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Heterocycles in the Treatment of Neglected Tropical Diseases

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Abstract:

Background: Neglected tropical diseases (NTDs) affect a huge population of the world and the majority of the victims belong to the poor community of the developing countries. Until now, the World Health Organization (WHO) has identified 20 tropical diseases as NTDs that must be addressed with high priority. However, many heterocyclic scaffolds have demonstrated potent therapeutic activity against several NTDs.

Objective: There are three major objectives: (1) To discuss the causes, symptoms, and current status of all the 20 NTDs; (2) To explore the available heterocyclic drugs, as well as their mechanisms of action (if known), that are being used to treat NTDs; (3) To develop general awareness on NTDs among the medicinal/health research community and beyond.

Methods: The 20 NTDs have been discussed according to their alphabetic orders along with the possible heterocyclic remedies. The current status of treatment with an emphasis on the heterocyclic drugs (commercially available and investigational) has been outlined. In addition, a brief discussion of the impacts of NTDs on socio-economic conditions is included.

Results: NTDs are often difficult to diagnose and the problem is worsened by the unhealthy hygiene, improper awareness, and inadequate healthcare in the developing countries where these diseases primarily affect poor people. The statistics include the duration of suffering, the number of individuals affected, and access to healthcare and medication. The mechanisms of action of various heterocyclic drugs, if reported, have been briefly summarized.

Conclusion: Scientists and pharmaceutical corporations should allocate more resources to reveal the in-depth mechanism of action of many heterocyclic drugs that are currently being used for the treatment of NTDs. Analysis of current heterocyclic compounds and the development of new medications can help in the fight to reduce/remove the devastating effects of NTDs. An opinion-based concise review has been presented. Based on the available literature, this is the first attempt to present all the 20 NTDs and related heterocyclic compounds under the same umbrella.

Keywords: Neglected tropical diseases, NTDs, Bacterial, Viral, Heterocycles, Heterocyclic drug, Parasite, Infection, Infestation.

1. INTRODUCTION

Neglected tropical diseases (NTDs) are responsible for the prolonged misery and suffering of people across the world. NTDs, unfortunately, exist in those countries that are financially backward with no appropriate healthcare available. NTDs have a devastating impact on the health and social life of human beings. However, because these diseases are often neglected, human suffering is perpetuated by the lack of research and development of novel treatments. According to the WHO, there are approximately 20 different categories of diseases that may be classified as neglected tropical diseases. Neglected tropical diseases affect over 149 countries around the world and are responsible for the loss of billions of dollars in economic costs. The 20 diseases that are relevant to this discussion include Buruli ulcer, Chagas' disease, Dengue, Severe dengue and Chikungunya, Dracunculiasis (guinea-worm disease), Echinococcosis, Foodborne trematodiases, Human African trypanosomiasis (sleeping sickness), Leishmaniasis, Leprosy (Hansen's disease), Lymphatic filariasis, Mycetoma, Onchocerciasis (River blindness), Rabies, Scabies, Schistosomiasis, Soil-transmitted helminthiases, Snakebite envenoming, Taeniasis/Cysticercosis, Trachoma and Yaws. Some of these diseases are transmitted by carriers. The lack of proper sanitation and the subsequent proliferation of vectors exacerbate the problem. For example, Leishmaniasis is caused by the infection of the leishmania protozoan and is carried by the female phlebotomine sandflies. Affected people are often left without treatment or cure. Complete cure of leishmaniasis is possible by early-stage detection and access to appropriate sanitation and health care facilities [1].

On the other hand, 'heterocycles' or 'heterocyclic compounds' are mostly organic compounds in which at least one cyclic (ring) framework is present that contains one or more heteroatom(s) as ring constituent. Heteroatom signifies any non-carbon atom (except hydrogen) and the most widely used heteroatoms, that are present in heterocycles, are nitrogen, oxygen, sulfur, phosphorus, etc. Several heterocyclic moieties are found as important pharmacophores (molecular scaffolds that are responsible for pharmacological activity) in drug discovery research. Heterocycles, therefore, are an interesting and extremely important focal point in the search for new drugs to combat neglected tropical diseases. It was reported that nine out of the twenty-one best-selling drugs in 2013 were heterocyclic compounds [2]. This promising number indicates that heterocycles play a highly significant role in medicinal chemistry and drug

development research. Because of the presence of heteroatom(s) as ring-constituent(s), heterocycles are candidates for better binding with the disease-causing proteins through extended protein-ligand interactions as compared to their carbocyclic counterparts. Therefore, if one describes in detail and understands the mechanism of action of various heterocycles in neglected tropical diseases, there is a greater probability of developing effective heterocyclic drugs for the treatment of NTDs. This explanatory discussion is focused on the pharmacologically active heterocycles and their mechanisms of action in the treatment of neglected tropical diseases. Commercially available heterocyclic drugs that are being used for the treatment of NTDs have been presented in Figure 1. Investigative heterocyclic molecules (mostly patented) that are under various pre-clinical/clinical trials are shown in Figure 2. An overview of the 20 neglected tropical diseases, their present status, and available treatments have been briefly presented in Table 1. To the best of our knowledge, based on the available literature, this is the first comprehensive effort to summarize the possible biological and environmental causes, current status, various influencing factors, and socio-economic impacts of NTDs that correlate the effectiveness of heterocyclic compounds in the treatment of 20 NTDs.

<Figure 1>

<Figure 2>

<Table 1>

Table **1.** An overview of the NTDs, their current status and available treatments as defined by the WHO.

Neglected tropical disease (NTD)	Number of cases	Global impact	Primary drug and/or method of treatment	Ref.
Buruli ulcer	2015: 2046 2016: 1920 2017: 2209	33 Countries including Africa, North and South America, Asia and Western Pacific regions	Rifampicin Clarithromycin Streptomycin Moxifloxacin	[3]
Chagas' disease	6 to 7 million	Primarily in 21 Latin American countries	Nifurtimox Benznidazole	[6]
Dengue and severe dengue	95% credible interval indicates 284-528 million infections per year	Majority of Asian and Latin American states with global outbreaks (128 countries and 3.9 billion at risk)	Vaccine Fluid Level Regulation	[9]
Dracunculiasis	Middle 80s: 3.5 million 2007: < 10,000 2012: 542 2013: 148 2014: 126 2015: 22 2016: 25 2017: 30	Reduced severity compared to '80s	Currently no treatment is available	[13]
Echinococcosis	Approximately 1 million people at any time	Found on all continents, excluding Antarctica	Deworming Surgery Albendazole	[17]
Foodborne trematodiases	200,000 infections estimated annually	East Asia and South America have the highest rates, 2 million life years lost per year	Praziquantel Triclabendazole	[20]
Human African trypanosomiasis (Sleeping sickness)	3 epidemics: 1896-1906, 1920, 1970-1990's 1998: 40,000 reported (300,000 total) 2009: 9878 2015: 2804 Number of cases (actual): 20,000	36 sub-Saharan African countries affected, at-risk population of 65 million	Pentamidine Suramin Melarsoprol Elornithine Nifurtimox	[26]

Leishmaniasis	700,000 to 1,000,000 cases per year	20,000 – 30,000 deaths per year. Affects highly impoverished people	Sodium Stibogluconate Meglumine Antimoniate Miltefosine Amphotericin B Deoxycholate Lipid Formulations Paromomycin Gentamycin Thermotherapy (Temperature therapy)	[30]
Leprosy	2016: 108 Prevalence rate of 0.29/10,000; 16 million treated	Eliminated as a public health problem achieved in 2000.	Dapsone Rifampicin Clofazimin	[34]
Lymphatic filariasis	2000: 120 million affected people, 40 million were disabled 6.7 billion treatments administered since 2000	856,000,000 people across a total of 52 countries remain at risk.	Albendazole Ivermectin Diethylcarbamazine Citrate	[37]
Mycetoma	Data is lacking (non-notifiable disease)	Endemic disease in Africa, Asia, Europe, and Latin America	Antibiotics Antifungals	[41]
Onchocerciasis (River blindness)	1974-2002: 40 million Africans treated 2015: 119 million Africans treated 2016: 132 million Africans treated 2015: 11/13 regions prevented disease transmission in the Americas.	Only 1% of infected people reside outside of 31 African countries. Isolated cases in Latin America and Yemen.	Ivermectin	[43]
Rabies	Thousands of deaths and cases per year, primarily in Africa.	It occurs in 150 countries and regions globally. Present on all	Vaccine Immunoglobins	[49]

