodeficiency Virus.
4. WASH: Water, sanitation and hygiene.
5. NGOs: Non-Governmental Organization.
6. DNA: Deoxyribonucleic Acid.
7. IL-12: Inter-Leukin 12.
8. GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor.
9. US-FDA: United States- Food and Drug Administration.
10. CVD: Centre for Vaccine Development.
11. TPX: Thioredoxin peroxidase.
12. TSP: Tetraspanin.
13. ALT-2: Abundant Larval Transcript 2.
14. HSP: Heat Shock Proteins.
15. GST: glutathione S-transferases.
16. Col4: Collagen 4.
17. VAH: Vespid Venom Allergen.
18. MMR: Measles, Mumps, and Rubella.
19. MMRV: Measles, Mumps, Rubella, and Varicella.
20. VZV: Varicella Zoster Vaccine.
21. YF-Vax: Yellow Fever Vaccine.
22. Good Manufacturing Practises.
23. BCG: Bacillus Calmette-Guerin.
24. STHs: Soil-transmitted helminth.
25. mRNA: messenger Ribonucleic Acid.

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