		continents excluding Antarctica.		
Schistosomiasis	2016: 206.4 million people required preventative intervention In 2000, according to WHO data, death rate is estimated to be 200,000 annually	Incidence has been reported in 78 countries. It has been inferred that 91.4% of cases occur in Africa.	Praziquantel	[54]
Soil-transmitted helminth infections	1.5 billion people are currently infected with the disease	Infections are concentrated in the regions of Africa, the Americas, Asia, and China.	Deworming	[58]
Snakebite envenoming	5.4 million receive snakebites per year, with close to 2.7 million of these cases involving envenoming The result of this includes between 81,410 to 137,880 deaths and amputation and disability in higher numbers.	Most of the cases occur in Africa, Asia, and Latin America.	Antivenom	[61]
Taeniasis cysticercosis	The number of people suffering from neurocysticercosis is approximately 2.56-8.30 million.	Affects those in Africa, Asia, and Latin America and inhibits daily life. Loss of 2.8 million life-years (*T. solium)*	Praziquantel Niclosamide Albendazole (corticosteroids and anti-epileptics may be used)	[65]
Trachoma	Responsible for visual loss in 1.9 million people. 2016: 190.2 million people at risk 2016: 260,000 received surgery and 85,000,000	41 countries have people suffering from the disease. Lost productivity approximately 2.9-5.3 billion USD (8 with trichiasis)	Azithromycin Surgery	[68]

	received antibiotics			
Yaws	8/13 endemic countries experienced greater than 45,000 cases	73 countries previously endemic and 13 currently confirmed endemic.	Azithromycin Benzathine Penicillin	[73]

2. Buruli ulcer

Buruli ulcer is a neglected tropical disease that is caused by the bacterium *Mycobacterium ulcerans*. The disease is named after the Buruli district in Uganda where early cases were detected. Although the disease is specific to the skin but in some cases, the bone may also be affected seriously. The mechanistic actions of the frequently used drugs have not been studied in detail. Until now, the disease has been reported from 33 countries in the world. The disease is very toxic and eventually, total disability may result. Generally, the treatment for the disease is given by a mixture or cocktail of antibiotics. It is very interesting to note that every single antibiotic that is used in the fight against Buruli ulcer contains a structure that possesses a heterocyclic moiety (Figure 1). One combination is rifampicin and streptomycin in a prescribed amount of approximately 10 mg/kg of the bodyweight to be taken once a day for rifampicin and 15 mg/kg of the bodyweight for streptomycin. Another is the combination of rifampicin and clarithromycin in dosages of 10 mg/ kg of the bodyweight once daily and 7.5 mg/kg of the bodyweight twice daily, respectively. A third, unverified combination that has demonstrated better results in isolated, non-clinical trial, is a combination of a 10 mg dose of rifampicin with 400 mg of moxifloxacin once a day. There are three primary categories of the disease (Figure 3). The first category is characterized by a small abrasion, the second by plaques including those that are ulcer forming and may contain swelling, and the third involving bone inflammation [3]. Thus, it seems clear that there is almost no specific and extremely effective drug for the treatment of Buruli ulcer. It has been reported that 2-piperazin-1-yl-4*H*-1,3-benzothiazin-4-one derivatives (Figure 2) exhibited better activity although extensive clinical trials are required. Substituted derivatives of the compounds may lead to developing new viable molecules that can be used for more effective treatment of Buruli ulcer [4].

<Figure 3>

3. Chagas' disease

Chagas' disease (named after the Brazilian sanitary physician Carlos Chagas, widely known as American trypanosomiasis) is caused by a vector-borne parasite, *Trypanosoma cruzi*. Apart from humans, the presence of *T. cruzi* has also been detected in more than 150 species of mammals and marsupials [5]. This disease, through its impact on human health, is a significant economic and social problem. Currently, about 6-7 million people are infected by this disease. Unfortunately, appropriate health care development requires huge money. For example, in 2008 Columbia spent 267 million dollars to remediate the devastating impact of Chagas' disease. The cost of insecticide to prevent this treatment would have been a mere 5 million dollars. As Benjamin Franklin said, "An ounce of prevention is worth a pound of cure." The feces and urine of the triatome bug are involved in infection. The insect bites the human on the epidermis and expels waste products shortly afterward. The organismal waste contains parasites that the bug has picked up, and when an individual move to brush away the bug or scratches the wound, these wastes are agitated into the wound; this allows entry into the circulatory system. Waste products may be incorporated into the eyes and mouth and regions where the epidermis has been broken. The disease also may be transmitted by vertical transmission, organ transplant operations, and the ingestion of food that is laced with contaminants. [6].

When discussing Chagas' disease, as of now, there are only two main drugs used in clinical care, although neither of these is particularly potent. These two drugs are nifurtimox and benznidazole (Figure 1). Both drugs exhibit significant toxicity and produce the best results for those who exhibit acute symptoms of the disease. In patients who have been immunocompromised, the drugs exhibit a reduced therapeutic efficacy. The chemical basis of both medications' efficacy involves the process of reduction of the nitro group. For nifurtimox, the reaction is involved in producing a negatively charged nitro containing moiety, which is further responsible for the synthesis of reactive oxygen that imparts pharmacological activity. Benznidazole reacts in a fashion such that many stable, regularly occurring covalent bonds in macromolecules are altered. More specifically, the mode of action involves the formation of nitro anion radicals by nitroreductase II, which subsequently induces the activity of redox cycling. Radicals, by their nature, allow single electron transfer reactions to take place leading to the ultimate production of

superoxide. Also, DNA mutilation is encouraged by reduction reactions. Here a pair of electrons is used to reduce nitro to nitroso groups. This process undergoes catalysis by nitroreductase I. In a biological system, many structures are susceptible to oxidation or reduction; this explains both the effectivity and the side effects of these medications. The balance between the two is determined by specificity. It is notable that both the drugs involve the heterocycle moiety. Some other molecules are currently under the developmental stage to remediate the side effects and increase the potency of treatment. The heterocyclic drugs posaconazole, and ketoconazole-terbinafine combination (Figure 1) are currently in the clinical trial phase [7]. Recently, 2-ferrocenyl benzimidazole [2-(Ferrocyn-2-yl)-1*H*-benzimidazole] has been reported [8] that demonstrated about 2.5 times better activity than the positive control (nifurtimox) on INC-5 *Trypanosoma cruzi* strain. The compound was synthesized following a one-step microwave-assisted green procedure. The structure of 2-(Ferrocyn-2-yl)-1*H*-benzimidazole is shown in Figure 2.

4. Dengue/Severe Dengue and Chikungunya

Both dengue and chikungunya are classified as neglected tropical diseases. Unfortunately, approximately half of the world's population is at risk from these two neglected tropical diseases. Like Chagas' disease, dengue is transmitted through a vector. The vector is specifically harbored by female mosquitoes of the *Aedes* genus, including *Aedes aegypti* and *Aedes albopictus*. *Aedes aegypti* is a common vector of both dengue and chikungunya viruses. Many Asian and Latin American regions have been affected and many new patients are infected and die every year due to these two diseases. When referring to dengue, four diseases actually are being considered. Each strain of the virus is labeled as DEN-#, where # represents the numbers 1-4. Somewhat beneficially, those who are infected by a particular DEN variant are generally granted immunity. However, this does not preclude the infection of other DEN derivatives. Due to the lack of a consensus of dengue infection prevalence, some estimates vary from 390 million new infections a year to a staggering 3.9 billion people who are assumed to be at risk for infection. One of the compounding factors is that an infected female mosquito is able to carry the virus indefinitely. Quite ironically, the infected human patient becomes the mechanism for the further propagation and subsequent infection of more carriers. Treatment of dengue is very non-specific and presents a large challenge.Besides, 75.38% of those infected

with dengue are asymptomatic carriers of the viral infection. Although, medical intervention can have a significant impact on mortality rate, mostly by regulation of fluid levels, a medication for dengue fever could have a great impact. Regulation by medication or by vector control would be particularly useful as the virus originally came from cattle, and thus its propagation may not be completely halted. The first dengue vaccine was developed and introduced by late 2016 and is now being recommended to individuals older than 9 up to the age of 45 years [9].

There is hope, however, especially in the synthesis and use of heterocyclic drugs. Substituted and unsubstituted phenyl-heteroaryl-aryl compounds have been shown to exhibit antiviral activity against strains of the dengue virus. However, the activity of the compounds seems non-specific. In that case, the compounds may be effective against a multitude of viruses that generate pathological symptoms in humans [10]. Four benzimidazolium derived nitrile-functionalized mononuclear-Ag(I)-N-heterocyclic carbene and binuclear-Ag(I)-*N*-heterocyclic carbene (Ag(I)-NHC) hexafluorophosphate (Figure 2) complexes were shown to demonstrate in vitro antibacterial activity. The intercalating action of nuclease on DNA was demonstrated as the mechanism of action and thus larvicidal activity was demonstrated against *Aedes albopictus*. The toxicity to the insect was increased in a dose-dependent manner, a useful property for a drug-like molecule [11].

5. Dracunculiasis

Dracunculiasis (also known as Guinea-worm disease) is a parasitic disease that is currently under control. It is wonderful to note that since the 1980's the number of cases has dropped from approximately 3.5 million cases to only 30 cases in the year 2017. However, occurrences of dracunculiasis have been recorded even in 2018 in Chad, South Sudan and Angola [12]. A schematic diagram of dracunculiasis is presented in Figure 4.

The mechanism behind this decrease can be attributed to the concerted efforts of the WHO and the United States CDC (Centers for Disease Control and Prevention) in developing a campaign for eliminating dracunculiasis. Ongoing monitoring and certification of countries after the improvement of water supplies has ensured lasting results. The disease is transmitted through contaminated water supply sources that contain water fleas that are infected with guinea worm larvae. The guinea worm is taxonomically identified as *Dracunculus medinensis* and the disease

process generally is not fatal but results in annoyance and discomfort for many days. Following initial infection, approximately one year later, a worm is expelled from a blister formed on the lower body. The worm then releases larvae into the water source that is almost always used to bathe and douse the irritable wound. If the water is not sequestered as biohazardous waste, the cycle begins again. The initial ingestion of water fleas infected with guinea worm larvae is what allows the transmission of the actual disease-causing parasite. The water fleas are killed and lysed in the stomach, and from the remains of the water flea, the larvae of the guinea worm are released. The worms penetrate the gut wall and move throughout the body and finally, a female worm becomes fertile and migrates to the lower limbs and is released. The subsequent release of offspring into the water allows further reincorporation of the worm into more water fleas when water fleas prey on the guinea worm larvae. This leads to another infectious cycle. Therefore, the availability of safe drinking water and proper sanitation are important to prevent the transmission of dracunculiasis. Unfortunately, no treatment is currently available for this disease [13].

<Figure 4>

An interesting development for this disease, especially because the incidence is so low, is the development of new low molecular weight molecules that can be used generally in the treatment of those pathological infections caused by parasites. Natural heterocyclic chamigrane endoperoxide, merulin A derivatives, obtained in *Endophytic fungi*, demonstrated positive laboratory effectiveness against parasitic infections [14]. It is important to note that merulin A is under trial for the treatment of another NTD African sleeping sickness. Therefore, it seems that although no specific work is being done to make a medication for dracunculiasis parasitic disease, there are continued efforts for other neglected tropical diseases which in turn may confer positive benefits in the treatment process for related diseases.

6. Echinococcosis

Echinococcosis is one of the most severe parasitic tropical diseases (Figure 5). The general classification of echinococcosis is multifactorial in that four unique diseases fall under this category. These diseases are cystic echinococcosis, alveolar echinococcosis, polycystic echinococcosis and finally unicystic echinococcosis. Cystic echinococcosis and alveolar

echinococcosis are the most troublesome due to their abundance. From the parasitic perspective, there are two distinctive hosts: intermediate and definite. The intermediate hosts are those animals that consume contaminated food or water that is laced with the eggs of the parasite. The parasite then uses the intermediate host to develop and proliferate in the living tissue. Tertiary consumers ingest the infected tissue of the lower trophic level organisms and are the definite host. The developed tapeworm is stored in the intestinal organs of the definite host. Humans can be considered as an intermediate host, although humans are not directly involved in the cycling of the parasite. Cystic echinococcosis is caused by *Echinococcosis granulosus* and alveolar echinococcosis is caused by *Echinococcosis multilocularis*. Even though a variety of hosts may be implicated, cystic echinococcosis preferentially utilizes the dog-sheep-dog cycle of infection and alveolar echinococcosis uses small carnivore/mammalian like domesticated dogs and cats. Symptoms for cystic echinococcosis include the formation of hydatid cysts in the lungs and liver and can lead to nausea, cough, vomiting, pain in the chest, and shortness of breath. Weight loss and weakness also can result. Incubation may last multiple years and may not be accompanied by any symptoms. For alveolar echinococcosis the growth of a tumor-like mass in the liver can be accompanied by subsequent metastases to adjacent tissues. This spread of the disease will allow the parasite to infect the rest of the body and can lead to fatality as well as weight loss, pain in the abdomen and eventually hepatic failure [15,16].

The treatment of these diseases is just as complicated as their method of infection. The treatment of cystic echinococcosis involves either a technique where a puncture and subsequent aspiration technique is employed, surgery, drug administration or allowing a natural progression and subsequent expulsion of the disease. For alveolar echinococcosis, an intensive surgery, related in many ways to tumor removal, must proceed along with drug utilization to prevent infection. It is important to note that currently a heterocyclic benzimidazole drug, albendazole (brand name: Albenza; Figure 1), is used for this purpose (anti-parasitic activity). However, random surgery especially after metastasis may afford temporary pain relief but does not provide a permanent solution. Thus, treatment is primarily focused on the removal of worms from hosts, using vaccines for hosts and removing diseased animals from a population [17].

<Figure 5>

Apart from albendazole, another heterocyclic drug mebendazole (brand name: Emverm), containing a benzimidazole core, is frequently used for the treatment of echinococcosis. Both albendazole and mebendazole showed promising results by reducing infection in the treatment of echinococcosis. The common pharmacophore in these heterocyclic compounds is the guanidine-fused benzimidazole. Notably, some other neglected tropical diseases such as Human African trypanosomiasis, Buruli ulcer, Chagas' disease, Onchocerciasis, Leishmaniasis, Taeniasis Cysticercosis, and Lymphatic Filariasis are responsive to guanidine-containing heterocyclic derivatives. The guanidine-containing scaffold seems to allow antiprotozoal and antiparasitic action to occur [18]. In 2017, it has been reported that a few amino alcohol-containing heterocycles might be used to treat the disease. It was determined that the invention will facilitate the discovery of lead compounds that can treat echinococcosis and will hopefully usher in a targeted drug development process [19].

7. Foodborne trematodiases

As the name suggests, the disease is transmitted by eating contaminated foods that contain trematode worms. These foods can come from a variety of sources. Of particular importance is unprocessed/undercooked or raw food including vegetables, fish and other and crustaceans that nurture the tiny larvae of the worms. Interestingly the parasites are unable to be transmitted directly to human hosts and must pass through multiple intermediary hosts before the transmission to a human may occur. The first host must always be a freshwater snail. The second host may involve either a fish which lives in non-saline environments or various crustacean species. Additionally, a lack of a second intermediate host is possible. The terminal host must be a mammalian species. Therefore, there are two mechanisms of infection: Eating an infected host (fish, crustaceans, etc.), or consuming larvae infested vegetables found in aquatic environments. Depending on the specific infectious species and the organ from which the adult worms are found, effects are organ and patient-specific. Generally, the disease leads to chronic conditions and is unnoticed until much later after infection. In the cases of both clonorchiasis (infectious parasite: *Clonorchis sinensis;* carrier: fish) and opisthorchiasis (infectious parasite: *Opisthorchis viverrini;* carrier: fish), the formation of bile duct cancer and severe inflammation of the various bile ducts may occur due to presence of the worms. Fascioliasis (infectious parasite: *Fasciola hepatica/gigantica;* carrier: aquatic vegetables) is characteristically associated with symptoms

occurring in the larger bile ducts in addition to the gallbladder where aching, anemia, inflammation as well as jaundice are common symptoms. Regarding paragonimiasis (infectious parasite: *Paragonimus spp.;* carrier: crustaceans), the symptoms that occur are respiratory, including cough with bloody regurgitation, pain in the chest, trouble respiring and a febrile state. Therefore, depending on the particular parasite and the part of the body (organ) that hosts the parasite, the symptoms are different [20].

Effective and specific medication has been developed for the treatment of foodborne trematodiases. For clonorchiasis and opisthorchiasis, a tricyclic azaheterocycle, praziquantel (Figure 1) should be given in a dosage of 25 mg/kg of the bodyweight 3 times per day for 3 days. For preventative purposes, 40 mg/kg of the bodyweight should be delivered once. For fascioliasis, a benzimidazole derivative, triclabendazole (Figure 1) is generally recommended in the manner of 10 mg/kg of body weight once and if ineffective, the dose may be repeated. For preventative measures, 10 mg/kg of the bodyweight may be given in a single administration. Alternatively, in the case of infection with paragonimiasis, praziquantel may be given in the amount of 25 mg/kg of the bodyweight for 3 times a day for 3 consecutive days. For prevention, triclabendazole is prescribed once in the amount of 20 mg /kg of the body weight [20]. Figure 6 represents the key features of foodborne trematodiases.

<Figure 6>

Notably, artemisinin derivatives were also shown to be inhibitors of trematode worms and demonstrated the potential of becoming good alternative drugs for the treatment of this disease. Artemisinin (Figure 1) derivatives and synthetic trioxolanes demonstrated significant *in vivo* efficacy under laboratory conditions. Once again, derivatives of both compounds are heterocyclic in nature. Interestingly, artemisinin derived drugs such as artesunate and artemether have already been proved as highly safe and effective drugs in malaria treatment, so it is somewhat logical to think that a positive benefit may be had with artemisinin derivatives in the treatment of foodborne trematodiases [21]. Heterocyclic drug development for this disease seems promising.

8. Human African trypanosomiasis (Sleeping sickness)

Human African trypanosomiasis, also known as sleeping sickness, is indigenous to thirty-six sub-Saharan countries. The vector-borne disease is transmitted by the tsetse fly. The parasite of this disease belongs to the genus *Trypanosoma*. Agricultural communities seem to exhibit a particularly high incidence of the disease. This can be logically attributed to the greater presence of the vector. There are two distinct forms of the disease: *Trypanosoma brucei gambiense*, which causes more than 98% of trypanosomiasis sleeping sickness cases and a less common form of the disease caused by *Trypanosoma brucei rhodesiense*, responsible for the remaining 2% of all infections, endemic to Uganda. Unfortunately, the disease may result in asymptomatic conditions for multiple years and when symptoms do manifest, the nervous system is often already detrimentally affected. It is interesting to note that Chagas' disease which is also known as American trypanosomiasis, is caused by another *Trypanosoma* species called *Trypanosoma cruzi*. American trypanosomiasis is considered a different disease than African trypanosomiasis because of differences like transmitting species, symptoms, classification, and methods of treatment. [22]. In human *African trypanosomiasis* (HAT) the routes of infection include vertical transmission, insect transmission, contamination by unsterile needles, and transmission because of sexual contact. There are two main phases of infection. In phase one, the parasite proliferates in the lymphatic and circulatory system and results in a febrile condition, discomfort, and itching. In the following phase, parasites cross the blood-brain barrier, exposing the brain: thus, the central nervous system experiences devastating effects from the parasitic infection. Profound psychological pathology such as confusion and disruption of sleep cycle regulation (from which the name of the disease is derived) is observed. Without treatment, the disease is often fatal [23].

Five different drugs are currently used for treatment; treatment is often difficult and complex, especially if the central nervous system is implicated. Treatment can persist for a period of up to 24 months and is difficult to administer. Treatment options are defined by the two major stages of infection. During stage one infection, pentamidine is used due to the relatively low risk of adverse effects. Suramin can alternately be administered despite causing allergic reactions and urinary tract issues. Both heterocyclic and non-heterocyclic drugs are used for this treatment. In the second stage of infection, a triazolyl dithiarsolan derivative (melarsoprol) is administered as a remedy for both disease forms. However, the infection is resistant to treatment by this drug in many portions of Africa and contains arsenic and therefore may result in toxicity. The drug is used as a primary remedy for rhodesiense infection and in the follow-up treatment of gambiense

infection. Eflornithine is less toxic than melarsoprol, however, is only effective against the gambiense infection type. This drug is also non-heterocyclic drug. Combination therapy of eflornithine along with a furan derivative, nifurtimox, was approved by the FDA (Food and Drug Administration) in 2009. This combination therapy has proven as an effective treatment for the second stage infection against the gambiense form of the disease, although the combination has not been adequately tested against the rhodesiense variant [24-26]. The structures of the two heterocyclic drugs, melarsoprol and nifurtimox, are shown in Figure 1. Here it is important to mention that although nifurtimox is a registered drug for American trypanosomiasis, it is not permissible to use as a primary medication itself in the treatment of human African trypanosomiasis although the combination therapy of nifurtimox with eflornithine is an accepted strategy for the first-line treatment of human African trypanosomiasis.

There are other heterocyclic antiprotozoal agents that showed potential activity against the disease. Quinolone derivatives, specifically, 4-quinolones containing a cyclic or acyclic amine at position 7 have been reported as potent *in vitro* inhibitors of parasitic activity. The compounds showed selectivity, did not significantly affect macrophages and did not harm normal cells that could be potentially disturbed by treatment with other drugs [27]. In a relatively recent finding, it was demonstrated that gold-containing heterocyclic compounds demonstrated excellent activity against *Trypanosoma brucei* parasites. These complexes were gold (1) *N*-heterocyclic carbene derivates. The complex was found to achieve its therapeutic effect in two unique ways. Complete removal of the flagella used in movement and total degradation of the infecting species' basic cytoskeletal structure was responsible for the biological activity [28] of the hit gold (1) *N*-heterocyclic carbene derivate. This preliminary study thus demonstrates a promising future for this organometallic/heterocyclic hybrid. Currently, an imidazole derivative (fexinidazole) has successfully completed clinical trials (phase II/III) for the *gambiense* form of HAT but clinical trials for the other form (*rhodesiense*) of HAT has not yet been completed. It is extremely interesting to note that another new heterocyclic drug candidate, acoziborole (an oxaborole derivative) has recently demonstrated significant therapeutic activity in phase I and II clinical trials against both forms of HAT (*gambiense* and *rhodesiense*). Acoziborole is currently undergoing phase III clinical trials. This medication is expected to be orally deliverable as a single dose. If this expectation comes to fruition, the treatment of HAT, for both forms, will be

very simple and economical [25]. The structure of fexinidazole and acoziborole are shown in Figure 1.

9. Leishmaniasis

Leishmaniasis is not a single disease, but rather a group of health disorders (Leishmaniases), caused by protozoan infection by one of more than 20 unique species of the genus *Leishmaniasis*. To make matters worse it is non-selectively transported by over 90 species of tiny (only 2-3 mm long) infected female sandflies [29]. There are three major forms of leishmaniasis disease that include visceral leishmaniasis (also called kala-azar), cutaneous leishmaniasis, and mucocutaneous leishmaniasis. The visceral form is a deadly disease and causes death in most of the patients who are not treated systematically. Symptoms include a febrile condition, liver and spleen size enlargement (swelling), and anemic conditions. Cutaneous leishmaniasis is the most frequently encountered form and causes lesions in the skin such as ulceration. Close to one million cases occur every year. The mucocutaneous form greatly affects the mucous membranes, specifically those present in the throat, mouth and nasal cavities [30].

<Figure 7>

Treatment options are widely varied. A pentavalent (Sb^{+5}) antimonial (sodium stibogluconate, Figure 1) has been used as the first-line medication for many years. It is a good heterocyclic drug that is frequently used to treat all three types of leishmaniasis. Apart from that a few non-heterocyclic drugs like meglumine antimoniate, miltefosine, and paramycin, are also used in certain cases where resistance may occur. The intravenous (IV) dose of sodium stibogluconate may vary from 20 mg/kg of the bodyweight to an upper limit of 50 mg/kg of the bodyweight. An unsaturated lactone (amphotericin B, Figure 1) deoxycholate is a heterocyclic drug with a macrolactone core that may be administered to affected patients at a concentration of 0.75-1 mg/kg of the bodyweightonce in a day for 15 to 20 days. The use of lipid formulations of amphotericin B (liposomal amphoterin B) is also very common. Paromomycin, an amino sugar heterocyclic drug, has also been shown to be effective and is administered in a dose of 15-20 mg/kg of the bodyweight for 3 weeks to treat visceral leishmaniasis. Certain combinations of the drugs mentioned above were shown to be beneficial in some cases.

For the cutaneous form, paromomycin (Figure 1) alone and in combination with gentamicin has demonstrated good results. Both drugs are heterocyclic (Figure 1). There are two oxane (tetrahydrofuran) and one oxolane (tetrahydropyran) moieties present in paromomycin while gentamicin contains two oxolane subunits. The Pentavalent antimonial, discussed previously, may also be administered. Temperature therapy, including extremes of temperature (hot and cold), applied locally may produce a beneficial effect.

For the mucosal form, pentavalent antimonial may be delivered in a dosage of 20 mg/kg of the body weight once in a day for 30 days. Liposomal amphotericin B deoxycholate may also be given. Amphotericin B should be given 20-45 times in a disease cycle at a concentration of 0.7-1 mg/kg of the body weight in each time. Pentamidine and miltefosine are non-heterocyclic drugs that also may be administered. A combination of antimonials with the xanthine derivative pentoxifylline (Figure 1) can also yield good results for a patient [31].

The research and development of heterocyclic *N*-oxide containing compounds seem to hold promise for the future of heterocyclic drug development. This molecular pharmacophore may demonstrate general positive effects against other diseases including Chagas' disease, tuberculosis, and malaria. The most interesting and potentially beneficial compounds were found to be quinoxaline 1,4-di-*N*-oxide, indolone *N*-oxide, furoxan, benzofuroxan, and benzimidazole *N*-oxide [32]. Recently, a benzimidazole-based compound, 2-(phenanthren-9-yl)-1*H*-benzimidazole (Figure 2) demonstrated comparable pharmacological activity (*in vitro*) with the positive control amphotericin B [18].

10. Leprosy

Leprosy is a chronic bacterial disease caused by the bacterium *Mycobacterium leprae*. Leprosy is also called 'Hansen's disease' in the namesake of Dr. Gerhard Hansen who discovered the bacterium *M. leprae* in 1873. The development of pathology and symptoms occurs over a span of time ranging from 1 year up to 20 years. This is due to the slow proliferation rate of these bacteria. The infection results in the degradation of the limbs, skin, eyes, and nerve tissue [33]. The disease has prevailed since ancient times, however, appropriate monitoring by WHO and the introduction of multiple effective drugs has been particularly useful in combatting leprosy. Figure 8 summarizes a dramatic improvement in the treatment of leprosy.

<Figure 8>

Dapsone was the first drug (non-heterocyclic) that was introduced for the treatment of leprosy. Unfortunately, patients began to develop resistance to this drug. Therefore, the WHO introduced multi-drug therapy (MDT) that included mainly two heterocyclic drugs: rifampicin and clofazimine (Figure 1). The core of rifampicin is a macrolactam unit that is attached with a tetrahydrofuran and a piperazine subunit. Clofazimine contains a phenazine heterocyclic moiety in its core. Dapsone is a tertiary component of this MDT. This MDT has been demonstrating excellent effectiveness for the treatment of leprosy worldwide. Over 16 million patients have been cured of the disease in the last two decades [34]. The use of an amide, derived from a cyclic 6- or 7-membered amine, as a potentiator is currently being studied. The mechanism of activation is believed to proceed through the monooxygenase EthA enzyme pathway [35]. Currently, this MDT is available around the world (by courtesy: WHO) free of charge and will be available until 2020. Presently, around 250,000 people are infected by the bacterium *M. leprae*, mostly those from less developed countries. Accordingly, an extension of free MDT after 2020 (Figure 8) is highly required and a justified request in line with the principle of the 'one world' concept. Previously, leprosy was thought to be highly contagious and the general public was highly fearful of this disease. Isolation of the patient and discrimination was very common. This stigma is being weakened by continuous education and easy access to this MDT. Leprosy is completely treatable if treated in a timely manner [36].

11. Lymphatic filariasis

Lymphatic filariasis, known commonly as elephantiasis, targets the lymphatic system and can lead to an exponential increase in the size of specific body parts. This disease puts 856 million people at risk globally, and 36 million currently suffer from chronic symptoms. The infection is caused by microscopic, thread-like worms (parasites) that are carried by mosquitoes. The infection is caused by three parasites classified as nematodes. These include in order of prevalence, *Wucheria bancrofti*, *Brugia malayi* and *Brugia timori*. The worms produce pathology by their sustained residence in the lymphatic system during their lifespan of 6-8 years. The number of larvae produced can range in the millions. The infected individual then serves as a repository for the uptake of larvae by a mosquito. The incorporated larvae then mature within

the mosquito and the larvae may be deposited on the skin near the site where a mosquito bite is made. The larvae then enter the body and find a suitable location to mature and the cycle is repeated. A variety of mosquito genera including the *Culex*, *Anopheles*, and *Aedes* genus have been found to be carriers of the disease. Tissue size growth (lymphoedema), epidermis and tissue level thickening, elephantiasis and hydrocele are all symptoms of the disease. Incidences of inflammation due to the immune response and/or bacterial infection as a result of lowered immunity are also encountered. The disease is often very embarrassing and disrupts the social lives of the affected individuals. Figure 9 summarizes the worldwide impact of the disease [37].

<Figure 9>

According to WHO recommendation, mass drug administration (MDA) is being introduced which involves the annual administration of preventive chemotherapy to the population determined to be at risk of obtaining lymphatic filariasis. Although MDA is not entirely able to kill the adult parasites in a patient, it can effectively prevent the spread of microfilariae from a patient's bloodstream to a healthy person's bloodstream through mosquitoes. Later, the WHO modified its recommendation to suggest a treatment that could remove the majority of microfilariae from a patient's bloodstream in a few weeks. Interestingly, the current recommendation includes the administration of three heterocyclic drugs: albendazole, ivermectin, and diethylcarbamazine citrate (Figure 1). This triple drug administration involves the administration of 400 mg of albendazole (benzimidazole-based drug) in a single dose combined with ivermectin in a dose of 150-200 mcg/kg of the bodyweight, and diethylcarbamazine citrate (DEC, a piperazine analog) in a dose of 6 mg/kg of the patient's bodyweight [38]. The treatment has been profoundly successful with an estimated savings of 24 billion dollars that would have been forfeited due to productivity loss. An interesting development has been recently reported which involves the introduction of thiazolidine containing compounds in the treatment of lymphatic filarial parasites. In the study being referenced, the *in vitro* activity of the thiazolidine containing compounds were tested against *Brugia malayi*. The scaffold demonstrated a beneficial effect and a good therapeutic index. Thus, these molecules might have the potential for the future treatment of this disease [39].

12. Mycetoma, Chromoblastomycosis and other deep mycoses

Mycetoma is a disease that infects the subcutaneous tissue. This includes skin, bone, and muscle. Multiple microorganism species (bacterial and/or fungal) may result in infection, however, the infection is caused by either a bacterial or fungal organism. Generally, direct puncture of the tissue by a contaminated object through a minor trauma or penetration results in infection. Due to the lack of proper footwear in many countries, this chronic disease occurs primarily in the foot, but other parts of the body can be affected. Although barefoot rural populations in endemic areas are mostly affected, the risk of infection in these areas is widespread. The disease has recently (Figure 10) been recognized as an NTD but it is still under the category of 'not notifiable' which means reporting of the disease is not required by law. Accordingly, data related to mortality, morbidity, and global burden are not known. Consequently, no recommended monitoring and treatment procedures exist. The disease most likely cannot be transmitted from human to human. The symptoms include damage to the subcutaneous tissue. The disease is often characterized by the formation of painless masses below the cutaneous layer along with sinuses that secrete and discharge the infecting species. The slow development of symptoms often results in amputation and secondary bacterial and/or fungal infection. Secondary infection can lead to sepsis in severe cases. In contrast to mycetoma, the reason for chromoblastomycosis has been linked to fungal infection. Chromoblastomycosis is a similar type of chronic NTD that affects the skin including cutaneous and other tissues by causing polymorphic tumoral or nodular lesions. Among other fungal species, three particular species *viz*. *Fonsecaea pedrosoi*, *Phialophora verrucose* and *Cladophialophora carrionii,* are responsible for chromoblastomycosis infection [40].

<Figure 10>

As stated earlier, mycetoma, chromoblastomycosis, and other deep mycoses are badly neglected diseases and currently, no systematic treatments are available. Based on the nature of the infection, antibiotics and/or antifungal drugs are administered for mycetoma whereas antifungal treatment is required for chromoblastomycosis. Due to the lack of a universal treatment policy, various antibiotics and/or antifungal drugs (mostly heterocyclic) are used in different parts of the world. Treatment options are poor and involve the use of a cocktail of antibiotics and antifungal medications. Surgical operation is required in many cases. The treatment is costly, inaccessible and ineffective in many incidences [41]. Recently, a new series

of triazole containing pyrimidine derivatives have been developed that claims to be effective against the fungal infections of mycetoma [42]. A general structure of the compound is shown in Figure 2.

13. Onchocerciasis

Onchocerciasis is commonly known as river blindness; this disease is propagated by a parasitic vector. After trachoma, onchocerciasis is the second leading cause, due to parasitic infection, of blindness worldwide. The specific vector is female blackflies belonging to the genus *Simulium*. These blackflies commonly breed near pools of moving water. Thus, this infection has a high incidence of occurrence near water sources such as streams and rivers. Pathology is caused by the movement of mature worms, termed filarial worms, to different portions of the eyes and epidermis. The specific species of worm that causes the disease is *Onchocerca volvulus*. An infected human may also serve as a reservoir for the further propagation of the worm once a female blackfly ingests microfilariae from an infected human when taking a blood meal. The larvae develop to some extent in the blackfly, and the female blackfly becomes a carrier of the disease. The dead worms in the body produce a significant inflammatory response and can be responsible for severe bouts of itching. Progressive vision loss including the formation of eye lesions; partial to complete blindness may occur. Raised areas of the skin are usually indicative of the presence of adult worms. About 99% of patients live in Africa. Out of 20.9 million cases, 14.6 million cases resulted in skin disease and 1.15 million cases resulted in visual impairment [43-45].

The current method of treatment is the administration of the heterocyclic spiro-macrolide drug ivermectin (Figure 1) until the infection is cleared. The drug may need to be administered every six months for a duration spanning 10-15 years. The drug has shown great success in Africa where the majority of cases occur [43,44]. It has been reported that pyrazinyl and pyridinyl derivatives could successfully inhibit the inflammatory response and could be developed as useful drugs for treating symptoms of this disease [46]. Another recent report has shown that fused heterocyclic thiazole-benzimidazole-piperazinyl-thiadiazolyl hybrids and the corresponding Mannich bases synthesized therefrom were shown to possess potent filaricidal activity. The pharmacological activity of these compounds was better than that of the positive

control thiabendazole. The report is interesting as both the Mannich base analog and final product are heterocyclic molecules and showed potent filaricidal activity [47].

14. Rabies

Rabies, a commonly known zoonotic disease, causes approximately 59,000 deaths annually around the world and about half of the cases are attributed to children or young adults under the age of 15. The prevalence of rabies is not to be understated as its distribution includes over 150 countries. The disease is viral, caused by the transmission of rabies virus of the genus *Lyssavirus* (family: *Rhabdoviridae*) to the human body. Primary transmission occurs through dogs in 99% of cases. The immediate cleansing of a wound sustained in an incidence with an animal infected with rabies is critical and affects prognosis. Vaccination of dogs serves as a promising treatment for eradication of this disease because of their ubiquity in many cultures and overwhelmingly singular responsibility for causing the disease. The preemptive vaccination of susceptible human populations is also crucial. Initial symptoms include local burning sensations and discomfort near the site of contact. Subsequent neurological effects occur due to inflammation of the brain and spinal cord (paralytic). This inflammation can be fatal. Two distinct variants of the disease exist. Furious rabies results in specific symptoms such as the phobia of moving air and water as well as a hyperactive state. Death often follows in a few days resulting from cardiac and respiratory system failure. The second form, paralytic rabies, generally results in the paralysis of muscles in a manner that can be described as migratory from the initial infection site. A comatose state is induced, and death follows. Paralytic rabies is responsible for approximately 80% of rabies cases. Notably, in the Americas, dog transmission is not as ubiquitous, and rabies is more commonly transferred through bat bites. Death from ingestion of tainted animal tissue meat, human transmission and rodent to human transmission are undocumented. Transfer of the disease from other carnivores is extremely rare. Rabies is treated by either preventive vaccination of dogs and humans, or immediate administration of rabies immunoglobin after a rabid animal encounter has occurred. The immunoglobin treatment is followed by the administration of an antiviral like ribavirin (Figure 1). Ribavirin is a ribofuranosyl triazole derivative that is frequently recommended to combat rabies virus. Unfortunately, the cost of treatment in countries such as Asia and Africa can be more than 20 times the average daily income earned [48,49].

Recently, a series of pyrazolo-fused pyridine molecules has been demonstrated to possess antiviral activity for a panel of viruses, including rabies. The general structure of the compound [50] is presented in Figure 2. Also, heterocyclic 3-Substituted 1,3,4-oxadiazole and thiadiazoles have been found to exhibit antiviral activity against rabies. The mechanism of action includes the downregulation of a cell death pathway and/or of suppressing an immunosuppression signaling pathway. Therefore, the molecule acts as an immunomodulator and induces antiviral activity against rabies [51].

15. Scabies and other ectoparasites

Scabies (along with other ectoparasites) is one of the newest members to join the NTD family along with chromoblastomycosis and other deep mycoses, and snakebite envenoming. In 2017, scabies was identified by the WHO as a neglected tropical disease [52]. Human scabies is highly contagious, and it is caused by the parasite *Sarcoptes scabiei var hominis* (itch mite). Scabies is caused by the infestation of the tiny mites in the exterior layers of the skin. Scabies infestation may become more problematic by a secondary bacterial infection that could result in septicemia, post-streptococcal glomerulonephritis like renal disease and rheumatic cardiac disease. Scabies has very recently been included in the list of NTDs; systematic data is not currently available. The current treatment of scabies includes oral administration of the heterocyclic macrolide ivermectin (Figure 1) in the case of pre-bacterial infection (primary management). To treat post-bacterial infection (secondary management) several heterocyclic antibiotics/antiseptics are prescribed [52,53].

16. Schistosomiasis

Schistosomiasis is the next disease to be considered. The disease is caused by parasitic blood flukes belonging to the genus *Schistosoma*. In 2017 only, 220.8 million individuals were infected and needed preventive treatment, but only 102.3 individuals were treated. In 2016, a staggering 53.7% remained untreated. The larval form of the parasite is harbored by snails. These snails live in freshwater and are responsible for the subsequent release of the larval parasites into water sources. These larvae then infiltrate the skin of a human and undergo maturation. The mature worms reside in the circulatory system and eggs are released. The eggs are either incorporated into tissues producing symptoms or excreted from the body, allowing

contamination of further sources to occur. The eggs give rise to larvae in the water allowing for the cycle of infestation to begin anew. However, there are different forms of the disease caused by unique species of worm. *Schistosoma haematobium*, *Schistosoma mansoni*, *Schistosoma japonicum*, *Schistosoma mekongi*, *Schistosoma guineensis* (and the similar *Schistosoma intercalatum*) are all implicated in producing the symptoms characteristic of intestinal schistosomiasis. However, *Schistosoma haematobium* is implicated in urogenital schistosomiasis. Symptoms produced in the intestinal form include discomfort, diarrhea, blood in the feces, and enlargement of organs including the liver and spleen. Abdominal blood pressure may also be elevated. Urogenital schistosomiasis is characterized by blood in urine, tissue damage including fibrosis, and kidney failure in later stages. Cancer of the bladder, hepatic failure, as well as male and female-specific urogenital issues may result, resulting in ectopic pregnancies and loss of fertility in certain cases.

Regarding treatment, a heterocyclic pyrazinoisoquinolinone derivative, praziquantel (Figure 1) is a highly effective drug against all the parasitic worm species that cause the disease. This heterocyclic drug is inexpensive, has minimal side effects and is clinically effective in reducing symptoms of the disease [54,55]. Previously discussed amino alcohol heterocyclic compounds that could be useful in treating echinococcosis may also be useful in treating schistosomiasis [19]. Interestingly, in a new study, it was reported that heterocyclic oxazine derivatives demonstrated *ex vivo* efficacy against the specific parasite *Schistosoma mansoni*. The molecules had a low cytotoxic effect in normal cell lines, indicating that the heterocycles are specific towards targeting disease-causing organisms. A considerable benefit would be granted by the development of this drug as a backup to oral praziquantel. The mechanism of action of the oxazine derivatives is the destruction of the outer layer that encapsulates adult worms [56].

17. Soil-transmitted helminthiases

Soil-transmitted helminthiases are certain types of infections that are caused by multiple organisms, commonly known as intestinal worms. The particular species are*Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus* and *Ancylostoma duodenale*. This disease currently affects 1.5 billion people worldwide. This is almost a quarter of the world's population! The disease derives its name from that method of transmission of the eggs of the worms from the fecal excretions of infected individuals into open-air/soil. The eggs are produced by worms

residing in the intestine of an infected individual. Interestingly, because the worms do not replicate in the host, reinfection is the primary factor that allows the disease to continue to persist in individuals. Fresh fecal matter containing eggs is not infective; eggs do not immediately mature in the soil. The eggs generally take 2 to 3 weeks to mature. However, once maturation does occur, *Necator americanus* and *Ancylostoma duodenale* eggs do not just merely become infective by simple ingestion as with the other species, but rather hatch and produce larvae which can infect humans through direct skin contact. The primary methods of ingestion of the other species' eggs include the consumption of contaminated food and water that contains the organisms. Depending on the concentration of worms in the body, a person may be asymptomatic or express stunted growth, anemic symptoms, loose stools, discomfort, weakness, and severe nutrient loss because the helminths feed on host blood and tissues [57,58].

The primary strategy of controlling morbidity due to soil-transmitted helminths should include proper sanitation, hygiene, and availability of clean drinking water. Treatment includes administration of the two heterocyclic benzimidazole drugs mebendazole and albendazole, given in 500 mg and 400 mg dosages, respectively. These treatments have been previously shown to be effective against lymphatic filariasis (solely, albendazole) and echinococcosis and have a good safety record. Both drugs are low-cost and can be orally administered quite easily [57,58]. Recently, thiazolid-4-one containing substituted chloro-quinoline derivatives have shown highly promising results for the treatment of this disease [59]. In addition, a novel series of Schiff base derivatives of 1,8 naphthyridine (a heterocyclic compound) demonstrated significant anthelmintic activity. This study was assessed using albendazole as control and measuring the time of paralysis for the species *Perionyx excavatus* and *Pheritima posthuma* [60]. These heterocyclic molecules have shown present effectiveness and future promise against soil-transmitted helminthiasis.

18. Snakebite envenoming

Snakebite is considered as a neglected health issue in many countries. As a result, reliable data is not available. However, according to the WHO estimation, approximately 5.4 million people experience snakebites each year and about half of that number (2.7 million) face envenoming. Currently, there is no heterocyclic drug for the treatment of snakebite envenoming; antivenom immunoglobulins are used to reverse or inhibit snakebite envenoming. Snakebite

envenoming has been included only for the thoroughness of the discussion. It is estimated that snakebite envenoming is responsible for about 81,000 to 138,000 deaths each year. Severe effects include respiratory failure, hemorrhage, paralysis, kidney function failure and limb injury that could result in amputation. Statistics on snakebites and envenomation including death and disability counts are presented briefly in Figure 11. Because of their smaller body mass, the children face greater symptomatic consequences than adults. Immunoglobulin treatment is effective, but it is not always easily available because of insufficient production, marketing, and distribution issues. As this disease is concentrated in the rural areas of less developed countries, it is often prohibitively expensive to gather data and to arrange for the production of quality antivenoms for affected individuals [61].

<Figure 11>

Although there is no heterocyclic antivenom molecule available to date, a series of potential heterocyclic molecules have been patented that could be used for treating the skin lesions and related damages that occur as a result of envenomation. These compounds consist of imidazoquinoline amines, imidazopyridine amines, 6/7-fused cycloalkylimidazopyridine amines, imidazonaphthyridine amines, tetrahydroimidazonaphthyridine amines, oxazolopyridine amines, oxazoloquinoline amines, thiazolopyridine amines, thiazoloquinoline amines, and 1,2-bridged imidazoquinoline amines. These compounds would work by direct application to the site of envenomation and may help reduce the physical damage that envenomation causes [62].

19. Taeniasis/Cysticercosis

Taeniasis is a neglected tropical disease (a parasitic infection) that is caused by three different species of tapeworm. The pork tapeworm (*Taenia solium*), the beef tapeworm (*Taenia saginata*), and the Asian tapeworm (*Taenia asiatica*) are the individual species responsible for the pathology. The infection by the beef tapeworm may occur through the consumption of contaminated beef tissue and infection by *Taenia asiatica* may occur through the consumption of contaminated pig liver. The ingestion of these meats results in the residence of the adult tapeworm in the human intestine. This is known as Taeniasis. This infection does not result in significant clinical symptomology. Taeniasis symptoms caused by any of the three adult worm species are relatively mild and generally include abdominal discomfort, loose stools, pain, and constipation. These effects generally occur after maturation of the adult worms, which generally

takes 8 weeks. The effects will continue until treatment is administered or until the tapeworm dies (after a period of up to 2-3 years for the *Taenia solium* species). However, the species that causes a significant health problem globally is *Taenia solium.* This is because infection with this tapeworm after initially causing taeniasis may also cause cysticercosis [63]. Cysticercosis is much more devastating than taeniasis, as cysticercosis patients not only host tapeworms in their intestines but also host larvae (cysticerci) of the tapeworm in different body parts like the muscle, epidermis, eyes and perhaps most devastating, the central nervous system (CNS). The symptoms of cysticercosis include epileptic seizures, severe pain, convulsions and visual impairment [64]. The disease may result in fatality. The total number of people suffering specifically from this disease also termed neurocysticercosis, ranges from 2.56-8.30 million people. To make matters more difficult, for cysticercosis, the larval development period may vary on a case by case basis and symptoms may not appear for years. The impact of taeniasis/cysticercosis has been summarized in Figure 12.

<Figure 12>

Treatment of taeniasis, caused by adult worms, includes the singular, oral administration of a heterocyclic (pyrazino[2,1-a]isoquinolin-4-one) derivative, praziquantel, (Figure 1) in a dosage of 5-10 mg/kg of the body weight. Praziquantel acts as an effective deworming agent for taeniasis patients. In some cases, a non-heterocyclic drug (niclosamide) is also prescribed. Treatment of cysticercosis is more complex and patient-specific. Prolonged treatment with a combination of drugs is required. Praziquantel alone or in combination with albendazole is recommended. Both drugs are heterocyclic (Figure 1). The physical removal of cysts may induce an inflammatory response from the body, and corticosteroids may be administered to reduce the pain. Additionally, it is not uncommon for antiepileptic drugs to be administered in conjunction with the corticosteroids or independently in order to prevent seizures. Surgery may also be required. Interestingly, the regulation of a heterocyclic drug (oxfendazole) in pigs is of key importance. Oxfendazole, a benzimidazole anthelmintic agent (Figure 1) at a dose concentration of 30 mg/kg of the bodyweight is recommended as an anthelmintic drug for pigs and can prevent the transmission of the *Taenia solium* species [65,66]. Perhaps the most interesting heterocyclic development for this class of diseases is that of the guanidine containing heterocyclic compounds discussed previously. Because the compounds seem to have significant side-effects, appropriate

development of these heterocyclic compounds might be beneficial for the treatment of a wide array of patients. In addition, treatment may be simplified by the administration of such drugs in the case of multiple infection/infestation [18]. Moreover, *N*-oxide heterocyclic molecules may be potent against a wide array of neglected tropical diseases as previously discussed [32].

20. Trachoma

Trachoma is the leading cause of blindness worldwide due to a single parasitic infection, and it is responsible for vision loss in 1.9 million people. The blindness caused by this disease is irreparable. The disease is caused by a bacterium termed *Chlamydia trachomatis* and is considered a hygiene-related disease. The mode of infection is through direct physical contact, the sharing of clothes/towels used to wipe eyes, and the encounter of nasal discharge of infected individuals. The disease can also be transmitted by flies that incorporate the bacterium through direct contact with either an infected eye or nasal discharge of the patient. Symptoms include progressive visual impairment as a result of the scarring of the inner eyelid; this is perpetuated by multiple infections. This scarring physically changes the conformation of the eyelid so that it turns in on itself. This allows abrasive rubbing of the eyelashes against the eye. Once this occurs, further degradation of the eyeball/cornea will result in blindness [67,68].

<Figure 13>

The WHO has introduced SAFE [S stands for surgery if the disease is at an advanced stage, A stands for antibiotics to reduce/remove the bacterial infection, F stands for facial cleanliness, E indicates environmental protection to remove the bacterium] as a strategy to combat trachoma. As a part of antibiotic administration, the azaheterocyclic macrolide azithromycin (Figure 1) is widely used. In 2017, about 83.5 million trachoma patients were treated with azithromycin. [68]. Recently patented 2-amino-*N*-(heteroarylsulfinyl)-acetamide derivatives could demonstrate potent antibacterial activity against a wide array of bacteria, including *Chlamydia trachomatis*. The mechanism of action is the inhibition of the bacterial aminoacyl-tRNA synthetase. Therefore, the bacterial cell is unable to proliferate, and the disease-causing process is ceased [69]. In another patent, *N*-[3-[[4-(2-pyridyl)pyrimidin-2-yl] amino]phenyl]-4-[(piperazin-1-yl)methyl]benzamide derivatives were demonstrated to be effective antitrachomacidal agents for the treatment of trachoma [70]. The mechanism of action includes the inhibition of protein kinases in *Chlamydia trachomatis* that are highly associated

with trachoma. In particular, these heterocyclic compounds are effective inhibitors of Abelson protein kinases including, but not limited to, c-Abl1, c-Abl2, and c-kit [70]. These developments may lead to an excellent selective drug that can be used in treating trachoma. Mass antibiotic/drug administration will not result in the elimination of trachoma; for this purpose, health and environmental hygiene must also be seriously considered [71].

21. Yaws (Endemic treponematoses)

Yaws is a chronic bacterial infection, and the majority of victims are children in the age group ranging from 6-10: in some cases, up to age 15. Yaws is prevalent in the tropical jungle areas where the weather is relatively warm and humid. It is caused by the bacterium *Treponema pallidum*, which belongs to the subspecies *pertenue.* Infection is caused by direct skin contact as a result of minor injuries. The period of incubation can range from 9-90 days, with the mean value being 3 weeks. Yaws affects the skin, bone and cartilaginous tissues. It has been estimated that 89 million people live in areas endemic to Yaws. Yaws results in the production of a papilloma that is saturated with bacteria. This papilloma subsequently converts into an ulcer. The ulcer formation results in the highly contagious transfer of the disease by abrasions (in the absence of treatment). Secondary effects of yaws can include dactylitis, the formation of yellow raised areas and discomfort. Yaws infection may lead to another subtype called ‘bejel’, or endemic syphilis as well as pinta [72]. Figure 14 summarizes the current status of yaws worldwide [73].

<Figure 14>

The treatment of yaws involves the use of either of two heterocyclic antibiotics (Figure 1): azithromycin (oral administration) or benzathine penicillin (intramuscular administration). Interestingly, the benzathine penicillin injection was the only remedy for Yaws for more than 60 years, whereas the inclusion of oral azithromycin treatment is comparatively recent (2012). The dosage of azithromycin administered is 30 mg/kg of the body weight and must not exceed 2g in total. Benzathine penicillin injection can alternatively be used, although it is currently less convenient after the discovery of the high therapeutic efficacy of oral azithromycin. Currently, benzathine penicillin injection is primarily used as a backup treatment for those who do not respond well to azithromycin. The dosage is administered intramuscularly, at a concentration of 0.6 million units for those under the age of 10 and a concentration of 1.2 million units for those

aged 10 years or older. Both treatments are extremely effective and cure 95% of patients [73]. In 2011, patented heterocyclic tetrazolone derivatives were found to be potentially effective in curing antimicrobial diseases such as Yaws. Additionally, triazole derivatives were found to have a similar effect. Both series of compounds are implicated in the inhibition of the protein fatty acid synthase required for microbial sustenance and proliferation in Yaws [74,75].

22. CONCLUSION

Although the WHO has taken preventive and curative measures the past few decades, many NTDs are still literally 'neglected'. The large incidence of mortality, morbidity, and disability attributed each year due to NTDs is magnitudes higher than that of diseases like cancer, diabetes, HIV/AIDS, cardiovascular diseases, or central nervous system-related diseases that receive the majority of attention in developed countries. The WHO, along with several sister organizations, is continuing the effort to update and revise the data pertaining to those suffering from various NTDs worldwide. Unfortunately, a few known and/or unknown tropical diseases (for example, encephalitis, ringworm, etc.) are not yet included in the NTD list. In many parts of the world, in particular Africa and some parts of Asia and Latin America, there are no standard diagnostic procedures and health professionals do not have sufficient training to isolate a causative agent of a disease. The use of vague diagnoses such as 'viral fever' does not assist in the process of treatment. To overcome this problem, the governments, international health organizations, and WHO should work together to allocate funding and resources to institute a higher standard of care. Diseases do not pay attention to nationality, color, race, religion, origin or ethnicity, and the poor communities of the world are often the main sufferers of NTDs. All humans deserve proper treatment. This review indicates that most of the drugs that are currently being used for the treatment of various NTDs are heterocyclic in nature. Because of their unique character, heteroatom-containing compounds are capable of forming additional drug-protein interactions like hydrogen bonding, co-ordination, salt-bridge formation, etc. with diverse protein molecules. It is well known that different diseases are related to the upregulation or downregulation of various proteins, and additional protein-ligand interactions are crucial in imparting therapeutic activity by protein regulation. Heterocyclic molecules are implicated in the treatment of a plethora of NTDs, and it makes scientific sense to continue to exploit the therapeutic effects of diverse heterocyclic scaffolds. Because neglected tropical diseases often involve vast proportions

of the world's most vulnerable populations, easily administrable, stable and economical heterocyclic drugs are desperately needed. As NTDs mainly affect impoverished people, brutal reality is that most pharmaceutical companies are not interested in developing effective drugs for NTDs. Although the number afflicted is extremely large, the profit margin is small; disadvantaged people cannot afford medication. Unfortunately, research in this area is not greatly encouraged and consequently there is lack of funding. This pessimistic outlook must be changed, and resources must be put forth to address these diseases. Many of the NTDs are directly related to the poverty, hygiene, environment, nutrition, and lifestyle of the patients. As stated earlier, lacking of research funds and interest might be the two major reasons why detailed mechanisms of actions of most the drugs are still unknown. At the same time, although there is no direct way to control warm and humid weather which is one of the influencing factors for some of these diseases, but non-medical measures like emphasis on personal hygiene, appropriate sanitation, clean drinking water, vaccination, and nutrition should also be encouraged by the local/state/national government to combat NTDs. The treatment of NTDs requires a concerted approach that is as unique as all the people suffering from them. Global approaches to public welfare have worked wonders and eliminated endemic diseases in the past; there is no reason that the same cannot be achieved for NTDs.

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CONFLICTS OF INTEREST

The authors do not have any conflicting interests.

LIST OF ABBREVIATIONS

AIDS: Acquired immunodeficiency syndrome

CDC: Centers for Disease Control and Prevention

CNS: Central nervous system

DEN: Dengue virus

DNA: Deoxyribonucleic acid

FDA: Food and Drug Administration

HAT: Human African trypanosomiasis

HIV: Human immunodeficiency virus

MDA: Mass drug administration

MDT: Multi-drug therapy

NHC: *N*-heterocyclic carbene

NTD: Neglected tropical disease

SAFE: Surgery, Antibiotics, Facial cleanliness, Environmental protection

tRNA: Transfer ribonucleic acid

WHO: World health organization

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Table and Figure legends:

Table 1. An overview of the 20 neglected tropical diseases, their current status and available treatments as defined by the WHO.

Figure 1. Commercially available heterocyclic drugs that are being used for the treatment of NTDs

Figure 1 (Contd.). Commercially available heterocyclic drugs that are being used for the treatment of NTDs

Figure 2. Investigative heterocyclic molecules (mostly patented) that are under various pre-clinical/clinical trials.

Figure 3. Categorical occurrence of the three types of Buruli ulcer.

Figure 4. The marked reduction in disease that occurred throughout the years. Data from the time involving the 1980's is excluded as the case number was 3.5 million.

Figure 5. Significant impacts of echinococcosis: At a glance.

Figure 6. Important facts regarding foodborne trematodiasis.

Figure 7. Important facts about leishmaniasis.

Figure 8. The milestones of leprosy treatment.

Figure 9. The current state and previous history of treatment and prevalence of lymphatic filariasis.

Figure 10. Status of mycetoma and its current recognition as a neglected tropical disease.

Figure 11. The statistics pertaining to snakebites and envenomation including death and disability counts.

Figure 12. Impact and status of taeniasis/cysticercosis as well as prevention strategy.

Figure 13. Current impact and control of trachoma.**Figure 14.** Facts regarding yaws and its distribution.